Rate and determinants of antiviral treatment initiation for patients with HBeAg-negative chronic hepatitis B

Mutimer, David; Elsharkawy, Ahmed; Hathorn, Emma; Arunkumar, Selvi

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SHORT COMMUNICATION

Rate and determinants of antiviral treatment initiation for patients with HBeAg-negative chronic hepatitis B

David Mutimer[1,2] | Ahmed Elsharkawy[1] | Emma Hathorn[1] | Selvi Arunkumar[3]

[1]Liver and Hepatobiliary Unit, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[2]Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

[3]Health Informatics, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Correspondence
David Mutimer, Liver and Hepatobiliary Unit, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.
Email: david.mutimer@uhb.nhs.uk

Abstract

Most clinic attenders with chronic hepatitis B (CHB) are serum HBeAg-negative, and a minority will require suppressive antiviral treatment. Expert guidelines propose schedules for the monitoring of untreated patients, but the recommended frequency of patient review does not reflect recognised demographic determinants of HBeAg-negative chronic hepatitis. Also, the impact of patient ethnicity on risk has not been defined. The aim of our study was to determine the rates and determinants of antiviral treatment initiation in a large multi-ethnic cohort of CHB patients attending a single centre. We undertook a retrospective study using entirely electronic sources of patient information. Treatment initiation dates were identified from electronic pharmacy records. Crude and time-dependent statistical analyses were undertaken to identify rate and risk factors for treatment initiation. Treatment was initiated for 232/1256 (18.5%) patients with rates of 23.2% and 33.2% at 5 and 10 years. An increased risk of treatment was associated with male sex (RR 1.803), older age at presentation (RR 1.027 per year increase) and with non-Black ethnicity (RR 1.654). Patient sex, baseline age and ethnicity also determined risk for treatment in the subset of patients with normal serum ALT and low HBV DNA at baseline, though overall treatment rate in this group was low (only 2% per annum). Thus, patient demographics permit risk stratification for treatment initiation and could determine to a significant extent the frequency of review required for untreated HBeAg-negative patients. Black ethnicity is associated with a significant reduction in risk of treatment initiation.

KEYWORDS
antiviral treatment, epidemiology, guidelines, hepatitis B, viral hepatitis

1 | INTRODUCTION

Most patients with HBeAg-negative CHB have chronic infection without chronic hepatitis, and a minority eventually require antiviral treatment.[1] For those patients that lie below the recommended threshold for commencement of antiviral therapy, the main purpose of follow-up is to identify progression from chronic infection to chronic hepatitis. Studies have identified predictors of

Abbreviations: ALT, serum alanine transaminase; Anti-HBe, antibody to HBeAg; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus DNA; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IgM anti-HBc, IgM antibody to hepatitis B core antigen; RR, relative risk.

HBeAg-negative chronic hepatitis, including male sex, older age at HBeAg seroconversion and HBV genotype,[2-5] but the possible role of patient ethnicity in the development of chronic hepatitis has not been explored. The main aim of our study is to examine the rate and determinants of risk for initiation of antiviral treatment in a multi-ethnic cohort of patients with HBeAg-negative CHB.

2 | PATIENTS AND METHODS

The adult HBV population attending the QEH reflects the ethnic diversity of the local population. The 2021 UK National Census found that 48.7% of the people of Birmingham were white, 29.9% were Asian (referring to the South Asian population), 1.1% Chinese and 10.9% Black (see census.gov.uk acquired 16/1/2023).

At the time of first hospital registration, National Health Service (NHS) patients are asked to identify their ethnicity, though some patients (about half) decline to do so.

Chronic hepatitis B patients are managed according to agreed protocols in line with published guidelines.[1] At each patient visit, the HBeAg, anti-HBe, HBsAg, serum HBV DNA and biochemical liver function tests are measured. Fibroscan is performed periodically in untreated patients. Data for this study were extracted from multiple electronic sources and included basic demographic information, laboratory data, electronic prescribing data, and clinical disease and event healthcare coding. For the analysis presented below, data were collected and up to date on 27 June 2022. The collection and analysis of these data for the specified purpose of this study were approved by the Hospital's Research and Development Department (code CARMS-18897). Statistical analyses were performed using the Excel add-in statistical package, Statpages.

3 | RESULTS

We identified 3661 individual patients with a positive test for serum HBsAg attending the QEH between 4 January 2001 and 27 June 2022 (Figure S1). After exclusions, 3220 patients remained, the baseline HBeAg/anti-HBe status was known for 3144, and self-declared ethnicity was known for 1812 of these. Table S1 illustrates, for each ethnic group, the percentage of patients at different age thresholds who were HBeAg-negative. At any age threshold, Black ethnicity patients were more likely to be HBeAg-negative.

We confined our analysis to a population of 1784 consecutive HBeAg-negative patients with baseline evaluation since 1 January 2009. This period coincides with the routine availability of entecavir and tenofovir (which received NICE approval in England in 2008 and 2009, respectively) and with the publication of the EASL 2009 Clinical Practice Guidelines (which had been updated to account for the availability of these second-generation nucleoside analogues). After further refinements, the final study population comprised 1256 patients, of which 232 patients were eventually treated with entecavir or tenofovir. This was a real-life study of patients attending a single centre, and management was according to published guidelines. For patients with laboratory results in the grey zone, treatment commencement was at the discretion of the consultant physician.

The primary analysis examined the rate and determinants of antiviral treatment in the cohort of 1256 patients. A second analysis examined the rate and determinants of antiviral treatment in a subpopulation of 624 patients who had baseline values of HBV DNA < 2000 IU/mL and a normal serum ALT (defined as <40 U/mL in men and <30 in women).

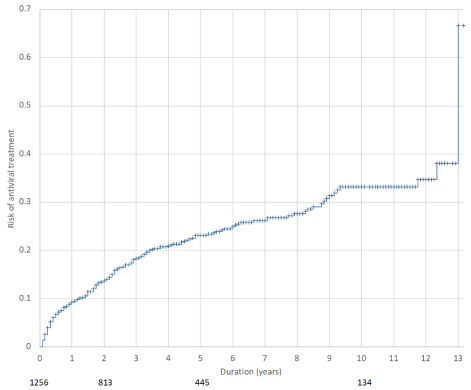
Time to treatment was the interval from baseline visit to first prescription of antiviral, and untreated patient follow-up was censored at the time of most recent clinic visit. Figure 1 shows the risk of antiviral treatment for the cohort for the duration of follow-up. Risk for treatment initiation was 23.2% and 33.2% at 5 and 10 years, respectively. Risk for treatment was substantially greater in the first 5 years in comparison with years 6–10 after baseline visit (Figure 1b). Treated patients were more likely to be male, were older at baseline, were less likely to have black ethnicity, had higher serum HBV DNA titre, higher serum ALT and higher fibroscan values (all statistically significant) (Table 1a).

A total of 1024 untreated patients were followed for a total of 4818 years (mean 4.71, median 5.0, range 0.17–13.17 years). During follow-up of untreated patients, we observed a significant decline in serum HBV DNA, serum ALT and fibroscan values (Table 1a).

Cox analysis assumes constant risk for duration of follow-up. For this reason, we have confined the Cox and Kaplan–Meier analyses to the first 5-year period after baseline. Male sex (HR 1.803), baseline age (HR 1.027 per year increase), Black ethnicity (HR 1.654 for non-Black vs Black patients) and baseline serum HBV DNA (HR 1.565 per

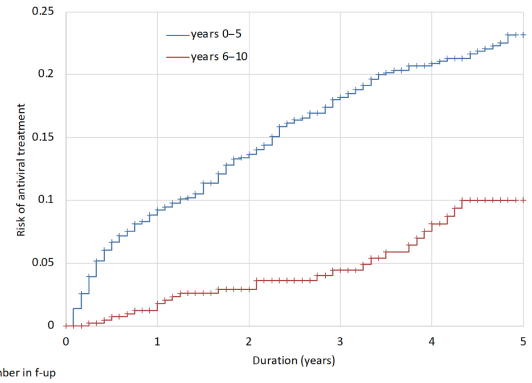
FIGURE 1 (A) Risk of antiviral treatment commencement for population of 1256 patients. Risk for treatment initiation was 9.2%, 13.6%, 23.2% and 33.2% at 1, 2, 5 and 10 years, respectively. (B) Comparison of risk for first versus second 5-year intervals of observation (log rank $p < .001$). Risk for treatment was substantially greater in the first 5 years (23.2% cumulative risk) in comparison with years 6–10 (10% risk) after baseline visit. (C) Risk of antiviral therapy versus patient sex during first 5 years of follow-up (log rank $p < .001$). (D) Risk of antiviral therapy versus baseline age (during first 5 years of observation) (log rank $p < .001$). (E) Risk of antiviral treatment versus ethnicity (log rank $p = .0155$). A = (south) Asian, B = Black, C = Chinese, W = White ethnicity. (F) Risk of antiviral treatment versus ethnicity (Black versus non-Black) (log rank $p = .003$). (G) Risk of antiviral treatment versus baseline serum HBV DNA (measured in IU/mL) (log rank $p < .001$). The risk for antiviral treatment was low for patients with baseline serum DNA measurement <2000 IU/mL and for those with baseline values between 2000 and 20,000 IU/mL. In the group with baseline titre 2000–20,000 IU/mL, the distribution of values was skewed towards lower baseline values, and the treatment rate was only 48/253 (19%). Of 205 untreated patients in this group at baseline, 53 (26%) had titre 2000–3000 IU/mL, and 163 (80%) had baseline titre <10,000 IU/mL. (H) Risk of treatment within 5 years of baseline according to age and gender (log rank $p < .001$). F > 45 = Female older than 45.

(A)



in f-up	1256	813	445	134
treated	0	142	204	229
censored	0	301	607	893

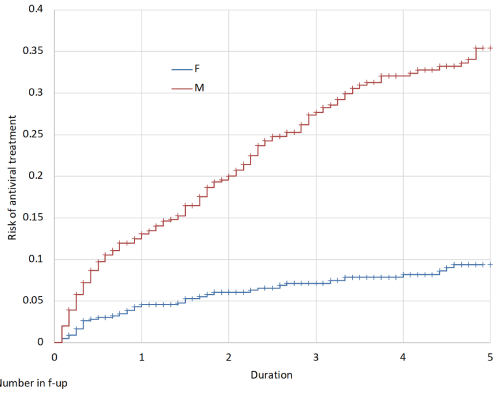
(B)



Number in f-up

years 0–5	1256	981	813	646	534	445
years 6–10	445	371	300	230	172	134

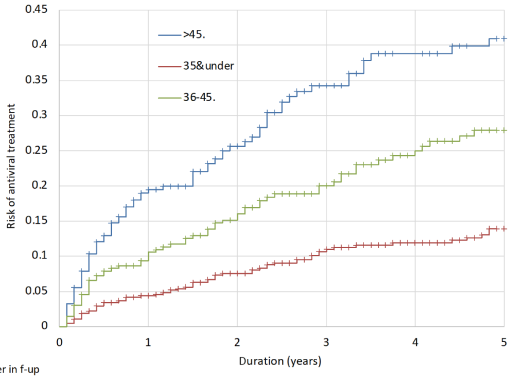
(C)



Number in f-up

Female	555	447	381	314	269	225
Male	701	534	432	334	267	220

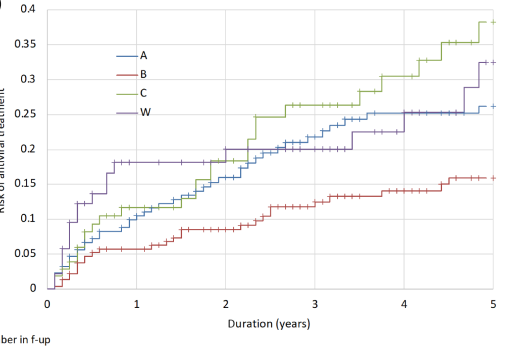
(D)



Number in f-up

>45	279	202	156	120	101	87
36–45	336	261	222	177	147	121
35&under	641	518	435	351	288	237

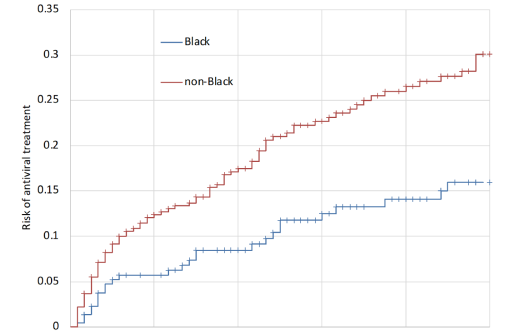
(E)



Number in f-up

Asian	219	179	150	124	113	100
Black	223	192	162	137	117	103
Chinese	105	81	72	58	47	34
White	89	62	54	47	36	26

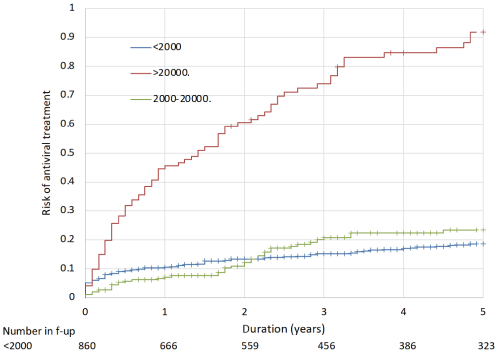
(F)



Number in f-up

Black	223	192	162	137	117	103
non-Black	413	319	275	228	192	160

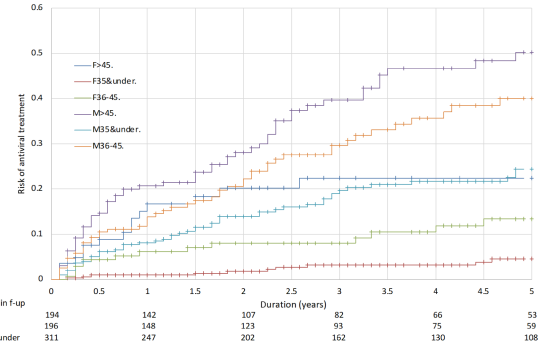
(G)



Number in f-up

<2000	860	666	559	456	386	323
2000–20000	256	208	171	132	107	88
>20000	150	96	82	70	60	55

(H)



Number in f-up

M >45	194	142	107	82	66	53
M36-45	196	148	123	93	75	59
M <35&under	311	247	202	162	130	108
F >45	85	63	52	41	37	34
F36-45	140	117	100	84	74	62
F35&under	330	271	233	189	160	129

TABLE 1 (a) Comparison of patients who were treated ($n = 232$) versus those never treated ($n = 1024$). M–W Mann–Whitney U test. (b) Cox analysis of demographic and baseline laboratory values as possible determinants of treatment initiation during first 5 years after baseline. The analysis includes those patients with a full set of data, limited by the number with self-declared ethnicity.

	Treated (A)	Not treated baseline (B)	Not treated most recent (C)	Statistic
(a)				
Number	232	1024		
Sex m:f	184:48	517:507		Chi-square $p < .001$
Baseline age (years)				
Mean, median, range	42.9, 42, 16–83	37.1, 34, 16–86		M–W test $p < .001$
Ethnicity (%)				
Asian	50 (22.8%)	169 (77.2%)		Chi-square $p = .214$ Chi-square $p = .003$ (for Black vs non-Black)
Black	37 (16.6%)	186 (83.4%)		
Chinese	27 (25.7%)	78 (74.3%)		
White	19 (21.3%)	70 (78.7%)		
Undeclared	99 (16%)	521 (84.0%)		
HBV DNA (IU/mL, log)				
Mean, median (number of patients)	3.76, 3.58 ($n = 230$)	2.70, 2.71 ($n = 983$)	2.47, 2.51 ($n = 983$ pairs)	A vs B MW test $p < .001$ B vs C mean change −0.23, Wilcoxon test $p < .001$
Male ALT (U/mL)				
Mean, median (number of patients)	70, 37 ($n = 183$)	52, 29 ($n = 511$)	31, 27 (510 pairs)	A vs B MW test $p < .001$ B vs C mean change −20.7, Wilcoxon test $p < .001$
Female ALT (U/mL)				
Mean, median (number of patients)	36, 26 ($n = 48$)	30, 19 ($n = 507$)	21, 18 ($n = 499$ pairs)	A vs B MW test $p < .001$ B vs C mean change −8.8, Wilcoxon test $p = .002$
Fibroscan score (kPa)				
Mean, median (number of patients)	7.57, 6.1 ($n = 144$)	5.55, 5.1 ($n = 693$)	5.15, 4.9 ($n = 419$ pairs)	A vs B MW test $p < .001$ B vs C mean change −0.39, Wilcoxon test $p = .043$

	Treated	Not treated	Cox univariate	Cox multivariate	Hazard ratio (95%CI)
(b)					
Number	113	481			
Sex m:f	86:27	247:234	$p < .001$	$p = .010$	1.803 (1.150–2.830)
Baseline age (years)					
Mean, median, range	45.5, 44, 17–81	37.7, 35, 16–85	$p < .001$	$p < .001$	1.027 (1.014–1.040) (per year increase)
Ethnicity					
Black:non-Black	27:86	189:292	$p = .001$	$p = .024$	1.654 (1.068–2.563)
HBV DNA (IU/mL, log)					
Mean, median	3.96, 3.58	2.69, 2.68	$p < .001$	$p < .001$	1.565 (1.410–1.736) (per log increase)
ALT (U/mL)					
Mean, median	68, 34	53, 24	$p = .150$	$p = .522$	1.000 (0.999–1.001)

log increase) were significantly and independently associated with risk for treatment initiation (Table 1b). Figure 1E compares Black, White, Chinese and Asian ethnicities. Log rank comparison of the 4 populations was statistically significant ($p = .015$). However, pairwise comparisons showed that there was not a statistically significant difference between any pair of Asian, Chinese and White cohorts, though each of those cohorts was statistically different from the Black cohort. So, Figure 1F compares Black with non-Black patients (log rank $p = .003$). Figure 1H demonstrates in bivariate analysis that the risk for initiation of treatment is strongly determined by sex and baseline age.

For years 6 to 10 beyond baseline, risk for antiviral treatment was only 2% per annum, and there was no significant impact of sex, baseline age or ethnicity on risk (Figure S2a–c).

The next analysis examined the risk of treatment initiation for a cohort of 624 patients who had low serum HBV DNA (<2000 IU/mL) and a normal serum ALT (<40 U/mL in men, <30 U/mL in women) at baseline. Of 624 patients, 66 eventually commenced antiviral treatment. Again, treated patients were more likely to be male and were older at baseline ($p < .001$ for both). Untreated patients were also more likely to be Black ($p = .06$) (Table S2a).

In Cox analysis (Table S2b), male sex (HR 1.898, $p = .097$), baseline age (HR 1.020 per year increase, $p = .055$) and Black ethnicity (HR 3.054 for non-Black vs Black patients, $p = .008$) were associated with risk for treatment initiation (see corresponding Kaplan–Meier analyses in Figure S3a–d).

4 | DISCUSSION

There are significant differences between ethnic groups with respect to the timing of HBeAg loss and seroconversion. Livingston and colleagues found that median age at HBeAg clearance was 16 years for genotype F and 48 years for genotype C.[6] Studies in Chinese ethnicity cohorts show earlier loss of HBeAg in genotype B than in genotype C patients and suggest that the earlier loss of HBeAg may confer a lower risk for the later development of HBeAg-negative chronic hepatitis.[5] The low rate of initiation of treatment during follow-up of Black ethnicity patients in our study cohort may be related to the relatively young age at HBeAg loss.

In our primary analysis, the risk for treatment initiation was substantially increased in the first 5 years of follow-up. Treated patients were more likely to be male, were older at baseline and were more likely to have non-Black than Black ethnicity. Clinical studies have shown a clear preponderance for males to develop HBeAg-negative hepatitis.[2–5] The impact of baseline age on risk is consistent with the observations of Chu and colleagues who found that the risk for HBeAg-negative hepatitis was proportional to age at presentation and argued that older cohorts included patients who underwent HBeAg seroconversion at an older age.[2,4] This association of baseline age with risk for HBeAg-negative hepatitis was also observed in a cohort of Indian patients infected by genotypes A and D.[3] Thus, the association of risk with age at presentation has been observed in more than one ethnic group and in several HBV genotypes.

We looked separately at 624 patients with both HBV DNA and serum ALT values below thresholds for treatment at baseline. The treatment initiation rate was only 2% per annum during the first 10 years of observation, and (as observed for the entire study population of 1256 patients) treatment initiation was more likely for males, for patients who were older at baseline, and for non-Black ethnicity.

Figure 1H shows that risk for treatment initiation can be stratified according to patient sex and patient age at presentation. Risk varies from less than 1% per annum (young females) to 10% per annum (for older males). This 10-fold variation in risk might guide frequency of follow-up for untreated patients. Published guidelines propose quite frequent review of low-risk patients but without consideration of the basic demographic determinants of risk.[1,7,8] Our analysis invites a more bespoke approach to patient review after baseline blood tests and non-invasive fibrosis assessment (Table S3). Risk assessment is based on patient sex, age at baseline, and serum HBV DNA and ALT at baseline. We sorted patients into 3 risk groups according to the predicted annual risk during the first 5 years following baseline, and a schedule for patient review could be tailored accordingly.

AUTHOR CONTRIBUTIONS

David Mutimer designed the study, analysed the data and wrote the paper. He is guarantor of the manuscript. Ahmed Elsharkawy designed the study and reviewed the document for intellectual content. Emma Hathorn reviewed the document for intellectual content. Selvi Arunkumar designed the study, acquired the data from electronic sources and reviewed the document for intellectual content.

FUNDING INFORMATION

There are no external sources of funding for this study.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

David Mutimer https://orcid.org/0000-0001-6648-7446
Ahmed Elsharkawy https://orcid.org/0000-0001-5369-3734

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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