Distinct virologic trajectories in chronic hepatitis B patients identify heterogeneity in response to nucleotide analogue therapy

Tingyan Wang[1,2], Cori Campbell[1,2], Gail Roadknight[1,3], Stephanie Little[1,3], Alexander Stockdale[4,5], Stacy Todd[5], Karl McIntyre[6], Andrew Frankland[6], Jakub Jaworski[7], Afzal Chaudhry[7], Ben Glampson[8,9], Luca Mercuri[8,9], Dimitri Papadimitriou[8,9], Christopher R. Jones[9,10], Kinga A Varnai[1,3], Theresa Noble[1,3], Hizni Salih[1,11], Cai Davis[12,13], Ashley Heinson[12,13], Michael George[12,13], Florina Borca[12,13], Josune Olza[12], Louise English[14], Luis Romão[14], David Ramlakhan[14], Eleni Nastouli[15,16], Salim Khakoo[17], Will Gelson[18], Graham Cooke[8,9,19], Kerrie Woods[1,3], Jim Davies[1,11,20], Philippa Matthews[2,3,21,22,23], Eleanor Barnes[2,3]

[1] NIHR Oxford Biomedical Research Centre, United Kingdom, [2] University of Oxford, Nuffield Department of Medicine, United Kingdom, [3] Oxford University Hospitals NHS Foundation Trust, NIHR Health Informatics Collaborative, United Kingdom, [4] Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, United Kingdom, [5] Liverpool University Hospitals NHS Foundation Trust, Tropical Infectious Diseases Unit, Royal Liverpool Hospital, United Kingdom, [6] Liverpool University Hospitals NHS Foundation Trust, Liverpool Clinical Laboratories, United Kingdom, [7] Cambridge University Hospitals NHS Foundation Trust, United Kingdom, [8] Imperial College Healthcare NHS Trust, NIHR Health Informatics Collaborative, United Kingdom, [9] NIHR Imperial Biomedical Research Centre, United Kingdom, [10] Imperial College London, Department of Infectious Disease, United Kingdom, [11] University of Oxford, Nuffield Department of Population Health, United Kingdom, [12] University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre, United Kingdom, [13] University of Southampton, Clinical Informatics Research Unit, Faculty of Medicine, United Kingdom, [14] NIHR University College London Hospitals Biomedical Research Centre, United Kingdom, [15] UCLH, Department of Clinical Virology, United Kingdom, [16] UCL Great Ormond Street Institute of Child Health, Department of Infection, Immunity and Inflammation, United Kingdom, [17] University of Southampton, School of Clinical and Experimental Sciences, Faculty of Medicine, United Kingdom, [18] Cambridge University Hospitals NHS Foundation Trust, Cambridge Liver Unit, United Kingdom, [19] Imperial College London, Faculty of Medicine, Department of Infectious Disease, United Kingdom, [20] University of Oxford, Department of Computer Science, United Kingdom, [21] The Francis Crick Institute, London, UK, United Kingdom, [22] University College London, Division of Infection and Immunity, United Kingdom, [23] University College London Hospital, Department of Infectious Diseases, United Kingdom

Introduction

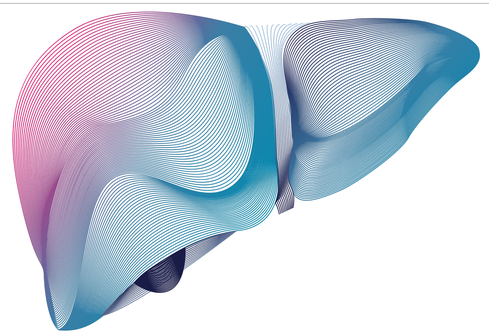
- The longitudinal patterns of HBV DNA viral load (VL) of chronic hepatitis B (CHB) patients on treatment are not well characterised in the UK population.
- However, understanding the phenotypes of treatment responses is crucial for patient stratification for better care.

Aim

- To characterise virologic trajectories in CHB patients on nucleotide analogue (NA) therapy using large-scale electronic health records
- To identify demographic/laboratory/clinical determinants of HBV DNA VL trajectories for CHB patients on treatment

Method

- We studied a cohort of 8,028 CHB patients from 6 large teaching hospitals in England with longitudinal follow-up, established by the National Institute for Health Research (NIHR) Health Informatics Collaborative (HIC) from electronic patient record systems.
- We included adults who had two or more VL measurements with > 6 months of follow-up on VL for analysis.
- We applied latent class mixed models to investigate the patterns of VL trajectories since the earliest treatment date recorded (defined as baseline).
- Repeated and various number of measurements at different time points for patients were considered in the approach, by including fixed effects, and random effects and slope for individuals.
- The number of VL classes was determined by the Bayesian information criteria, the Akaike information criteria, the discrimination, the odds of correct classification, the relative entropy, and the interpretability of the model.
- We performed multinomial logistic regressions to assess the determinants of VL trajectories at baseline.



Contact: tingyan.wang@ndm.ox.ac.uk

Table 1

Characteristics	Overall	Class 1	Class 2	Class 3	Class 4	Class 5	P-value
Number of patients	740	557	53	74	24	32	
Gender = Male	439 (59.3)	360 (64.6)	14 (26.4)	34 (45.9)	14 (58.3)	17 (53.1)	<0.001
Age, years	44 [35, 55]	46 [37, 56]	39 [30, 47]	41 [34, 51]	38 [31, 50]	34 [29, 48]	<0.001
Ethnic group							
Asian	299 (40.4)	219 (39.3)	21 (39.6)	34 (45.9)	12 (50.0)	13 (40.6)	<0.001
Black	109 (14.7)	83 (14.9)	9 (17.0)	11 (14.9)	1 (4.2)	5 (15.6)	
White	164 (22.2)	134 (24.1)	8 (15.1)	15 (20.3)	5 (20.8)	2 (6.2)	
Mixed/other ethnicity	75 (10.1)	48 (8.6)	15 (28.3)	7 (9.5)	1 (4.2)	4 (12.5)	
Not reported	93 (12.6)	73 (13.1)	0 (0.0)	7 (9.5)	5 (20.8)	8 (25.0)	
HBeAg status							
Negative	287 (38.8)	228 (40.9)	29 (54.7)	18 (24.3)	4 (16.7)	8 (25.0)	<0.001
Positive	199 (26.9)	108 (19.4)	16 (30.2)	40 (54.1)	14 (58.3)	21 (65.6)	
Not available	254 (34.3)	221 (39.7)	8 (15.1)	16 (21.6)	6 (25.0)	3 (9.4)	
HBV VL, log10 IU/ml	2.5 [1.5, 4.3]	1.8 [1.5, 2.6]	3.7 [3.0, 4.1]	5.9 [4.8, 7.1]	5.7 [4.0, 8.1]	6.3 [5.1, 7.2]	<0.001
ALT, IU/L	31 [21, 58]	29 [21, 50]	21 [19, 35]	76 [42, 118]	29 [14, 37]	56 [36, 102]	<0.001
Treatment regimens							
TDF	340 (45.9)	252 (45.2)	28 (52.8)	34 (45.9)	11 (45.8)	15 (46.9)	0.095
ETV	132 (17.8)	102 (18.3)	9 (17.0)	17 (23.0)	3 (12.5)	1 (3.1)	
ETV+TDF	82 (11.1)	53 (9.5)	8 (15.1)	8 (10.8)	5 (20.8)	8 (25.0)	
LAM/ADE+TDF	49 (6.6)	42 (7.5)	2 (3.8)	4 (5.4)	0 (0.0)	1 (3.1)	
LAM/ADE+ETV	39 (5.3)	36 (6.5)	1 (1.9)	1 (1.4)	1 (4.2)	0 (0.0)	
Other regimens	98 (13.2)	72 (12.9)	5 (9.4)	10 (13.5)	4 (16.7)	7 (21.9)	

Table 1 presents baseline characteristics of the overall study cohort and stratified by virologic trajectory. Data are the number (%) or median (IQR). VL, viral load; ALT, alanine aminotransferase; TDF, tenofovir disoproxil fumarate; ETV, entecavir; LAM, lamivudine; ADE, adefovir.

Figure 1

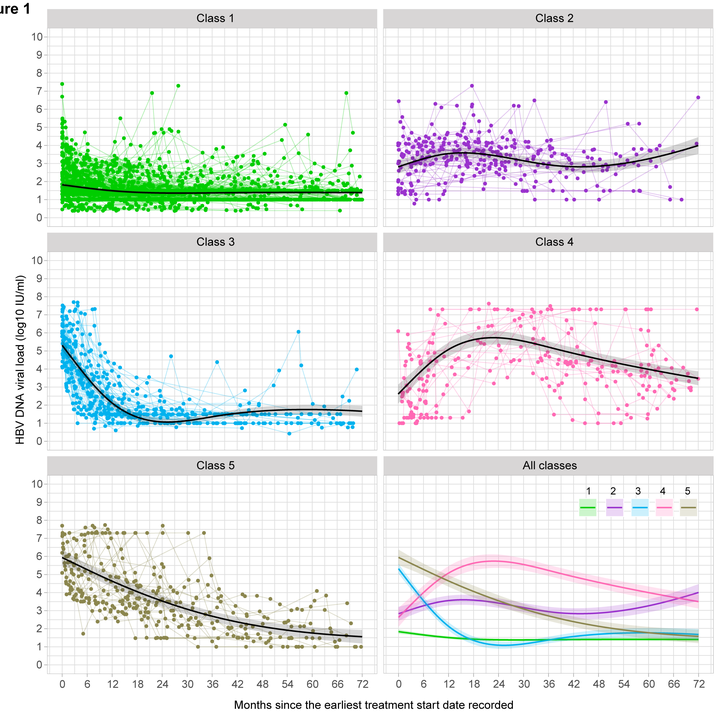


Figure 1 shows individual trajectories of HBV DNA viral load (VL) and their patterns ('classes 1-5') for chronic hepatitis B patients on treatment. The five VL patterns were identified using latent class mixed model. Dots represent the real values of VL, and solid lines with shading area represent the predicted VL trajectory patterns with 95% confidence intervals.

Figure 2

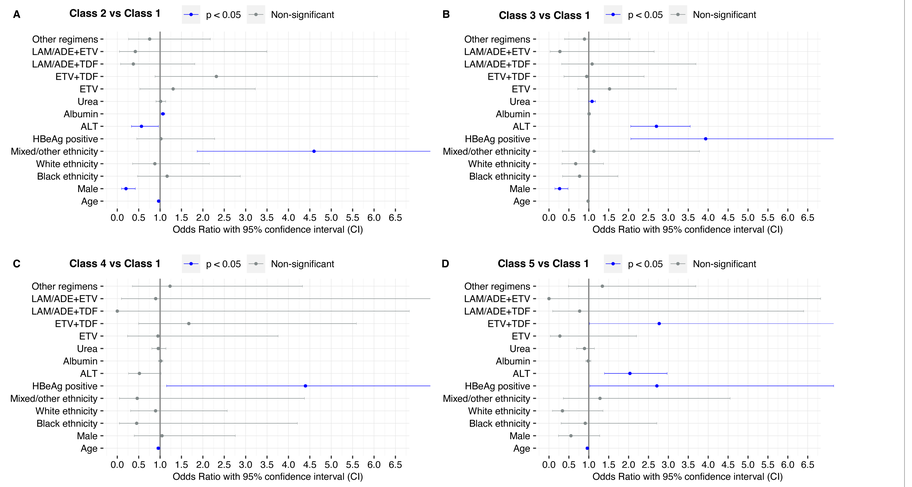


Figure 2 shows Baseline determinants of HBV VL trajectory patterns for chronic hepatitis B patients on treatment using multivariable multinomial regression analysis.

Results

- We identified 740 patients (Table 1) on nucleos/tide analogue (NA) treatment with longitudinal VL data, with a median follow-up duration of 3.3 years (interquartile range [IQR], 1.6-5.2 years). The total number of VL measurements was 4,642 (median [IQR], 5 [3-8] measurements per patient).
- Five mutually exclusive patterns of VL trajectories were identified (Figure 1), i.e., class 1 (N = 557, 75.3%) – '**VL long term suppressed**', class 2 (N = 53, 7.2%) – '**persistent viraemia with moderate VL**', class 3 (N = 74, 10.0%) – '**VL suppressed as expected**', class 4 (N = 24, 3.2%) – '**VL non-suppressing with high VL**', and class 5 (N = 32, 4.3%) - '**VL slowly suppressed**'. Baseline characteristics stratified by class are presented in Table 1.
- Univariable analysis showed that baseline age, sex, ethnicity, HBeAg status, ALT, albumin, urea, and treatment regimens, were associated with the VL classes identified.
- After multivariable analysis, the following independent determinants (all $p < 0.05$) measured at baseline were identified (the reference was class 1): i) age, sex, Mixed or Other ethnicity, albumin, ALT for class 2, ii) sex, HBeAg status, ALT, urea for class 3, iii) age, HBeAg status for class 4, and iv) age, HBeAg status, ALT, combination treatment drugs of entecavir and tenofovir disoproxil for class 5 (Figure 2).

Conclusions

- There is heterogeneity in virologic response to antiviral treatment with NA agents, and complete virologic suppression for CHB patients on current standard antiviral treatment can be slow.
- Some of this variability is statistically associated with demographics and laboratory parameters.
- Enhanced understanding of treatment response can be used to inform better risk-stratification, improved patient-centric clinical care, and as a foundation to understand the impact of novel therapies as these become available.

Acknowledgements: This research has been funded by the NIHR HIC and supported by NIHR Biomedical Research Centres at Cambridge, Imperial, Oxford, Southampton, and University College London Hospitals. The authors would like to thank all the research nurses and research admin staff at the contributing sites for their help in data collection and submission. The views expressed in this poster are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

Ethics Approval: The research database for the NIHR HIC viral hepatitis theme was approved by South Central - Oxford C Research Ethics Committee (REF Number: 21/SC/0060).