Multiple risk factors for persistent HBV viraemia in an adult receiving nucleos/tide analogue therapy

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ABSTRACT

Diagnosing and treating chronic hepatitis B virus (HBV) infection are key interventions to support progress towards elimination of viral hepatitis by 2030. Although nucleos/tide analogue (NA) therapy is typically highly effective, challenges remain for viral load (VL) suppression, including medication access, incomplete adherence and drug resistance. We present a case of a long-term HBV and HIV coinfected adult prescribed with sequential NA therapy regimens, with episodes of breakthrough viraemia. Multiple factors contribute to virological breakthrough, including exposure to old NA agents, initial high HBV VL, therapy interruptions, intercurrent illnesses and potential contribution from resistance mutations. The case underscores the importance of individualised treatment approaches and adherence support in achieving HBV suppression. Furthermore, it emphasises the need for improved clinical pathways addressing education, support and access to care, particularly for marginalised populations. Comprehensive data collection inclusive of under-represented individuals is crucial for maintaining retention in the care cascade and informing effective interventions.

KEY MESSAGES

⇒ Hepatitis B virus (HBV) viraemia may persist or rebound in adults receiving nucleos/tide analogue (NA) treatment; a number of factors may collectively reduce the success of treatment in mediating long-term HBV suppression.
⇒ We illustrate a complex case where multiple factors contribute to non-suppressed HBV viral load (VL) on NA treatment.
⇒ We raise awareness of diverse factors which may be contributing to non-suppressed HBV VL, and advocate for improved clinical pathways and comprehensive data collection to improve care and address knowledge gaps surrounding VL non-suppression on treatment.

BACKGROUND

In line with international goals to eliminate viral hepatitis as a public health threat by 2030,[1] there is a global drive to diagnose, treat and prevent hepatitis B virus (HBV) infection. Nucleos/tide analogue (NA) agents suppress HBV DNA to below quantifiable thresholds in the majority of people receiving treatment. However, viraemia persists in a proportion of those offered treatment (up to 20% after 1 year in a recent population analysis[2]), attributed to a range of influences which may include drug resistance due to the selection of polymorphisms (resistance-associated mutations (RAMs)) in the viral reverse transcriptase (RT). Resistance is predictably selected by exposure to lamivudine (3TC), which also influences susceptibility to entecavir (ETV) and adefovir (ADV).[3] In contrast, resistance to tenofovir (TFV) is uncommon due to a high genetic barrier.[4 5]

We here describe the case of an adult in whom HBV viraemia has not been consistently suppressed on treatment, to highlight a vulnerable population with risk factors for virological breakthrough.

HBV CASE REPORT: PRESENTATION, INVESTIGATIONS AND TREATMENT

An adult man received treatment for HBV and HIV coinfection over a period of 26 years in a central London clinic (figure 1). We retrospectively reviewed data from his routine clinical records.

At initial diagnosis, HBV viral load (VL) was 8.5 $\log_{10}$ IU/mL and hepatitis B 'e' antigen (HBeAg) was positive. He screened negative for hepatitis D virus infection. Antiretroviral therapy (ART) was commenced, with HIV suppression from 3.7 $\log_{10}$ RNA copies/mL to undetectable. Subsequently, HBV was diagnosed and HBV VL progressively suppressed on HBV-active regimens containing 3TC (from baseline), switched to ADV (year 8) and then TFV (year 12), prescribed in line with changing guidelines. HBeAg was undetectable by year 13 (although he did not develop anti-HBe). He received successful intercurrent treatment for hepatitis C virus infection.

Due to illness and emergency hospital admissions unrelated to bloodborne virus infection, he was unable to sustain NA treatment, with documented gaps at intervals between years 22 and 25. HIV and HBV rebounded, with associated liver inflammation (peak alanine aminotransferase (ALT) 902 IU/L), and HBeAg status reverted to positive. On reinstating HBV-active ART (including TFV and emtricitabine), HIV VL suppressed within 1 month, but HBV VL remained persistently elevated between 3.3 and 9.9 $\log_{10}$ IU/mL (figure 1).

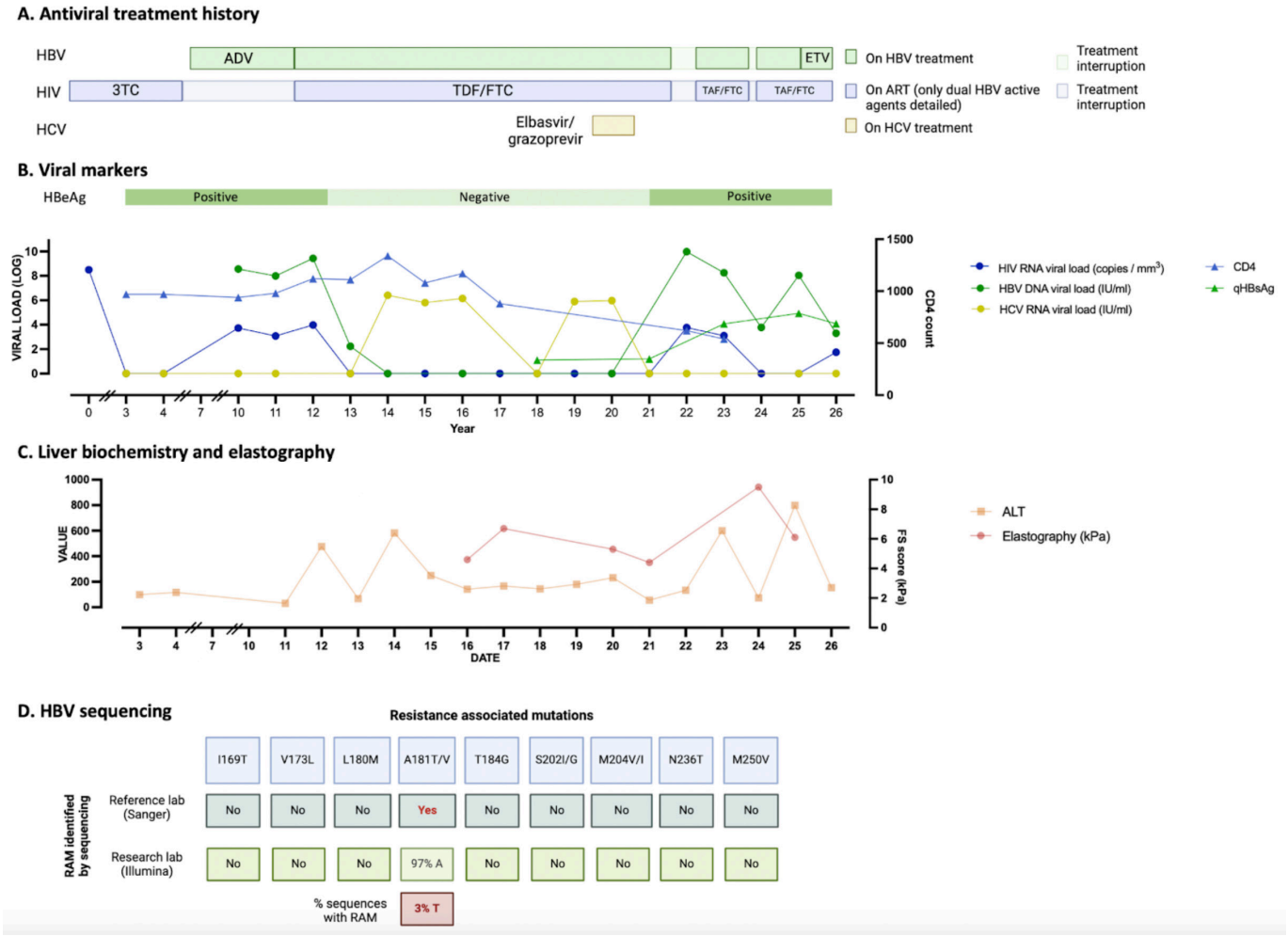

Figure 1 Summary details of non-suppression of HBV VL in an adult prescribed with antiviral therapy. (A) Timeline showing antiviral treatment for HBV, HIV and HCV, showing years since diagnosis on x-axis. (B) Timeline showing trends in viral loads for HBV, HIV and HCV, in addition to CD4+ count, quantitative HBsAg (qHBsAg) and HBeAg status (NB: x-axis not to scale). (C) Timeline showing ALT and liver elastography scores (NB: x-axis not to scale). (D) Resistance-associated mutations (RAMs) listed in EASL guidance[8] mapped to the HBV polymorphisms identified in HBV sequenced from this individual through Sanger and Illumina sequencing. 3TC, lamivudine; ADV, adefovir; ALT, alanine aminotransferase; ART, antiretroviral therapy; EASL, European Association for the Study of the Liver; ETV, entecavir; FTC, emtricitabine; FS, fibroscan (liver elastography), HBeAg, hepatitis B 'e' antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load.

A clinical diagnostic laboratory identified the presence of a resistance mutation at position 181 in the HBV RT sequence (A181T) and reported potential drug resistance to 3TC, ADV and telbivudine. HBV Illumina sequence analysis[6] demonstrated dual infection with HBV genotypes A and G (online supplemental methods), and confirmed the A181T polymorphism, although only in a minority of quasi-species (figure 1B). Alongside support to optimise adherence, ETV was added (in keeping with clinical guidelines[7 8]), followed by an HBV virological response to 2.4 $\log_{10}$ IU/mL after 1 month and 3.2 $\log_{10}$ IU/mL at 4 months.

DISCUSSION

A number of factors can collectively reduce the success of NA treatment for HBV, including high baseline VL, HIV coinfection, exposure to historical regimens with low genetic barrier to resistance, therapy interruptions, physical and mental health comorbidities and complex barriers to continuity of care. These are inter-related and are likely to have a cumulative influence.

Individuals with these characteristics may be in vulnerable or marginalised groups, are unlikely to be eligible for clinical studies, and may experience social stigma and discrimination. These influences mitigate against their inclusion in laboratory data, clinical cohorts and trials.[4] There is a need for focus on equitable representation of the real-world challenges of life-long therapy to fill this current 'blind spot' (*further discussed in our Editorial*[9]).

The contribution of drug resistance is doubtful in our patient, as A181T alone is not a recognised cause of tenofovir disoproxil fumarate resistance[10]; a resistant phenotype would typically require multiple associated RAMs. More clinical and in vitro data are still needed to ascertain the relative contributions of different RAMs, alone and in combination. Adding HBV active agents, and providing adherence support, resulted in progressive reduction in viraemia over time to <2000 IU/mL, but not to undetectable.

Persistent HBV viraemia poses risks of transmission and long-term inflammatory/fibrotic liver disease (indicated by elevated ALT in this case), highlighting the need for intervention. Service improvements should focus on flexible, patient-centric access to information, consistent supplies of medication, avoiding

out-of-pocket costs and providing access to peer support, particularly for those coping with other health and/or social challenges and for whom there are barriers to care access. As HBV treatment eligibility expands and we work towards elimination targets, research is needed to better determine the factors that contribute to the presence and impact of persistent viraemia, and to optimise surveillance and clinical intervention.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the South East Coast–Brighton & Sussex Research Ethics Committee (study title: Characterising and modifying immune responses in chronic viral hepatitis; REC reference: 11/LO/0421; IRAS project ID: 43993). Written informed consent was obtained.

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SUPPLEMENTARY MATERIAL

Supplementary methods

Sanger sequencing and resistance reporting was undertaken by University College London Hospitals clinical diagnostic virology laboratory. Illumina HBV whole genome sequencing was performed in Oxford with a previously described protocol [9], with the addition of micrococcal nuclease for host nucleic acid depletion and sequencing on Illumina Miseq v3 with 2x300bp paired end reads. Bioinformatic workflow as described previously [9].

Supplementary Table 1: HBV drug resistance report from a clinical diagnostic virology laboratory, based on a serum sample submitted during rebound (year 25).

Polymorphisms in HBV reverse transcriptase (RT) codons 91-285 are listed, and summary of the interpretation of the resistance profile as reported by clinical diagnostic virology laboratory (based on https://hbv.geno2pheno.org/).

Genotype	Polymorphisms in RT domain	Clinical interpretation of resistance associated mutations
Dual infection with genotypes A and G	I53IS, T54A, I103V, N118D, I121S, N122H/I/L, N123D, N124H, M129L, W153R, V163I, A181T, V207I/M, L217R, I253V, V266A/I/T	• Lamivudine – resistant (181T) • Telbivudine - resistant (181T) • Adefovir – resistant (181T) • Entecavir – susceptible • Tenofovir - susceptible

Supplementary Table 2: Resistance associated mutations (RAMs) listed in EASL guidance [7], Genotype A/G consensus and polymorphisms identified in HBV isolated from this individual.

RAM	Reference sequence (NB. same aa for Geno A/G at all given sites)	Patient HBV sequence (UCLH report)	Patient HBV sequence (Illumina data)		Clinical interpretation from EASL guidance (if detected)			
			Consensus	Minority variant	LAM	ETV	ADV	TDF/ TAF*
I169T (in combination)	I		I (100%)					
V173L (in combination)	V		V (99%)	G (1%)				
L180M	L		L (100%)					
A181T/V	A	A, T	A (97%)	T (3%)	I	S	R	I
T184G (in combination)	T		T (100%)					
S202I/G (in combination)	S		S (100%)					
M204V/I	M		M (100%)					
N236T	N		N (100%)					
M250V (in combination)	M		M (100%)					

The amino acid substitution profiles are shown in the left column and the level of susceptibility is given for each drug: S (sensitive), I (intermediate/reduced susceptibility), R (resistant).

ETV, entecavir; TDF tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; ADV, adefovir

*In vitro data for tenofovir, in vivo data for TDF, no clinical data for TAF.