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Poster for you

# Detection and characterization of anti-preS1 antibodies in HDV-infected patients under Bulevirtide treatment.

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## Introduction

Bulevirtide (BLV) has recently been approved in Europe for the treatment of patients chronically infected with HDV. BLV is a viral entry inhibitor that binds with high affinity to the sodium taurocholate co-transporting polypeptide (NTCP), the cell receptor for HBV and HDV. BLV is a synthetic, myristoylated peptide specific to the N-terminal preS1 sequence of the HBV large envelope protein (1). Since HDV virions use preS1 as a receptor binding domain (RBD), BLV binding to NTCP blocks the virion entry pathway (2).

Our hypothesis was that daily injection of BLV could induce the production of anti-preS1 antibodies. Such antibodies could play an ambivalent role in patients, either by binding to HDV virions and thus enhancing the antiviral effect of BLV, or by binding to BLV itself, hence reducing its antiviral effect.

**In this study, we sought to establish the anti-preS1 antibody status of BLV-treated patients.**

## Methods

The study was conducted on a cohort of 21 BLV-treated individuals who were included in the BuleDelta observatory cohort (ANRS HD EPO1), for a total of 160 plasma samples, including a sample at baseline for each patient, and samples covering both the treatment and post-treatment periods for up to 168 weeks.

Anti-preS1 antibody levels were measured using an in-house peptide-based ELISA. Antibodies were then characterized to identify anti-preS1-specific epitopes, using an overlapping peptide library of 15 residues covering the 2-48 preS1 amino acid sequence.

## Results

The results of a longitudinal analysis show that: i) anti-preS1 antibodies were detected in the plasma samples of all 21 patients. In most patients, antibodies were detected early during treatment, reaching a peak at week-48, followed by a decline that initiated during or after treatment **(Figure 1)**; ii) Both IgM and IgG antibodies were detected during the on- and off-treatment periods, with variable IgM/IgG ratios: high levels of both IgM and IgG were maintained during and post-treatment for some patients, whereas in others, IgM, or IgG, was predominant **(Figure 2)**. iii) The anti-preS1 specific epitopes were distributed throughout the preS1 aas 2-48 peptide including the RBD **(Figure 3)**. iv) For most patients who's defined by a decrease of HDV viremia by ≥ 2 log (3), there was a negative correlation between serum HDV RNA and anti-preS1 levels (e.g., patients B1, B3, B7, B15, and B16).

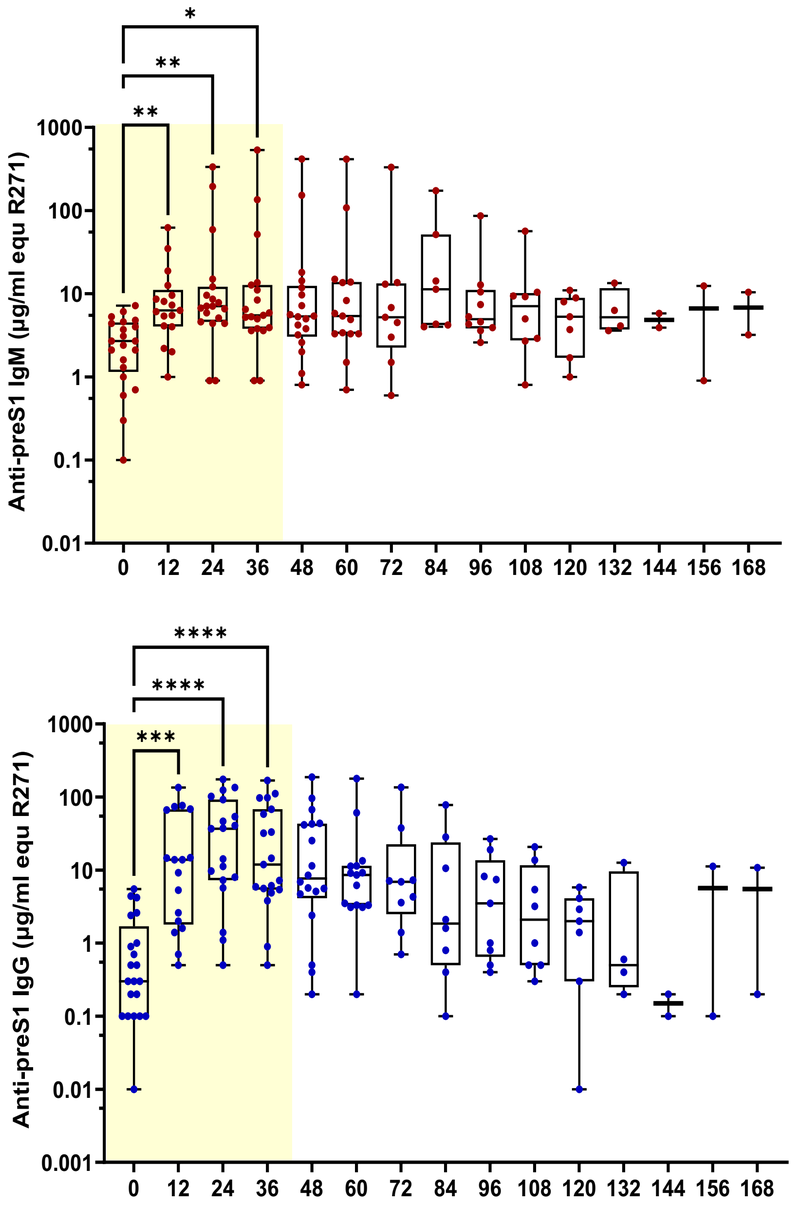


**Figure 1: Anti-preS1 antibodies and HDV RNA profiles.** Anti-preS1 IgM (top) and IgG (middle). The yellow-shaded area corresponds to the early treatment period (all patients are under treatment. Beyond week-36, treatment was discontinued in an increasing number of patients.

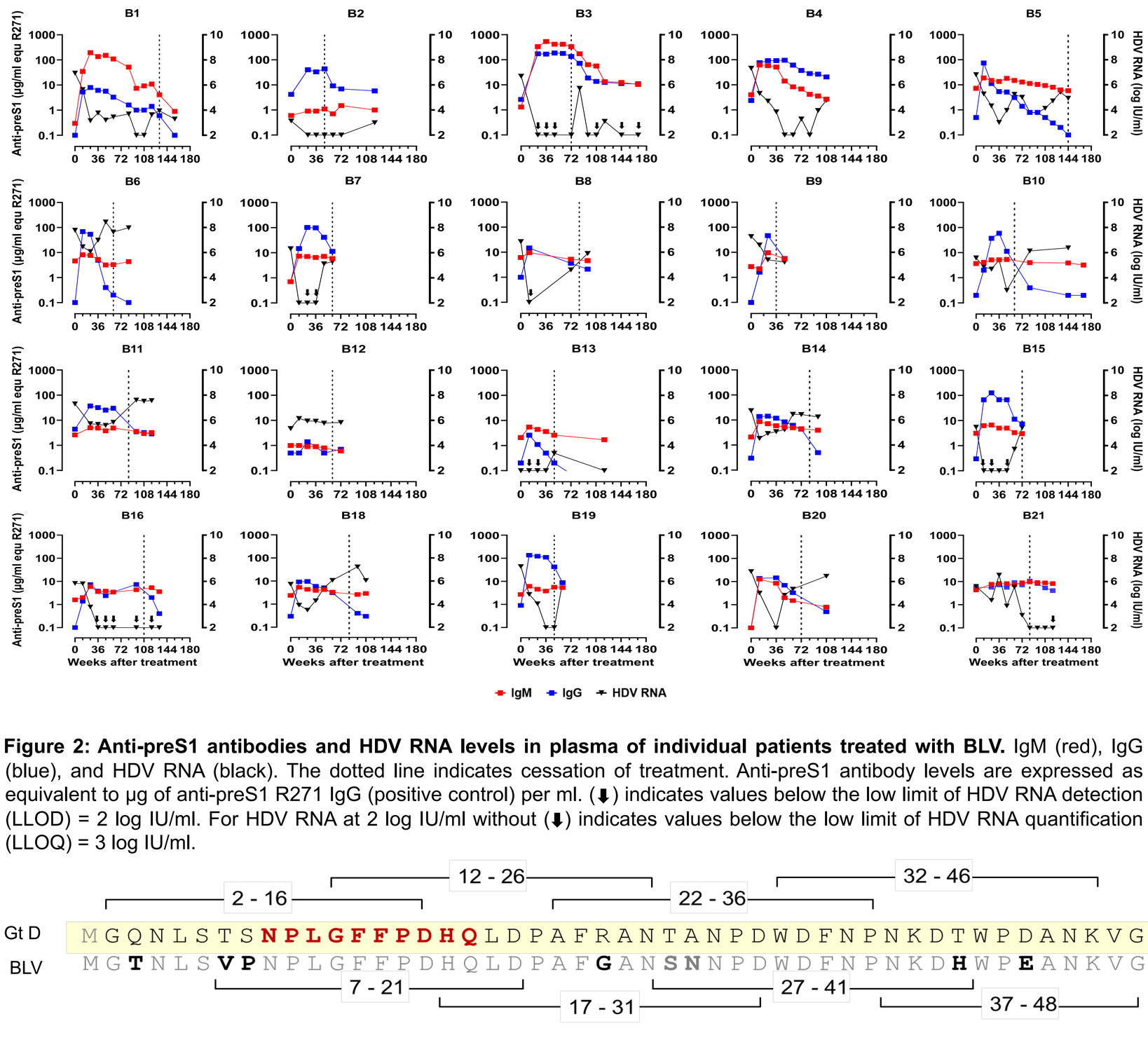


**Figure 2: Anti-preS1 antibodies and HDV RNA levels in plasma of individual patients treated with BLV.** IgM (red), IgG (blue), and HDV RNA (black). The dotted line indicates cessation of treatment. Anti-preS1 antibody levels are expressed as equivalent to µg of anti-preS1 R271 IgG (positive control) per ml. (⬇) indicates values below the low limit of HDV RNA detection (LLOD) = 2 log IU/ml. For HDV RNA at 2 log IU/ml without (⬇) indicates values below the low limit of HDV RNA quantification (LLOQ) = 3 log IU/ml.




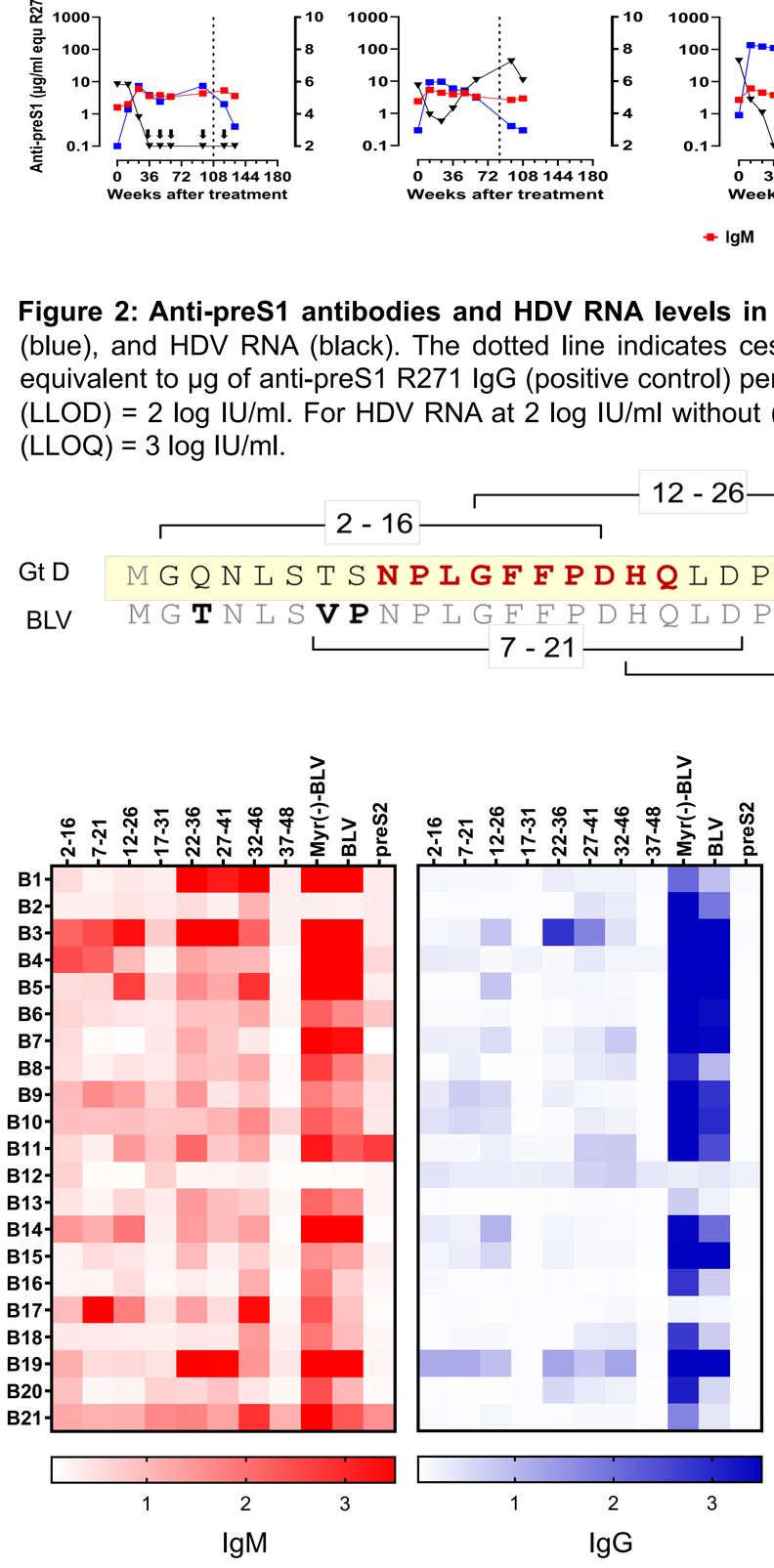


**Figure 3: Mapping of BLV-induced anti-preS1 epitopes.** The preS1 2-48 aas peptide (Genotype D) is indicated (red letters indicate RBD). Heat map of anti-preS1 IgM (red) and IgG (blue) specific epitopes is shown, based on OD values. The preS1 2-48 peptide, and Myr-preS1 2-48 (BLV) were used as positive controls, while preS2 122-144 was used as negative controls. Note that mapping was performed using genotype D specific peptides.

## Conclusion

Our results show that anti-preS1 antibodies were induced in all patients treated with BLV. Anti-preS1 were of both IgM and IgG types and detected during and post-treatment.

The observed negative correlation between serum anti-preS1 and HDV RNA levels during treatment may indicate that antibodies could contribute to the antiviral effect of BLV.

Alternatively, as bystanders of treatment, anti-preS1 antibodies could serve as markers of compliance to treatment.

## *References*

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3. EASL Clinical Practice Guidelines on hepatitis delta virus. J Hepatol. 2023 Aug;79(2):433-460.