ANRS HD EP 01 HEPDELTA

(Information for researchers)

National cohort monitoring patients co-infected with hepatitis B and Delta viruses

Topics	**Content**
In a nutshell	- Coordinating investigator: Pr Fabien Zoulim - Co-ordinating investigator: Dr Hélène FONTAINE - Delegated coordinating investigator: Dr Miroslava SUBIC-LEVRERO
	Structure/teams : - CIC Inserm 1414 - Rennes University Hospital - Aix Marseille University - Inserm U1259 at Tours University Hospital - Inserm UMR1137 in Paris - Avicenne Hospital in Bobigny - University Hospital Freiburg, Germany (Klinik für Innere Medizin II)
	Start date/End date of study : Feb 2020/30 Jun 2028
	Estimated enrolment: 800
	Status : *In progress*
	Pathology : *VHB/VHC/VIH*
	Sponsor and funder : *ANRS MIE*
Project presentation	This is an observatory of patients infected with HDV, whether treated or not, followed up in French centres. The natural history of patients infected with HDV is poorly understood. It is generally accepted that viral hepatitis Delta is the most severe form of viral hepatitis. However, these studies go back a long way and are often carried out in specific populations (Asian patients, American patients, etc.). The natural history of VHD patients treated in France is not known. Patients with hepatitis B-Delta have complex medical histories due to the severity of their liver disease and associated co-morbidities. It is also possible that some patients never develop severe liver disease. This cohort will make it possible to identify factors associated with worsening liver disease. Many new treatments are or will be available for these patients. They will therefore be able to receive a variety of treatment regimens, ranging from long-term monotherapy to time-limited combined treatment or a succession of several lines of treatment. The adverse effects of these treatments will of course be collected. Factors predictive of response to treatment may also be investigated. These real-life data will be important in providing information to guide therapeutic adjustments. It should be remembered that the main objective of this cohort, initially called "Buledelta", was to evaluate the efficacy of bulevirtide treatment as standard care in patients co-infected with HBV/HDV. Assessment of efficacy was based on therapeutic response, defined as a reduction in Delta RNA of at least 2 log10. The ANRS HD EP01 BuleDelta cohort was evaluated by the ANRS MIE Cohort Evaluation Committee on 25 November 2021. This committee issued recommendations concerning the cohort's name and scientific scope. In agreement with the Scientific Advisory Board of the study, the Sponsor validated the change of name of the cohort, and the modification of the objectives, judgment criteria and selection criteria.
Publications	Treatment with Bulevirtide in HIV infected patients with chronic hepatitis Delta. ANRS HD EP01 BULEDELTA & compassionate cohort". **DOI:https://doi.org/10.1016/j.jhepr.2024.101057 - JHEP Reports** "Effect of Peg-IFN on the viral kinetics of HDV infected patients treated with

	bulevirtide". **DOI:https://doi.org/10.1016/j.jhepr.2024.101070 - JHEP Reports**
Study type	*Cohorte nationale, prospective et retrospective, multicentrique……*
Main objective	The main objective is to study the natural or treated history of patients infected with HDV according to different management modalities..
Secondary objectives	- Assess HDV virological response - Assess HBV virological response - Assess hepatic response (biochemical and fibrosis) - Assess clinical response (occurrence of hepatic events, mortality) - Assess treatment safety (in treated patients) - Assess quality of life and patient's reported outcomes
Ancillary and exploratory objectives	- To assess the immunological response to bulevirtide treatment (immunological sub-study) - To evaluate the kinetics of the editing rate under bulevirtide (virological sub-study) - To analyse the experiences, needs and barriers during treatment in immigrant patients treated with bulevirtide (qualitative sub-study) - To analyse viral dynamics under bulevirtide treatment and the implications for the optimisation of anti-HDV treatments (viral kinetics sub-study) - to analyse the anti-preS1 antibodies induced by bulevirtide treatment in patients with chronic hepatitis Delta (AntiPreS1 sub-study).

Summary :

Inclusion criteria	*• Patient adulte (≥ 18 ans),* *• Ayant une infection, par le virus de l'hépatite Delta (sérologie positive)* *• Ayant donné son consentement libre, éclairé et écrit, co-signé par l'investigateur (au plus tard le jour de l'inclusion et avant tout examen réalisé dans le cadre de la recherche) (article L1122-1-1 du Code de la Santé Publique)* *• Etant affilié ou bénéficiaire d'un régime de sécurité sociale (article L1121-11 du Code de la Santé Publique) ou de l'Aide Médicale d'Etat (AME)*
Non-inclusion criteria	*Age ≥ 18 years,* *- Presenting a co-infection with hepatitis B and Delta viruses,* *- Who gave his written informed consent before any intervention and the day of inclusion at the latest,* *- Affiliated to Health Insurance or to the "Aide Médicale d'Etat" (request for exemption pending).*
Primary endpoint::	*This is a cohort in which many events will be studied. As the objectives are multiple, no primary endpoint has been defined.*
Secondary endpoints :	*• HDV virological outcomes* *• HBV virological outcomes* *• Hepatic outcomes* *• Clinical outcomes* *• Tolerance to treatments*

	• *Quality of life and other patient reported outcomes (socio-economic status, self-reported symptoms, behavioral factors, adherence to treatments) (self-administered questionnaires)*
Follow-up procedures	Patients are followed up at Week 4, Week 8, Week 12 and then every 12 weeks until the end of follow-up scheduled for 30/12/2027.

Ancillary study list

Project title	Analysis of HBV- and HDV-specific CD8+ T-cell responses in HBVc/HDV patients (during and after treatment)
Project summary	The aim of this substudy is to analyze the evolution of the function and phenotype of HBV- and HDV-specific CD8+ cell responses in patients with chronic hepatitis B and D, during and after treatment with bulevirtide monotherapy or bulevirtide and interferon combination. The modification of HBV- and HDV-specific CD8+ T cell responses during chronic infection is well established, with in particular an "exhausted" phenotype and altered effector functions of these CD8+ cells. However, the restoration of these responses after antigen elimination is not well understood. Based on recent analyses in chronic HCV infection, we hypothesize that bulevirtide treatment alone may partially restore the role of HDV-specific CD8+ T cells, and bulevirtide plus interferon treatment may restore HBV-specific immune responses to HBsAg seroconversion. We also hypothesize that partial restoration of the immune functions of HBV- and HDV-specific CD8+ T cells may help prevent viral relapse, thus meeting the criteria for a functional cure. This substudy provides a unique opportunity to better understand the dynamic impact of antigen concentrations and viral replication on HBV- and HDV-specific CD8+ cells in patients treated with bulevirtide monotherapy or dual therapy in combination with interferon.
Project start dates	February 2022
Data recipients in France	NA
Data recipient abroad	Liver Immunology Laboratory, University of Freiburg (Germany)
Identity and data controller	Inserm-ANRS MIE
Data and/or sample transfer	Transfer of data from inclusion centers (France) to the Liver Immunology Laboratory at the University of Freiburg (Germany)
Retention period for data and/or samples	15 years
Data category	Health data

Project title	Viral dynamics under bulevirtide treatment: implications for the optimization of anti-HDV therapies
Project summary	The effect of bulevirtide (BLV) on HDV viral dynamics is poorly understood due to the complexity of natural HDV dynamics and the lack of data available on large samples. In this project, we propose to apply the mathematical modeling tools developed for HCV to explore some key questions for the use of BLV in larger

	populations: -How effective is BLV in blocking infection of new cells in vivo? -What factors are associated with a better virological response to treatment? -Can we define algorithms for predicting treatment response based on early virological response? -Can treatment duration be optimized on the basis of early virological response?
Project start dates	February 2022
Data recipients in France	Inserm Unit - UMR1137
Data recipient abroad	NA
Identity and data controller	Inserm-ANRS MIE
Data and/or sample transfer	Transfer of data from CIC Inserm 1414 - CHU de Rennes to Unité Inserm - UMR1137
Retention period for data and/or samples	15 years
Data category	Health data

Project title	Evaluation of VHD Editing rate as a function of response to Bulevertide treatment
Project summary	Hepatitis delta virus (HDV) is a small, defective RNA virus, a satellite of hepatitis B virus (HBV), which requires HBV envelope proteins to form its own virions. The VHD genome has a single coding open reading frame (ORF), located on a replication intermediate, the antigenome, which encodes two proteins, the small protein or p24 and the large protein or p27. P27 is produced following a process of antigenome editing that modifies the amber/stop codon of p24 mRNA into the tryptophan codon, enabling the synthesis of p27 by the addition of 19 (or 20) C-terminal amino acids. The two delta proteins play different roles in the viral cell cycle: p24 activates genome replication, while p27 blocks replication and promotes virion morphogenesis and propagation. P27 is also involved in VHD pathogenicity. This protein is capable of increasing the activation of numerous transcription factors (notably STAT-3 or NF-kappa B) involved in inflammation, hepatic fibrosis, oxidative stress, carcinogenesis, etc. We recently showed that the editing rate differed according to the genotype of the infecting HDV strain, with HDV-5 showing the highest editing rate. Interestingly, in a recent large clinical study, we also showed that patients infected with HDV-5 genotype strains were at greater risk of developing cirrhosis than those infected with other genotypes such as HDV-1. We hypothesized that this observation might be related to the high editing rates of HDV-5. We therefore hypothesize that quantification of editing levels could be a predictive marker of the progression of Delta hepatopathy.
Project start dates	May 2022
Data recipients in France	Clinical Microbiology Laboratory - Avicenne Hospital

Data recipient abroad	NA
Identity and data controller	Inserm-ANRS MIE
Data and/or sample transfer	Transfer of samples from the ANRS MIE biothèque at Bordeaux University Hospital to the Clinical Microbiology Laboratory at Avicenne Hospital (CNR database for hepatitis B, C and Delta).
Retention period for data and/or samples	15 years
Data category	Health data

Project title	Determination and functional analysis of anti-preS1 antibodies induced by Bulevirtide treatment in patients with chronic hepatitis Delta.
Project summary	The aim of the study is to investigate the presence and function of anti-preS1 antibodies induced by Bulevirtide (BLV) treatment in patients suffering from hepatitis Delta. BLV is a synthetic peptide with an amino acid sequence identical to that of the preS1 domain of HBV envelope proteins, which determines the infectivity of HBV and HDV. BLV treatment can therefore induce the production of anti-preS1 antibodies in patients, which could : 1) neutralize the infectivity of HDV virions, for the benefit of treatment. 2) neutralize BLV, to the detriment of treatment. In this context, the presence of anti-preS1 antibodies in BLV-treated patients should be documented, and functional analysis of these antibodies in an in vitro infection model should be performed for a more complete interpretation of BLV's effects in vivo. The specific objectives are : 1) measure the level, and document the kinetics, of anti-preS1 antibodies in patients treated with BLV. 2) perform a functional characterization of anti-preS1 by measuring their ability to neutralize HDV infection in vitro, in the presence and absence of BLV, to reflect the treatment and post-treatment phases, respectively
Project start dates	June 2023
Data recipients in France	INSERM U1259, University of Tours
Data recipient abroad	NA
Identity and data controller	Inserm-ANRS MIE
Data and/or sample transfer	Transfer of data from CIC Inserm 1414 - CHU de Rennes to INSERM U1259, Université de Tours and transfer of ANRS MIE biothèque samples from CHU de Bordeaux to INSERM U1259, Université de Tours
Retention period for data and/or samples	15 years
Data category	Health data

Project title	Hepatitis B-Delta among immigrants. Experiences, needs and barriers during treatment: a qualitative approach

Project summary	The aim of the study is to gain a better understanding of the experiences, representations and barriers to access to care of immigrants in France who are carriers of hepatitis B-delta. This study will highlight the needs and barriers to effective care for the immigrant population infected with HBV Delta, and explore possible measures and interventions to overcome these barriers.
Project start dates	June 2023
Data recipients in France	UMR 1252 - SESSTIM
Data recipient abroad	NA
Identity and data controller	Inserm-ANRS MIE
Data and/or sample transfer	Data transfer from CIC Inserm 1414 - CHU de Rennes to UMR 1252 - SESSTIM
Retention period for data and/or samples	15 years
Data category	Health and socio-demographic data

Data and samples collected	**Biotech libraries**	Plasma
	Data	Clinical, biological, radiological, socio-demographic

B - How to access the collection

1- project submission: **via the sample request form on the website**

2- Project evaluation: **scientific committee or independent experts**

3- Provision of the collection: **final decision by the ANRS MIE management or Scientific Advisory Board.**

Contact e-mail address for submitting your project: **biobanque@anrs.fr**