UKB Research protocol

HDV-Europe: Prevalence and Outcome

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1.Background and Objective of Study

1.1 Background

Hepatitis D is caused by a defective RNA-virus, that is known to be among the smallest human pathogenic viruses. As it partly shares the viral entry into hepatocytes with HBV, a coinfection is mandatory (1). Besides a simultaneous infection with HBV and HDV, it might also occur in the sense of a superinfection to a preexisting HBV-infection (2). Though most of the acute infections recover spontaneously, a progression to chronic disease is well described (3). The persistence of HDV leads to an accelerated fibrosis progression and eventually to cirrhosis and an increased risk of developing hepatocellular carcinoma (HCC) as well (4, 5). With the widely established feasibility of immunization against viral Hepatitis B, numbers of HDV-infection in high-income countries are quite low. Nevertheless, the burden of chronic HDV-infection worldwide is high, as different studies estimate the number of patients from 12 million to up to 72 million (6-8).

In the subgroup of people living with HIV (PLWH), who are at increased risk for acquiring viral hepatitis in general, rates of HDV infection have been reported between 10%-20% of HIV/HBV-coinfected people, with variations according to region as well as transmission group. Particularly, early in the HV epidemic higher rates of HDV have been reported for HIV/HBV coinfected drug users. More recently, a shift from people who acquired HIV through drug injection (PWID) to men who have sex with men (MSM) has been reported with HDV coinfection rates of around 8% (9). Common for all PLWH with HBV/HDV-coinfection is a more rapid progression in liver disease (10), resulting in increased rates of decompensated cirrhosis and higher mortality (11, 12). Therefore, mandatory screening for HDV was implemented into current EACS guideline recommendations. However, there is still a lack of testing in daily routine, even at sites where testing is easily accessible and reimbursed. Moreover, most PLWH

who are coinfected with HBV are tested at initial HBV diagnosis, but after being put on antiretroviral treatment, which usually includes a tenofovir-based therapy a follow-up testing of HDV does not take place routinely.

1.2 Objective

The aim of this project is to set up a cross-sectional cohort study (France, Germany, The Netherlands, Poland, Spain, Switzerland, Italy, United Kingdom and Portugal) to assess the implementation of EACS guidelines for HDV-testing among PLWH with positive HbsAg and thereby evaluate the prevalence of HDV infection among HIV/HBV-coinfected in 2023, as well as corresponding risk factors. In addition to the testing itself, this study will also set up a cohort and databasee for future HDV studies among PLWH, including clinical, virological und laboratory parameters.

1. Analyze the rate of HDV-testing and evaluate the prevalence of HDV-infection by testing.
    a. Evaluation of former screening of HDV by assessing existing data at study sites.
    b. Determination of the HDV prevalence in European PLWH and HBV coinfection.
2. Setting up a database of all PLWH with HBV/HDV coinfection
    a. Analysis of transmission risk factors for HDV coinfection
    b. Asses the rate of HDV positive patients with ongoing HDV replication.
    c. Define the liver disease state by APRI score, fibroscan, ultrasound and routine laboratory test results.

2.Cohort Design and Methods

2.1 General

In this multi-center cohort study patients with documented HIV/HBV-coinfection (2 measurements of positive HBsAg > 6month interval and Anti-HBc-positive) will be evaluated for past HDV screening (last 24 months).

Eligible participants must be 18 years of age or older.

2.2 Study Centers and Accrual of Patients

To secure representative data, each cohort or clinic network will aim to enroll a sample size of at least 20% of all HIV/HBV-coinfected individuals in each country. France, Switzerland, Italy, and The Netherlands already have well established national cohorts which are representing more than 50% of all PLWH in their respective countries. In the remaining countries (Germany, Spain, Poland, Portugal, UK) well-defined cohorts in specialized HIV-clinics or networks of HIV-centers are existing, which allow for a sufficient recruitment. The overall number of participants is planned to reach at least 8000 HIV/HBV-coinfected persons. With an estimated 800.000 PLWH in the following 9 countries: Spain 150.00, France 190.000, Germany 93.000, England 106.000, Portugal 61.000, Italy 140.000, Poland 20.000, Switzerland 16.000, Netherlands 24.000, and an estimated HBV-Prevalence of 5%, this would lead to a cohort of around 40.000 HIV/HBV coinfected individuals. According to current data, 20% of HIV/HBV-coinfected PLWH are expected to have an HDV-infection, which should add up to 8000 individuals that would be needed to be studied. This should guarantee a representative sample size and would represent a highly meaningful European cohort for future HDV studies.

2.3 Accrual goal

A cohort of 8000 HIV/HBV-coinfected individuals with serological HDV-screening evidence.

3.Patient Inclusion and Exclusion Criteria

3.1 Inclusion-Criteria

Documented HIV-infection with current Hepatitis B infection, who are serological positive for HBSAg

Both, HIV- and HBV Infection must be confirmed by HIV ELISA and HBV HBsAg-testing (2 measurements of positive HBsAg > 6month interval).The viral load results will be included into the analyses, but are not part of the inclusion criteria.

As patients are enrolled retrospectively, data on liver enzymes (transaminases, gamma GT, AP, bilirubin) and viral load will be available, though this is not compulsory. Written informed consent will be provided prior to inclusion, or, if adequate, used from pre-exisitng cohort studies.

3.2. Exclusion-Criteria

PLWH with a cleared HBV-infection will be considered as HIV-monoinfected persons.Individuals younger than 18 years of age will be excluded from the analysis. Patients with any social condition or living circumstances which may interfere with the conduct of the study, as anticipated by the investigator, such as incapacity to adequately understand the study content or not willing to cooperate will be excluded from the study. For France, patients without adequate social security will be excluded.

4. Study Procedures

All participating PLWH will be recruited from the already existing national cohorts and defined networks of specialized HIV-clinics, respectively. This database will allow for the initial analysis of whether HDV screening was performed and allow to determine the HDV prevalence in the participating countries as well as study risk factors for HDV transmission.

Only patients who were alive in 2022 will be included into the study.

5. Plan of Analysis

Because of the observational nature of the study no predefined statistical power calculations can be made. Descriptive statistics will be used.

5.1 Epidemiology

- Prevalence of HDV among HBV-coinfected PLWH
- Description of populations at risk
- Transmission risk factors

Methods:

- Prevalence: Number of HDV-positive persons in relation to all HBV/HIV individuals of the database.
- Risk populations and transmission factors: Descriptive methods will be used to investigate populations at risk and transmission risk factors.

5.2 Define burden of disease

- Asses the rate of HDV-positive patients with ongoing HDV replication
- Define the liver disease stage by non-invasive methods (APRI, Fibroscan)

Methods:

- HDV-replication will be measured by commercially used PCR-testing kits. The proportion of HDV serological positive individuals with ongoing viral replication will be determined. This will be collected for all patients with positive HDV serology.
- The liver disease stage, which is expressed by the fibrosis stage, will be determined by APRI score. Furthermore, other non-invasive imaging techniques, including standard ultrasound as well as Fibroscan will be used where available to evaluate the degree of liver disease. In addition, standard laboratory parameters (see, eCRF codebook, annex xyz), which are part of the routine testing among PLWH control visits, will be documented. Changes over time will be evaluated and put in relation to medical imaging, as far as available.

6. Study withdrawals

Patients will be free to withdraw their consent at any time and without any reason. Withdrawal of consent will not affect the rights of the patient or their access to continuing medical care or treatment.

7. Ethics and research governance

7.1 Ethics

This retrospective muti-national cohort analysis has been submitted for ethical review to the ethics committee at Bonn University.

7.2 Good Clinical Practice

It is the responsibility of the treating physician to ensure that the collection of all diagnostic tests and other data for the study is in accordance with the principles of the declaration of Helsinki and its Tokyo, Venice, Hongkong, Somerset West and Edinburgh amendments, as

well as in agreement with further loco-regional laws and regulations. The study should be conducted according to ICH-Good Clinical Practice (GCP) Guidelines.

7.3. Informed Consent

It is the responsibility of the local investigator (including persons with delegated authority to consent patients) to obtain a written consent from each patient participating in the study prior to enrolment. Objective, methods, advantages as well as possible disadvantages of the study must be explained in an understandable way to the patient. Further, the patient must be informed that enrolment into the study is a voluntary. Enrolment must be signed by the patient, and signed written consent must be documented and a copy retained for the study documentation file.

7.4. Data Management

Data security will be assured for alle patients participating in the study. All data management will be performed according to GCP. Data analysis will be performed by Anders Boyd (cooperating scientist;Amsterdam University Medical Centers) conducting to GCP.

8. Milestones

The patients being recruited are already tied to the different center sites and preexisting data are available. After writing consent, a retrospective analysis of these data can take place. Recruitment of patients is planned to run from November 2023 until April 2024.

MS	Title	Work pkg. (nr.)	*Institution*	*Date (dd.mm.yyyy)*	*Proof of achievement/fulfillment*
1	Study protocol for multicentric approach	1	University Hospital Bonn	15.11.2023	Study protocol
2	Ethics approval	1	University Hospital Bonn	30.11.2023	Ethics approval achieved
3	Agreement with cooperating centers	1	University Hospital Bonn	XX.XX.2023	Signed agreement
4	Start of patient enrolment	2 and 3	University hospital Bonn cooperating centers	XX.XX.2023	Electronic database established
5	Reaching 50% of respective HBs-Ag positive patients	2 and 3	University Hospital Bonn and cooperating centers	XX.XX.2024	50% of eligible/reachable patient population enrolled
6	Finishing patient acquisition	2 and 3	University Hospital Bonn and cooperating centers	XX.XX.2024	100% of patient population enrolled
9	Data Analysis	4	University Hospital Bonn and cooperating centers. Final data analyses by University Medical Centers Amsterdam	XX.XX.2024	Data analyses completed, and preparation of manuscript

9. Data Protection

All patient data that are used, have already been collected and country related databases have been set up. The included data are to be within the treating physicians keeping. The values that are evaluated in this study are shared with the other participating physicians, though data containing personal information are excluded from this. Collected data will be analyzed, evaluated and presented in an anonymous form, ensuring confidentiality of patient data towards third parties.

10. Literature:

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