
ECOLE DOCTORALE PIERRE LOUIS DE SANTÉ PUBLIQUE A PARIS
ÉPIDÉMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMÉDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour l'Université Paris Cité : Isabelle Boutron

PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : INSTITUT PIERRE LOUIS D'ÉPIDÉMIOLOGIE ET DE SANTÉ PUBLIQUE (IPLESP)

NOM DE L'ÉQUIPE : ÉPIDÉMIOLOGIE CLINIQUE DES MALADIES VIRALES CHRONIQUES

DIRECTEUR DE THÈSE : FABRICE CARRAT

ADRESSE : FACULTE DE MEDECINE, 27 RUE CHALIGNY, 75012 PARIS

TITRE DE LA THÈSE : MENTAL HEALTH AND ADDICTION AMONG PEOPLE INFECTED WITH HEPATITIS B AND C VIRUSES. ANALYSIS OF THE NATIONAL HEALTH DATA SYSTEM

CO-ENCADRANT ÉVENTUEL : MURIELLE MARY-KRAUSE

ÉQUIPE DU CO-ENCADRANT : ERES - ESSMA

LABORATOIRE : INSTITUT PIERRE LOUIS D'ÉPIDÉMIOLOGIE ET DE SANTÉ PUBLIQUE (IPLESP)

PRESENTATION DU SUJET

Context

In metropolitan France, the latest national prevalence survey of chronic viral hepatitis C and B carried out in 2016 reported estimated prevalences of 0.30% (IC95%: [0.13-0.70]) for chronic hepatitis C and 0.30% [0.13-0.70] for chronic hepatitis B. The estimated proportion of infected people knowing their status was 80.6% [44.2-95.6] and 17.5% [4.9-46.4], respectively (1). Since 2016, the arrival on the market of direct-acting antivirals for the treatment of chronic hepatitis C, with efficacy close to 100% in achieving virological cure, has led to the recommendation of universal treatment for this infection, with the aim of eradicating it by 2025 (2). In a study carried out on the French national health data system (SNDS), we estimated that 19% of patients with chronic hepatitis C would be eligible for treatment and not yet successfully treated in 2021 (3), i.e. around 15,000 infected people. With regard to hepatitis B, current management is based on the use of antivirals in patients with chronic hepatitis - principally tenofovir and entecavir, and several molecules or therapeutic strategies are currently being evaluated for the achievement of a functional cure defined by the undetectability of the HBs antigen (4). Nonetheless, while the prevalence of chronic hepatitis B has declined overall in Europe and France in recent years, notably as a result of falling incidences (5), an SNDS query indicates that in 2022, almost 115,000 people will be living with HBV in mainland France, of whom around 20% will require antiviral treatment (6).

Patients with chronic hepatitis B or C have social, demographic and behavioral profiles that differ from those of the general population, with an over-representation of drug users (one of the modes of contamination for these two infections) and, for the progression of these infections to cirrhosis, a strong link with alcohol consumption

Ecole Doctorale 393
Centre Biomédical des Cordeliers
15, rue de l'École de Médecine 75006 Paris
<https://ed393.sorbonne-universite.fr/>

Contact : ed393@sorbonne-universite.fr / Téléphone : 01.44.27.24.35

ÉCOLE DOCTORALE PIERRE LOUIS DE SANTÉ PUBLIQUE A PARIS
ÉPIDÉMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMÉDICALE

Directeur : Pierre-Yves Boëlle

Responsable pour l'Université Paris Cité : Isabelle Boutron

(7). These chronic infections are also more frequently encountered in patients with severe psychiatric illnesses (8,9), and chronic infection status is a source of stress, anxiety and mood disorders (10,11). To date, however, the evolution of mental health and addictions before and after effective treatment in people infected with hepatitis C virus (HCV), or upon initiation or cessation of antiviral treatment and eventual achievement of a functional cure in people infected with HBV, remains little explored. Studies measuring depressive disorders and anxiety before and after antiviral treatment in HCV-infected patients have produced contradictory results, and are based on very low-quality studies (12-14). In the case of patients with hepatitis B virus (HBV) infection, few studies have been carried out, and none to our knowledge links the stage of chronic infection with this virus ("inactive" infection or treated hepatitis) with mental health or addiction-related behaviors (11,15).

Objectives

The objectives of this thesis work are to identify the relationships between mental health and addictions and the management (and in particular antiviral treatments) of people living with HCV or HBV in the National Health Data System.

In particular, we will explore

- Impact of direct antiviral treatment on mental health and addictions (alcohol, drugs) in patients chronically infected with the hepatitis C virus.
- Interdependence between mental health and addictions and the care and status (chronic infection, chronic hepatitis) of people living with the hepatitis B virus.

Data

The main data source used for this thesis is the National Health Data System / Système National des Données de Santé (SNDS), enriched with data from the ANRS-CO22 Hepather cohort linked to the SNDS.

Since 2012, the CLEPILIR team at IPLESP has been coordinating the Hepather cohort of patients with hepatitis B (n=6600) and C (n=11400). For 85% of the patients in this cohort, data have been linked to the SNDS using a deterministic method (reconstitution of the identification number in the NIR directory). We have developed and validated various algorithms for identifying different phenotypes of these chronic infections in the SNDS (16), enabling us to build up national cohorts of people living with these infections - around 140,000 people with chronic HCV infection, and 115,000 chronic HBV carriers. In addition, within this cohort, data on addictions (drugs, alcohol, tobacco, cannabis) and quality of life (EQ5D, PROQOL-HCV, SF12) were collected at cohort inclusion (before 2015), during follow-up (every 2 years until 2024) and before and after treatment where appropriate.

ERES team (ESSMA in the new mandate) @IPLESP has expertise in the analysis of mental health and addictions. It collaborates, along with the CLEPILIR team, with the UMS CONSTANCES in which mental health measures using validated instruments (CES-D, anxiety scale,...) are collected longitudinally and chained with SNDS data. By chaining these cohorts with the SNDS, it will be possible to identify and validate the SNDS criteria used to measure mental health or addictions in the Hepather or CONSTANCES cohorts. Furthermore, if algorithms already exist to measure pathologies or disorders linked to excessive alcohol or tobacco consumption in the SNDS, we will have the opportunity to verify their relevance in chained data where these addictions are precisely collected.

Ecole Doctorale 393

Centre Biomédical des Cordeliers
15, rue de l'École de Médecine 75006 Paris
<https://ed393.sorbonne-universite.fr/>

Contact : ed393@sorbonne-universite.fr / Téléphone : 01.44.27.24.35

ECOLE DOCTORALE PIERRE LOUIS DE SANTÉ PUBLIQUE A PARIS
ÉPIDÉMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMÉDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour l'Université Paris Cité : Isabelle Boutron

Methods

A "self-controlled case series" design will be used to analyze the data. This scheme can be applied fairly easily to patients treated for hepatitis C, since the treatment is intended to cure the infection, is prescribed for a short period of time, and is not influenced by pre-treatment events describing mental health. It will need to be adapted for people living with HBV and hepatitis whose treatment is prescribed on an ongoing, long-term basis. In addition, analysis techniques will need to take into account the causal relationships that may exist between mental health and HBV infection, and the changes in mental health that occurred during the early years of the COVID-19 pandemic. Comparison with an age-, sex- and time-matched cohort of equivalent size will use a difference-in-differences method.

Collaboration with the ERES-ESSMA team for the identification and validation in the SNDS of markers of mental health or addiction, and with the Inserm Chair in Causal Inference (Charles Assaad, CIPHOD team) for the choice or development of adapted methods is already planned. Our team, which has been piloting several SNDS analysis projects since 2018, has the necessary methodological and technical expertise on these data.

Power and sample size

The cohorts of HBV- or HCV-infected people already identified in the SNDS are each over 100,000 people in size (>200,000 if we add a "control" cohort of uninfected people for comparison), and the follow-up will be 10 years; mental health events are not rare, and the exposures studied (treatment) are frequent: we can assume a power greater than 99% for the identification of even relatively low relative risk (i.e. $RR > 1.2$).

Provisional agenda

Semester 1 - SNDS training (if necessary), literature review on the subject, identification of relevant mental health or addiction criteria within the SNDS.

Semester 2 - analysis of mental health before and after HCV treatment - submission of article 1

Semester 3 - publication of article 1 and development of the analysis model for the HBV cohort

Semester 4 - analysis of mental health in people living with HBV - submission of article 2

Semester 5 - writing of thesis - publication of article 2

Semester 6 - defense

Articles

Article 1: mental health and addictions in people infected with the hepatitis C virus, before and after virological cure obtained by direct antiviral treatment.

Article 2: mental health and addictions in people living with HBV: impact of infection status, treatment and comparison with the uninfected population.

References

-
1. Brouard C, Saboni L, Gautier A, Chevaliez S, Rahib D, Richard JB, et al. HCV and HBV prevalence based on home blood self-sampling and screening history in the general population in 2016: contribution to the new French screening strategy. *BMC Infect Dis.* 28 oct 2019;19(1):896.
 2. plan_national_de_sante_publique__psnp.pdf [Internet]. [cité 5 avr 2024]. Disponible sur: https://sante.gouv.fr/IMG/pdf/plan_national_de_sante_publique__psnp.pdf

Ecole Doctorale 393
Centre Biomédical des Cordeliers
15, rue de l'Ecole de Médecine 75006 Paris
<https://ed393.sorbonne-universite.fr/>

Contact : ed393@sorbonne-universite.fr / Téléphone : 01.44.27.24.35

ECOLE DOCTORALE PIERRE LOUIS DE SANTÉ PUBLIQUE A PARIS
ÉPIDÉMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMÉDICALE

Directeur : Pierre-Yves Boëlle

Responsable pour l'Université Paris Cité : Isabelle Boutron

3. Lam L, Carrieri P, Hejblum G, Bellet J, Bourlière M, Carrat F. Real-world economic burden of hepatitis C and impact of direct-acting antivirals in France: A nationwide claims data analysis. *Liver Int.* 20 févr 2024;
4. Lim SG, Baumert TF, Boni C, Gane E, Levrero M, Lok AS, et al. The scientific basis of combination therapy for chronic hepatitis B functional cure. *Nat Rev Gastroenterol Hepatol.* avr 2023;20(4):238-53.
5. Polaris Observatory Collaborators. Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study. *Lancet Gastroenterol Hepatol.* oct 2023;8(10):879-907.
6. Lam L, Carrat F. Nationwide analysis of mortality and economic burden among chronic HBV-infected patients in France: a real-world study. 2023 International HBV meeting.; 2023 sept; Kobe, Japan.
7. Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. *J Hepatol.* sept 2018;69(3):718-35.
8. Rosenberg SD, Goodman LA, Osher FC, Swartz MS, Essock SM, Butterfield MI, et al. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness. *Am J Public Health.* janv 2001;91(1):31-7.
9. Hughes E, Bassi S, Gilbody S, Bland M, Martin F. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness: a systematic review and meta-analysis. *Lancet Psychiatry.* janv 2016;3(1):40-8.
10. Fortier E, Alavi M, Bruneau J, Micallef M, Perram J, Sockalingam S, et al. Depression, Anxiety, and Stress Among People With Chronic Hepatitis C Virus Infection and a History of Injecting Drug Use in New South Wales, Australia. *J Addict Med.* 2017;11(1):10-8.
11. Li G, Wang G, Hsu FC, Xu J, Pei X, Zhao B, et al. Effects of Depression, Anxiety, Stigma, and Disclosure on Health-Related Quality of Life among Chronic Hepatitis B Patients in Dalian, China. *Am J Trop Med Hyg.* mai 2020;102(5):988-94.
12. Slonka J, Piotrowski D, Janczewska E, Pisula A, Musialik J, Jaroszewicz J. Significant Decrease in the Prevalence of Anxiety and Depression after Hepatitis C Eradication. *J Clin Med.* 28 mai 2022;11(11):3044.
13. Gallach M, Vergara M, da Costa JP, Miquel M, Casas M, Sanchez-Delgado J, et al. Impact of treatment with direct-acting antivirals on anxiety and depression in chronic hepatitis C. *PLoS One.* 2018;13(12):e0208112.
14. Abdel Moez AT, El Hawary YA, Al Balakosy AM. Can successful treatment by direct-acting antivirals improve depression in chronic HCV patients? *Eur J Gastroenterol Hepatol.* 1 mai 2021;33(5):727-30.
15. Katcher JG, Klassen AC, Hann HW, Chang M, Juon HS. Racial discrimination, knowledge, and health outcomes: The mediating role of hepatitis B-related stigma among patients with chronic hepatitis B. *J Viral Hepat.* 26 févr 2024;
16. Lam L, Fontaine H, Lapidus N, Bellet J, Lusivika-Nzinga C, Nicol J, et al. Performance of algorithms for identifying patients with chronic hepatitis B or C infection in the french health insurance claims databases using the ANRS CO22 HEPATHER cohort. *J Viral Hepat.* mars 2023;30(3):232-41.

PRÉREQUIS, FORMATION :

MASTER DEGREE IN EPIDEMIOLOGY BIostatISTICS

CONTACT POUR CE SUJET : FABRICE CARRAT

EMAIL : FABRICE.CARRAT@IPLESP.UPMC.FR

TELEPHONE : 0672492496

SPECIALITE DE LA THESE

- | | |
|--|-------------------------------------|
| Santé publique - Epidémiologie | <input checked="" type="checkbox"/> |
| Santé publique - Epidémiologie clinique | <input type="checkbox"/> |
| Santé publique - Epidémiologie sociale | <input type="checkbox"/> |
| Santé publique - Epidémiologie génétique | <input type="checkbox"/> |

Ecole Doctorale 393

Centre Biomédical des Cordeliers

15, rue de l'Ecole de Médecine 75006 Paris

<https://ed393.sorbonne-universite.fr/>

Contact : ed393@sorbonne-universite.fr / Téléphone : 01.44.27.24.35

ECOLE DOCTORALE PIERRE LOUIS DE SANTÉ PUBLIQUE A PARIS
ÉPIDÉMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMÉDICALE

Directeur : Pierre-Yves Boëlle

Responsable pour l'Université Paris Cité : Isabelle Boutron

- | | |
|---|--------------------------|
| Santé publique - Biostatistique | <input type="checkbox"/> |
| Santé publique - Biomathématiques | <input type="checkbox"/> |
| Santé publique - Biostatistique et Biomathématiques | <input type="checkbox"/> |
| Santé publique - Informatique médicale | <input type="checkbox"/> |
| Santé publique - Imagerie biomédicale | <input type="checkbox"/> |
| Santé publique - Bioinformatique | <input type="checkbox"/> |
| Santé publique - Recherches sur les services de santé | <input type="checkbox"/> |
| Santé publique - Economie de la santé | <input type="checkbox"/> |
| Santé publique - Science des données | <input type="checkbox"/> |
| Santé publique – Prévention et promotion de la santé | <input type="checkbox"/> |

**SIGNATURE DU . DE LA DIRECTEUR.TRICE
DE THESE**

FABRICE CARRAT

**VISA DU .DE LA DIRECTEUR.TRICE DU
LABORATOIRE
(DÉROGATION DE SIGNATURE NON ACCEPTÉE)**

AVIS FAVORABLE

SIGNATURE

FABRICE CARRAT