Study Report P2-C1-010

DARWIN EU® - Characterization of patients with chronic hepatitis B and C

16/02/2024

Version 2.0

Contents

DOCUMENT HISTORY

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V1.0	19/01/2024	**Submission to EMA**
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Study Title	DARWIN EU® - Characterization of patients with chronic hepatitis B and C
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Active substance

No	Therapeutic Drug Class	ATC Code
1.	**Peginterferon**	
	Cepeginterferon alfa-2b	L03AB14
	Peginterferon -α-2a	L03AB11, L03AB61
	Peginterferon -α-2b	L03AB10, L03AB60
	Peginterferon alfacon-2	L03AB16
	Interferon alfa-2a	L03AB04
	interferon alfa-2b	L03AB05
2.	**Antivirals for treatment of HCV infections**	
	Ribavirin	J05AP01
	Telaprevir	J05AP02
	Boceprevir	J05AP03
	Faldaprevir	J05AP04
	Simeprevir	J05AP05
	Asunaprevir	J05AP06
	Daclatasvir	J05AP07
	Sofosbuvir	J05AP08
	Dasabuvir	J05AP09
	Elbasvir	J05AP10
	Grazoprevir	J05AP11
	Coblopasvir	J05AP12
	Sofosbuvir and ledipasvir	J05AP51
	Dasabuvir, ombitasvir, paritaprevir and ritonavir	J05AP52
	Ombitasvir, paritaprevir and ritonavir	J05AP53
	Elbasvir and grazoprevir	J05AP54
	Sofosbuvir and velpatasvir	J05AP55
	Sofosbuvir, velpatasvir and voxilaprevir	J05AP56
	Glecaprevir and pibrentasvir	J05AP57
	Daclatasvir, asunaprevir and beclabuvir	J05AP58
3.	**Antivirals for treatment of HBV infections**	
	Adefovir dipivoxil	J05AF08
	Entecavir	J05AF10

		Telbivudine	J05AF11
		Tenofovir alafenamide	J05AF13
		Tenofovir disoproxil fumarate	J05AF07
		Lamivudine	J05AF05
		Bulevirtide	J05AX28

Medicinal product	N/A
Research question and objectives	Research question: What were the characteristics of patients with chronic hepatitis B or chronic hepatitis C? Study objectives: 1. To report the number and percentage of patients diagnosed with chronic HBV or chronic HCV infection who initiated treatment with interferon or any specified antivirals, stratified by age, sex, calendar year, and country/database throughout the study period (2012 - 2022). 2. To report the number and percentage of patients diagnosed with chronic HBV or chronic HCV infection who underwent treatment with any specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022). 3. To characterize patients with chronic HBV or chronic HCV infection at the initiation of treatment with interferon or specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022). 4. To estimate the proportion of all patients with chronic HBV or chronic HCV infection, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
Country(-ies) of study	Estonia, France, Germany, Netherlands, Spain, and the United Kingdom
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1 DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Principal Investigator/ Clinical Epidemiologists	Dina Vojinovic Katia Verhamme Johnmary Arinze	IQVIA Erasmus MC Erasmus MC
Data Scientist(s)	Cesar Barboza Gutierrez	Erasmus MC
Data Partner*	**Names**	**Organization**
Local Study Coordinator/ Data Analyst	Antonella Delmestri James Brash Vianney Jouhet Verdy Guillaume Mees Mosseveld Miguel-Angel Mayer Angela Leis Juan Ramirez Raivo Kolde	University of Oxford – CPRD IQVIA - DA Germany CHUBX – France CHUBX – France Erasmus MC – IPCI PSMAR – IMASIS PSMAR – IMASIS PSMAR – IMASIS University of Tartu - Estonian Biobank

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

2 DATA SOURCES

This study was conducted using routinely collected data from 6 databases in 6 European countries (5 EU countries and United Kingdom). All databases were previously mapped to the OMOP Common Data Model (CDM).

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Integrated Primary Care Information Project (IPCI), The Netherlands

Detailed information on data sources is described below.

Country	Name of Database	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	End of calendar period covered
France	CHUBX	Secondary care (in and outpatients)	EHR	2.1 million	05/05/2023
UK	CPRD GOLD	Primary care	EHR	3 million	20/03/2023
Estonia	EBB	Hospital, primary care, registries and biobank	Claims	0.2 million	20/03/2023
Germany	IQVIA DA Germany	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023
Spain	IMASIS	Secondary care (in and outpatient)	EHR	0.6 million	31/12/2022
The Netherlands	IPCI	Primary care	EHR	1.4 million	21/03/2023

CWDBordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, IMASIS = Institut Municipal Assistencia Sanitaria Information System, IPCI = Integrated Primary Care Information Project, EHR = Electronic Heath record.

3 ABSTRACT (STAND-ALONE SUMMARY OF THE STUDY REPORT)

Title

DARWIN EU® - Characterization of patients with chronic hepatitis B and C

Rationale and Background

In 2015, UN Member States adopted Sustainable Development Goals (SDGs) for 2030 (1) with an 'urgent call to action' comprised of 17 goals/179 targets. EU/EEA countries are committed to monitoring progress towards these goals. Specifically, Target 3.3 states: 'By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases'. The 2016 WHO Global Health Sector Strategy (GHSS) (2) aims to eliminate viral hepatitis by 2030, and WHO EU has developed a hepatitis action plan to steer the implementation of the GHSS in Europe (3).

The European Centre for Disease Prevention and Control (ECDC) has developed a monitoring system for Hepatitis B Viral Infection (HBV) and Hepatitis C Viral Infection (HCV) aligned with indicators and targets of the GHSS and the WHO European Region Action Plan (4). Comprehensive data on the prevalence of chronic HBV or HCV infections and utilisation of antiviral treatments for chronic HBV or HCV infections are important to monitor progress towards the elimination targets related to treatment, to adjust prevalence estimates over time, and to support effective planning of prevention and control activities by countries.

To date, data collected by EU Member States and reported to ECDC come from a range of heterogeneous sources with different levels of quality and completeness. Several reasons contribute to this heterogeneous data collection including as the lack of standardised or electronic data systems in countries. Therefore, robust and timely data at national or subnational level generated through DARWIN EU will add to the available body of evidence and/or will help address current evidence gaps.

Research question and Objectives

Research question

What were the characteristics of patients with chronic HBV or chronic HCV?

Study objectives

1. To report the number and percentage of patients diagnosed with chronic HBV or chronic HCV infection who initiated treatment with interferon or any specified antivirals, stratified by age, sex, calendar year, and country/database throughout the study period (2012 - 2022).
2. To report the number and percentage of patients diagnosed with chronic HBV or chronic HCV infection who underwent treatment with any specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
3. To characterize patients with chronic HBV or chronic HCV infection at the initiation of treatment with interferon or specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
4. To estimate the proportion of all patients with chronic HBV or chronic HCV infection, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).

Research Methods

Study design

- Population-level drug utilisation study: Population level drug utilisation study to estimate the number and percentage of individuals initiating (Objective 1) or undergoing (Objective 2) treatment with interferon or any of the specific antivirals of interests among patients with chronic HBV or chronic HCV infection.
- New drug user cohort study (Objective 3): Patient-level drug utilisation analyses to provide large scale characterization of chronic HBC or chronic HCV infections at the time of treatment initiation with interferon or any of the specific antivirals of interests).
- Population-level cohort study (Objective 4): Population-level descriptive epidemiology to estimate the proportion of all patients with chronic HBV or chronic HCV infection in the general population.

Population

Population-level drug utilisation: Population-level drug utilization analyses included all patients diagnosed with chronic HBV or chronic HCV infection in the respective databases from 2012 to 2022 (or the latest available date if earlier).

Patient-level drug utilisation: Patient-level drug utilization included all patients with chronic HBV or chronic HCV infection who were new users of interferon or any of the specific antivirals of interests in the respective databases from 2012 to 2022 (or the latest available date if earlier).

Population-level descriptive epidemiology: Population-level descriptive epidemiology analyses included all individuals in the respective databases from 2012 to 2022 (or the latest available date if earlier). Within this population, we estimated the proportion of all patients diagnosed with chronic HBV or chronic HCV infection.

Variables

Therapeutic drug classes of interest:

- Interferon: Cepeginterferon alfa-2b, Peginterferon -α-2a, Peginterferon -α-2b, Peginterferon alfacon-2, Interferon alpha-2a, and Interferon alpha-2b.
- Antivirals for treatment of HBV infections: Adefovir dipivoxil, Entecavir, Telbivudine, Tenofovir alafenamide, Tenofovir disoproxil fumarate, Lamivudine, and Bulevirtide.
- Antivirals for treatment of HCV infections: Asunaprevir, Beclabuvir, Boceprevir, Coblopasvir, Daclatasvir, Dasabuvir, Elbasvir, Faldaprevir, Glecaprevir, Grazoprevir, Ledipasvir, Ombitasvir, Paritaprevir, Pibrentasvir, Ribavirin, Ritonavir, Simeprevir, Sofosbuvir, Telaprevir, Velpatasvir and Voxilaprevir.

Conditions of interest:

- Chronic Hepatitis B Viral Infection (HBV)
- Chronic Hepatitis C Viral Infection (HCV)

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Integrated Primary Care Information Project (IPCI), The Netherlands

Sample size

No sample size was calculated for this study, as our primary focus is to describe characteristics of patients with chronic HBV or chronic HCV infection, regardless of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts with chronic HBV or chronic HCV infection ranged from 200 (CPRD GOLD) to 14,700 (IQVIA DA Germany) for HBV and from 200 (IPCI) to 17,000 (IQVIA DA Germany) for chronic HCV infection.

Data analyses

Population-level drug utilization analyses: The number and percentage of patients who were prescribed each of the pre-specified drugs from the designated list for the treatment of HBV or HCV infections were estimated in patients with chronic HBV or chronic HCV infections (Objective 1 and 2). The statistical analyses were performed based on OMOP-CDM mapped data using the "*PatientProfile"* R package, and stratified by age, sex, calendar year and data sources.

Patient-level drug utilisation analyses: Large-scale patient-level characterisation was conducted at time of treatment initiation, following the diagnosis of chronic HBV or chronic HCV infections, to describe patient demographics and medical history including the presence of co-morbidities and concurrent medication use (Objective 3). The index date was determined as the date of the first prescription of the specific therapeutic drug class for each individual. The statistical analyses were conducted using the "*DrugUtilization*" R package based on OMOP-CDM mapped data, and stratified by age, sex, calendar year and data sources.

Population-level descriptive epidemiology: The number and proportion (expressed as a percentage) of patients with chronic HBV infection or chronic HCV infection in the overall eligible population were estimated (Objective 4). The statistical analyses were performed based on OMOP-CDM mapped data using the *"PatientProfile"* R package, and stratified by age, sex, calendar year and data sources.

For all analyses, results were reported with a minimum cell count of 5, and any counts smaller than 5 were obscured to ensure privacy and confidentiality.

Results

In this study, using data from six different databases and during the study period between 2012 and 2022, we identified 19,352 patients diagnosed with chronic HBV infection (63% IQVIA DA Germany, 6.0% CPRD Gold, 11.5% CHUBX, 2,0% EBB, 11.4% IMASIS and 6.5% IPCI) and 24,421 patients diagnosed with chronic HCV infection (50% IQVIA DA Germany, 19% CHUBX, 19% IMASIS, 5% EBB and 1% IPCI). The median age of patients diagnosed with chronic HBV infection ranged from 37 to 53 years across different databases, while in chronic HCV infection ranged from 41 to 54 years, with the majority of patients being males.

The frequency of interferons or antiviral treatment initiation in patients diagnosed with chronic HBV infection varied across different databases ranging from 2.95% in CPRD GOLD to 7.87% in IQVIA DA Germany in primary care databases, from 11.73% in IMASIS to 13.45% in CHUBX in hospital databases to 15.41% in EBB during the whole study period. On the other hand, the frequency of interferons or antiviral treatment initiation in chronic HCV infection ranged from 4.43% in CPRD GOLD to 11.79% in IPCI in primary care databases, from 3.96% in CHUBX to 21.62% in IMASIS, and 50.65% in EBB during whole reporting period. The frequencies observed in prevalent use of interferons or antiviral treatment mirrored those of new use for both chronic HBV and chronic HCV infection in each database. Regarding specific drugs use, the most frequently prescribed medications were entecavir, tenofovir disoproxil, and peginterferon alfa-2a for patients with chronic HBV infection. For chronic HCV infection, the commonly prescribed drugs included glecaprevir, ledipasvir/sofosbuvir, ribavirin, sofosbuvir, and sofosbuvir/velpatasvir.

The most common comorbidities in patients diagnosed with chronic HBV infection encompassed hypertension, liver related disorders including cirrhosis of liver and hepatic fibrosis, alcohol dependence, tobacco dependence syndrome and type 2 diabetes mellitus. In patients with HCV infection, comorbidities at the index date and one year prior included hypertension, cirrhosis of liver, portal hypertension and esophageal varices without bleeding, tobacco dependence syndrome and alcohol dependence/abuse. Frequently prescribed medications for both infections included amoxicillin, paracetamol, and omeprazole.

The proportion of chronic HBV infection in the study population based on data from primary care databases was low and ranged from 0.01% to 0.16%. Similarly, the proportion of chronic HCV infection in the study population based on the data from primary care databases ranged from 0.01% to 0.59%.

Discussion

This study delved into the characteristics of patients with chronic HBV or chronic HCV. The findings revealed varying number of patients diagnosed with chronic HBV or chronic HCV initiating or undergoing treatment with interferons or antiviral medications across databases. Furthermore, the findings highlighted the most common drug-specific treatments in chronic HBV or chronic HCV. At the population level, the examination of proportion yielded varying number of patients diagnosed with chronic HBV or chronic HCV. The proportion of patients with chronic HBV and chronic HCV remained low in the study population covered by the primary care databases.

4 LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical Classification
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EBB	Estonian Biobank
ECDC	The European Centre for Disease Prevention and Control
EGCUT	Estonian Genome Center at the University of Tartu
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
GP	General Practitioner
HBV	Hepatitis B viral infection
HCV	Hepatitis C viral infection
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
IPCI	Integrated Primary Care Information Project
OHDSI	Observational Health Data Sciences and Informatics
OP	Outpatient
OMOP	Observational Medical Outcomes Partnership
SNOMED	Systematized Nomenclature of Medicine
STD	Sexually Transmitted Disease
WHO	World Health Organization

5 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason

6 MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	19th October 2023	
Final Study Protocol	6th December 2023	
Creation of Analytical code	6th November 2023	
Execution of Analytical Code on the data	December 2023	December 2023
Interim Study Report (if applicable)	Not applicable	
Draft Study Report	18th December 2023	18th January 2024
Final Study Report	To be confirmed	
Draft Manuscript (if agreed on)		
Final Manuscript (if agreed on)		

7 RATIONALE AND BACKGROUND

Viral hepatitis is a major public health concern, affecting millions of people worldwide; with hepatitis B and hepatitis C resulting in chronic infections. The World Health Organization (WHO) estimates that 354 million people worldwide live with hepatitis B or C (5) and that in 2019 1.5 million people were newly infected with chronic hepatitis B, and 1.5 million people were newly infected with chronic hepatitis C.(6) In 2021, 16,187 cases of hepatitis B virus (HBV) and 14,560 cases of hepatitis C infections were reported in EU/EEA Member States, corresponding to a crude rate of 4.7 cases per 100 000 population and 4.1 cases per 100 000 population respectively.(7, 8) WHO estimates that 1.1 million deaths occurred in 2019 due to these infections and their complications including liver cancer, cirrhosis, and other conditions.(6)

HBV infection is primarily transmitted through percutaneous inoculation or mucosal exposure to infectious body fluids. Most immunocompetent adults infected with HBV can clear the virus, but some develop chronic infection. HCV infection mainly transmitted through contact with infected blood and, less commonly, through sexual intercourse and perinatal transmission. About 30% of individuals who are acutely infected with HCV spontaneously clear the virus within 6 months, while the rest develop chronic infection. Chronic HBV/HCV infections are often asymptomatic but can lead to severe complications including cirrhosis and/or hepatocellular carcinoma if untreated.

Diagnosis of chronic HBV/HCV infections requires appropriate history and laboratory testing for serological markers. Specifically, there are multiple serologic markers to determine HBV status and to denote a possible chronic HBV infection, while the diagnosis of HCV infection includes detection of antibodies to HCV which indicate if someone has ever been exposed to the virus as well as direct testing for HCV RNA to identify active cases of infection. (9, 10)

Treatment of chronic HBV/HCV infection aims to suppress viral replication, reduce liver inflammation, and prevent disease progression. Antiviral therapies, including nucleoside analogues and interferons, are available. The choice of treatment depends on various factors, such as the severity of liver disease, and differs for each infection. The mainstay of therapy for HCV infection was injectable pegylated interferon and ribavirin, with a modest cure rate ranging from 40% to 60% and high rates of adverse events. However, the introduction of highly effective Direct-Acting Antivirals (DAAs) for chronic HCV treatment showed improvement in cure rates to 90% – 97%.(9, 10)

WHO's global hepatitis strategy, endorsed by all WHO Member States, set global targets of achieving 90% reduction in new chronic hepatitis B and C infections, a 65% reduction in deaths from hepatitis B and hepatitis C, and treatment of 80% of people living with these infections by 2023.(5) The 2016 WHO Global Health Sector Strategy (GHSS) aims to eliminate viral hepatitis by 2030 (11) and WHO EU has developed a hepatitis action plan to steer the implementation of the GHSS in Europe.(3) The European Centre for Disease Prevention and Control (ECDC) has developed a monitoring system for HBV/HCV aligned with indicators and targets of the GHSS and the WHO European Region Action Plan.(4) Nevertheless, comprehensive data on the prevalence of chronic HBV/HCV infections and utilization of antiviral treatments for chronic HBV/HCV infections are important to monitor progress towards the elimination targets related to treatment and to support effective planning of prevention and control activities by countries.

To date, data collected by EU Member States and reported to ECDC come from different sources with different levels of quality and completeness. Several reasons contribute to this heterogeneous data collection such as the lack of standardised or electronic systems to collect data across countries. Thus, robust, and timely data at national or subnational level generated through DARWIN EU will add to the available body of evidence and/or address current evidence gap.

8 RESEARCH QUESTION AND OBJECTIVES

Research question:

What were the characteristics of patients with chronic HBV or chronic HCV infection?

Study objectives

1. To report the number and percentage of patients diagnosed with chronic HBV or chronic HCV infection who initiated treatment with interferon or any specified antivirals, stratified by age, sex, calendar year, and country/database throughout the study period (2012 - 2022).
2. To report the number and percentage of patients diagnosed with chronic HBV or chronic HCV infection who underwent treatment with any specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
3. To characterize patients with chronic HBV or chronic HCV infection at the initiation of treatment with interferon or specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
4. To estimate the proportion of all patients with chronic HBV or chronic HCV infection, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).

Table 1. Primary and secondary research questions and objective

Objectives:	To estimate the number and percentage of individuals initiating (Objective 1) or undergoing (Objective 2) treatment with interferon or any of the specific antivirals of interests among patients with chronic HBV or chronic HCV infection, stratified by age, sex, calendar year and country/database during the study period (2012 - 2022). To characterize patients with chronic HBV or chronic HCV infection at the initiation of treatment with interferon or specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022) (objective 3). To estimate the proportion of patients with chronic HBV or chronic HCV infection, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022) (objective 4).
Hypothesis:	Not applicable
Population ***(mention key inclusion-exclusion criteria):***	Population level drug utilisation: all patients with chronic HBV or chronic HCV infection in the respective databases from 2012 to 2022 (or the latest available date if earlier. Patient-level drug utilization: all patients diagnosed with chronic HBV or chronic HCV infection who are new users of interferon or any of the specific antivirals of interests in the respective databases from 2012 to 2022 (or the latest available date if earlier). Population level descriptive epidemiology: all individuals in the respective databases from 2012 to 2022 (or the latest available date if earlier).
Exposure:	Therapeutic drug classes of interest: • Peginterferon: Cepeginterferon alfa-2b, Peginterferon -α-2a, Peginterferon -α-2b,Peginterferon alfacon-2, Interferon alpha-2a, and Interferon alpha-2b. • Antivirals for treatment of HBV infections: Adefovir dipivoxil, Entecavir, Telbivudine, Tenofovir alafenamide, Tenofovir disoproxil fumarate, Lamivudine, and Bulevirtide • Antivirals for treatment of HCV infections: Asunaprevir, Beclabuvir, Boceprevir, Coblopasvir, Daclatasvir, Dasabuvir, Elbasvir, Faldaprevir, Glecaprevir, Grazoprevir, Ledipasvir, Ombitasvir, Paritaprevir, Pibrentasvir, Ribavirin, Ritonavir, Simeprevir, Sofosbuvir, Telaprevir, Velpatasvir and Voxilaprevir
Comparator:	None
Outcome:	None

Time *(when follow up begins and ends):*	Population level drug utilisation: Follow-up started on the date of diagnosis of chronic HBV or chronic HCV infection during the study period. Patient-level drug utilization: Follow-up started on the date of incident prescription of interferon or any of the specific antivirals of interests. Population-level descriptive epidemiology: Follow-up started when patients fulfil inclusion criteria (i.e., present in the database between 1st of January 2012 and 31st of December). End of follow-up was defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever came first.
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: CHUBX (France), CPRD GOLD (UK), EBB (Estonia), IQVIA DA Germany (Germany), IMASIS (Spain) and IPCI (the Netherlands).
Main measure of effect:	The number and percentage of users of peginterferon or any of the specific antivirals of interests in patients with chronic HBV or chronic HCV infection. Large scale characterization of patients with chronic HBV or chronic HCV infection initiating treatment with interferon or any of the specific antivirals of interests. Number and proportion of patients with chronic HBV or chronic HCV infection in the general population.

9 RESEARCH METHODS

9.1 Study Type and Study Design

A cohort study was conducted using routinely collected health data from 6 databases. The study comprised three consecutive parts:

- *Cohort analysis* was used to estimate the number and percentage of individuals initiating (Objective 1) or undergoing (Objective 2) treatment with interferon or any of the specific antivirals of interests among patients with chronic HBV or chronic HCV infection.
- *New drug user cohort study* was used to characterize patients with chronic HBV or chronic HCV infection at the time of treatment initiation with interferon or any of the specific antivirals of interests (Objective 3).
- *Population-level cohort study* was conducted to assess the proportion of patients with chronic HBV or chronic HCV infection in the general population (Objective 4).

Table 2. Description of Potential Study Types and Related Study Designs

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Population Level DUS	Population Level Cohort	Off the shelf (C1)
Patient Level DUS	New drug/s user cohort	Off the shelf (C1)
Population-level descriptive epidemiology	Population-level cohort	Off the shelf (C1)

9.2 Study Setting and Data Sources

This study was conducted using routinely collected data from 6 databases in 6 European countries (5 EU countries and United Kingdom). All databases were previously mapped to the OMOP Common Data Model (CDM).

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Integrated Primary Care Information Project (IPCI), The Netherlands

For this study, we selected six databases from ten databases available in the DARWIN EU® Database Catalogue. The selection process was based on two primary criteria: data reliability and relevance to the research question at hand. These selected databases demonstrated substantial record counts for chronic HBV or chronic HCV infection and the drugs of interest. Moreover, they offered a good geographical spread, ensuring representation from diverse regions of Europe.

These suggested databases met the requirements for conducting a patient-level characterization, patient-level drug utilization study and population-level descriptive epidemiology, enabling us to characterize chronic HBV or chronic HCV infection. Additionally, by including databases from different settings, we captured both inpatient and outpatient drug prescriptions. The estimation of proportion of patients with chronic HBV or chronic HCV infection was confined to primary care databases exclusively. IQVIA DA Germany includes primary healthcare level but also outpatient specialist consultations. Therefore, Objective 4 of the study was not investigated within the hospital databases IMASIS and CHUBX.

Information on data sources used with a justification for their choice in terms of ability to capture the relevant data is described in a **Table 3**.

When it came to assessing the reliability of data sources, the data partners were asked to describe their internal data quality process on the source data as part of the DARWIN EU onboarding procedure. To further ensure data quality, we utilized the Achilles tool, which systematically characterized the data and presented it in a dashboard format that was inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, measurement value distribution was be compared against expectations for the data.

Additionally, the data quality dashboard (DQD) provided more objective checks on plausibility consistently across the data sources. In terms of relevance, a more general-purpose diagnostic tool, "*CohortDiagnostics*", was developed. This package evaluated phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provided additional insights into cohort characteristics, record counts and index event misclassification. Furthermore, timeliness was guarded by extracting the release dates for each dataset in the network and monitoring when data were out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it was important to have clear understanding of the time period covered by each released database, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contained a 'data density' plot. This plot displayed the number of records per OMOP domain on a monthly basis. This allowed to get insights when data collection started, when new sources of data were added and when until when data was included.

Table 3. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
France	CHUBX	Database covers hospital care settings where interferon or any specified antivirals may be prescribed/dispensed.	Secondary care (in and outpatients)	EHR	2.1 million	05/05/2023
UK	CPRD GOLD	Database covers primary care where interferon or any specified antivirals may be prescribed/dispensed.	Primary care	EHR	3 million	20/03/2023
Estonia	EBB	Database covers information from primary care and secondary care setting (insurance claims, digital prescriptions) where interferon or any specified antivirals are prescribed.	Biobank	Claims data	0.2 million	20/03/2023
Germany	IQVIA DA Germany	Databases covers primary care / outpatient specialist care setting interferon or any specified antivirals may be prescribed/dispensed.	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023
Spain	IMASIS	Database covers hospital care settings where interferon or any specified antivirals may be prescribed/dispensed.	Secondary care (in and outpatient)	EHR	0.6 million	31/12/2022
The Netherlands	IPCI	Database covers primary care where interferon or any specified antivirals may be prescribed/dispensed.	Primary care	EHR	1.4 million	21/03/2023

Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).(12)

Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD (13) comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients. In the regional distribution of currently contributing practices, the majority are from Scotland, accounting for 52% of all participating practices, while Wales contributes 28%. The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data is available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process. CPRD GOLD will be onboarded as Data Partner for DARWIN EU® in 2023.

Estonian Biobank – University of Tartu (Estonia)

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT). Its cohort size is currently close to 200,000 participants (“gene donors” >= 18 years of age) which closely reflects the age, sex and geographical distribution of the Estonian adult population. Genomic GWAS analysis has been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases and causes of death from national sources for each donor.

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings.(14) Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patients visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to GPs, Pediatric Medicine, Obstetrics / Gynecology, Orthopedic Surgery, Dermatology, Otolaryngology, Diabetic medicine, Urology, Neuropsychiatry, Cardiology, Gastroenterology, Pulmonary Disease, Rheumatology, Neurology, Psychotherapy, Child and Adolescent Psychiatry and Psychiatry practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

Integrated Primary Care Information Project (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.(15) The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996.(15) The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g., exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board.(15)

9.3 Study Period

The study period was from 1st of January 2012 until the earliest of 31st December 2022 or the respective data lock for the last database update (see **Table 3** for more details on each database's latest data).

9.4 Follow-up

To calculate the number and percentage of users of interferon or any of the specific antivirals of interests, follow-up started on the date of new diagnosis of chronic HBV or chronic HCV infection until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever came first.

For the patient-level utilization, study participants were followed up from the date of incident prescription of interferon or any of the specific antivirals of interests (index date) until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever came first.

For the population-level descriptive epidemiology, follow up started when patients fulfilled inclusion criteria i.e., present in the database between 1st of January 2012 and 31st of December 2022. End of follow-up was defined as the earliest loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever came first.

The operational definition of start of follow-up is described in **Table 4**.

Table 4. Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…[3]	Measurement characteristics/ validation	Source of algorithm
All patients from the database eligible for the study (i.e., present in the database during study period) and diagnosed with chronic HBV or chronic HCV infection – analysis of incident use of interferon or any of the specific antivirals of interests*	Date of diagnosis of chronic HBV or chronic HCV infection	Multiple	Incident	[-Inf., ID]	IP and OP	RxNorm	n/a	Use of interferon or any of the specific antivirals of interests	n/a	n/a
All patients from the database eligible for the study (i.e., present in the database during study period) and diagnosed with chronic HBV or chronic HCV infection – analysis of prevalent use of interferon or any of the specific antivirals of interests**	Date of diagnosis of chronic HBV or chronic HCV infection	Multiple	Prevalent	None	IP and OP	RxNorm	n/a	n/a	n/a	n/a
All patients from the database eligible for the study and diagnosed with chronic HBV or chronic HCV infection initiating treatment with interferon or any	Initiation of treatment with interferon or any of the specific antivirals of interests in patients diagnosed	Single entry	Incident	[-∞, ID]	IP and OP	SNOMED and RxNorm	n/a	Use of interferon or any of the specific	n/a	n/a

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…[3]	Measurement characteristics/ validation	Source of algorithm
of the specific antivirals of interests – Large scale characterisation	with chronic HBV or chronic HCV infection							antivirals of interests		
All patients from the database eligible for the study – analysis to estimate the proportion of patients with chronic HBV or chronic HCV infection	Patients present in the database from 2012 to 2022 (or the latest available date if earlier.	Multiple entries	Prevalent	n/a	IP and OP	SNOMED	n/a	n/a	n/a	n/a

[1] IP = inpatient, [3]Incident with respect to = provide a brief text description of what the patient is required to be incident to (e.g. incident user of Drug X), OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

*Incident use of interferon or any of the specific antivirals of interests – refers to patients diagnosed with chronic HBV or chronic HCV infection who initiated treatment with interferon or any specified antivirals in the study period.

**Prevalent use of interferon or any of the specific antivirals of interests – refers to patients diagnosed with chronic HBV or chronic HCV infection who underwent treatment with any specified antivirals in the study period.

9.5 Study Population with inclusion and exclusion criteria

For population-level drug utilization (Objective 1 and 2), the study population included all patients with chronic HBV or chronic HCV infection in the respective databases from 2012 to 2022 (or the latest available date if earlier).

For patient-level drug utilization (Objective 3), the study population included all patients with chronic HBV or chronic HCV infection who were new users of interferon or any of the specific antivirals of interests in the respective databases from 2012 to 2022 (or the latest available date if earlier), and no record of using the respective drugs in the year preceding the index date.

For population-level descriptive epidemiology (Objective 4), the study population included all individuals identified in the database from 2012 to 2022.

Table 5. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Chronic HBV or chronic HCV infection	Patients diagnosed with chronic HBV or chronic HCV infection during the study period. Concept sets in Table 1 and Table 2 of Appendix I	After	[-∞,0]	IP and OP	SNOMED	primary and secondary diagnosis code	All individuals within selected databases	n/a	n/a
Washout period	New users will be required to have no used interferon or any of the specific antivirals of interests before a "new" prescription	After	[-∞,ID]	IP and OP	n/a	n/a	All patients with chronic HBV/HCV infection	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable. Order of application – after (i.e., the first possible study entry date is first selected and then inclusion criteria are applied)

[2] For hospital databases and the EBB, both primary and secondary diagnosis codes will be used (thus, not only primary code for reason of admission).

9.6 Variables

9.6.1 Exposure

Exposure of interest was use (during study period) of interferon or any of the specific antivirals of interests:

- Interferon: Cepeginterferon alfa-2b, Peginterferon -α-2a, Peginterferon -α-2b, Peginterferon alfacon-2, Interferon alpha-2a, and Interferon alpha-2b.
- Antivirals for treatment of HBV infections: Adefovir dipivoxil, Entecavir, Telbivudine, Tenofovir alafenamide, Tenofovir disoproxil fumarate, Lamivudine, and Bulevirtide
- Antivirals for treatment of HCV infections: Asunaprevir, Beclabuvir, Boceprevir, Coblopasvir, Daclatasvir, Dasabuvir, Elbasvir, Faldaprevir, Glecaprevir, Grazoprevir, Ledipasvir, Ombitasvir, Paritaprevir, Pibrentasvir, Ribavirin, Ritonavir, Simeprevir, Sofosbuvir, Telaprevir, Velpatasvir and Voxilaprevir

Details of exposure are described in **Table 6**.

Table 6. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Incident with respect to…[3]	Measurement characteristics/ validation	Source of algorithm
Interferon or any of the specific antivirals of interest	List provided in 9.6.1 section and concept sets in Table 3 of Appendix II	[-Inf., ID]	Calendar year	Biobank, primary and secondary care	RxNorm	n/a	All patients diagnosed with chronic HBV or chronic HCV infection in the database during the study period	Previous use of interferon or any of the specific antivirals of interests	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable; [2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter); [3] Provide brief description on what patients is required to be incident to (e.g. when identifying incident users of drug, requirement may be that the patient is incident with respect to that drug).

9.6.2 Outcome

n/a

9.6.3 Other covariates, including confounders, effect modifiers and other variables (where relevant)

The study covariates for stratification included:

- Calendar year
- Age categories:
  - Children and adolescents: 1-17
  - Young adults: 18-44
  - Middle aged adults: 45-64
  - Older adults: 65 and over
- Sex: male of female

A list of pre-specified comorbidities and comedication was used for large-scale patient characterisation, identified as concept codes/descendants.

The following conditions were of interest (i.e., frequency of comorbidities was assessed at index date):

- Liver cirrhosis
- Alcoholic fatty liver
- Human immunodeficiency virus infection
- Sexually transmitted disease (STD)
- Diabetes mellitus
- Cardiovascular disease
- Hypertension
- Chronic kidney disease (CKD)
- Alcoholism

The following medication was of interest: Top 10 prevalent drugs in each data source.

Large-scale characterisation of baseline characteristics: the operational definition of the covariates is described in the **Table 7** below. Index date was the start of the (first) incident prescription during the study period. From this large-scale characterisation, we reported the top 10 of most frequent comorbidities.

Concept sets for comorbidities of interest are displayed in **Table 4** of **Appendix III**.

Table 7. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Comorbidities	Large-scale patient-level characterisation of new users with regard to underlying comorbidities	Counts	At index date (ID) and 365 days before ID	Primary care, secondary care and biobank	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Concomitant medication	Large-scale patient-level characterisation of new users with regard to concomitant medication	Counts	At index date (ID) and 365 days before ID	Primary care, secondary care and biobank	RxNorm	n/a	Persons with new use during the study period	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.7 Study size

No sample size was calculated for this study, as our primary focus was to describe characteristics of patients with chronic HBV or chronic HCV infection, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts with chronic HBV or chronic HCV infection ranged from 200 (CPRD GOLD) to 14,700 (IQVIA DA Germany) for HBV and from 200 (IPCI) to 17,000 (IQVIA DA Germany) for HCV infection.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources and on a simulated set of patients and quality control checks were performed. After all the tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the - by default - aggregated results.

The study results of all data sources were checked after which they were made available to the team and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical Methods

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the Complete Catalogue of Data Analysis which describes the type of analysis in function of the study type.

Table 8. Description of Study Types and Type of analysis

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Population level DUS	Off-the-shelf (C1)	- Number and percentage of users of Peginterferon or any of the specific antivirals of interest
Patient Level DUS	Off-the-shelf (C1)	- Characterisation of patient-level features
Population-level descriptive epidemiology	Off-the-shelf (C1)	- Proportion of patients with chronic HBV or chronic HCV infection

9.9.1 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts <5 were masked.

9.9.2 Main Statistical Methods

R-packages

We used the R package "*DrugUtilization*" for the patient-level drug utilization analyses including patient-level characterization, and "*PatientProfile"* package for the population-level estimation of drug utilization and the proportion of chronic HBV of chronic HCV infection.

Drug exposure calculations

Drug eras were defined as follows: Exposure started at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 30 days. The time between the two joined eras was considered as exposed by the first era as shown in **Figure 1**, first row. Note: dose was not considered for this study.

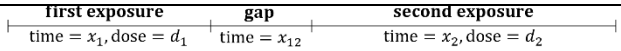
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$
				

Figure 1: Gap era joint mode

New user cohorts

New users were selected based on their first prescription of the respective drug of interest after the start of the study. New users were required to not have been exposed to the drug of interest anytime prior to the current prescription. If the start date of a prescription did not fulfil the exposure washout criteria of "anytime prior", the whole exposure was eliminated.

9.9.3 Methods to derive parameters of interest

Calendar time

Calendar time was based on the calendar year of the index prescription.

Age

Age at index date (date of diagnosis of chronic HBV or chronic HCV or date of new prescribing of the drug of interest) was calculated using January 1st of the year of birth as proxy for the actual birthday. Age categories are as following:

- Children and adolescents: 1-17
- Young adults: 18-44
- Middle aged adults: 45-64
- Older adults: 65 and over

Sex

Results for population-level analyses were presented stratified by sex.

Characterization of patient-level features

Objective 3: Large scale patient characterisation before/on index date (= date of prescription) was provided for patients with chronic HBV or chronic HCV infection initiating treatment with interferon or any of the specific antivirals of interest. In these patients, the number and proportion of patients with the comorbidities and drugs of interest (see section on covariates) was described at index date and in the one year prior to the index date (-365 to -1 day before index date).

9.9.4 Methods for proportion calculation

Proportion calculations

Proportion calculations were conducted separately for interferon or any of the specific antivirals of interest.

Objective 1: Proportion was calculated by dividing the number of patients with chronic HBV or chronic HCV infection who initiated treatment with interferon or any specified antivirals by the total number of patients with chronic HBV or chronic HCV infection at a particular time point.

Methodology for Proportion Calculation:

Numerator: the number of patients with chronic HBV or chronic HCV infection who initiated treatment with interferon or the specified antivirals during the specified time period.

Denominator: the total number of patients with chronic HBV or chronic HCV infection at the same particular time point.

Proportion (%) = (Number of Patients Initiating Treatment / Total Number of Patients with Chronic HBV or chronic HCV Infection) * 100

Objective 2: Proportion was calculated by dividing the number of patients with chronic HBV or HCV infection being on treatment with interferon or any specified antivirals by the total number of patients with chronic HBV or chronic HCV infection at a particular time point.

Methodology for Proportion Calculation:

Numerator: the number of patients with chronic HBV or chronic HCV infection that underwent treatment with interferon or the specified antivirals during the specified time period.

Denominator: the total number of patients with chronic HBV or chronic HCV infection at the same particular time point.

Proportion (%) = (Number of Patients That Underwent Treatment / Total Number of Patients with Chronic HBV or chronic HCV Infection) * 100

Objective 4: Proportion was calculated by dividing the number of patients with chronic HBV or chronic HCV infection by the total number of individuals present in each data source at a particular time point.

Methodology for Proportion Calculation:

Numerator: the number of patients with chronic HBV or chronic HCV infection during the specified time period.

Denominator: the total number of individuals present in each data source at the same particular time point.

Proportion (%) = (Total Number of Patients with chronic HBV or chronic HCV Infection / Total Number of Individuals present in each data source) * 100.

9.9.5 Sensitivity Analysis

None

9.10 Evidence synthesis

Results from analyses described in section 9.9 were presented separately for each database and no meta-analysis of results was conducted.

9.11 Deviations from the protocol

None

10 DATA MANAGEMENT

10.1 Data management

All databases were mapped to the OMOP common data model. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and was described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contain aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

10.2 Data storage and protection

For this study, participants from various EU member states processed personal data from patients which was collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study were already used for pharmaco-epidemiological research and had a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results.

11 QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners would have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and is evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining cohorts for drugs, a systematic search of possible codes for inclusion was identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). A pharmacist and/or medical doctor reviews the codes of the interest. This software allows the user to define a search strategy and using this then queries the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, DrugExposureDiagnostics(16) was run if needed to assess the use of different codes across the databases contributing to the study.

The study code was based on two R packages currently being developed to (1) characterize population-level estimation of drug utilisation and (2) characterize patient-level drug utilization using the OMOP common data model. These packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package was made publicly available via GitHub.

12 RESULTS

The results of this study can be assessed through an interactive web-application (“shiny app”) at https://data-dev.darwin-eu.org/EUPAS107650-broad/.

12.1 Population-level drug utilization

12.1.1 Participants

The number of individuals diagnosed with chronic HBV and chronic HCV infection across different databases from 2012 to 2022 is outlined in **Table 9**. In total, the participating databases collectively included 19,352 patients diagnosed with chronic HBV infection and 24,421 patients diagnosed with chronic HCV infection during the specified period.

The database that made the most substantial contribution to patients diagnosed with chronic HBV infection was IQVIA DA Germany (n=12,154, 62.80%). In contrast, primary care databases including CPRD GOLD (n=1,154, 5.96%) and IPCI (n=1,285, 6.64%), EBB (n=344, 1.78%), as well as hospital databases CHUBX (n=2,215, 11.45%) and IMASIS (n=2,200, 11.37%) had comparatively smaller contributions to the study population.

Similarly, for chronic HCV infection, reflecting in the main size of the database, IQVIA DA Germany (n=12,244, 50.14%) made the most substantial contribution to patients, followed by hospital databases CHUBX (n=4,623, 18.93%) and IMASIS (n=4,598, 18.83%). In contrast, CPRD GOLD (n=1,535, 6.29%), EBB (n=1,226, 5.02%) and IPCI (n=195, 0.80%) had smaller contribution to the overall study population.

The trends in number of patients diagnosed over time has shown variation over the years across different databases. For chronic HBV, there is a noticeable upward trend in the number of diagnosed in most databases. Specifically, CHUBX, EBB, IMASIS, IPCI, and IQVIA DA Germany databases consistently show an increase in diagnosed cases over this period. CPRD GOLD, on the other hand, exhibits a fluctuating trend with slight variations from year to year but no clear overall pattern. For chronic HCV, in particular, databases such as CHUBX, CPRD GOLD, EBB, IMASIS, and IQVIA DA Germany exhibit a similar pattern of an increase in numbers diagnosed with chronic HCV until around 2019, followed by either a stabilization or slight decrease in the number of diagnoses in 2020 and 2021. On the other hand, IPCI shows a consistent increase in numbers diagnosed from 2012 to 2021 without any notable decline. Detailed results can be assessed through an interactive web-application ("shiny app") at https://data-dev.darwin-eu.org/EUPAS107650-broad/.

Table 9. Number of individuals with chronic HBV and chronic HCV infection during the study period, per database

	CPRD GOLD UK	CHUBX France	EBB Estonia	IMASIS Spain	IPCI Netherlands	IQVIA DA Germany	Total N
Database population	17,216,081	2,410,703	209,457	1,066,675	2,781,698	41,974,403	65,659,017
Database population between 01/01/2012 and 31/12/2022	10,433,005	1,937,050	209,457	623,341	2,680,988	33,702,562	49,586,403
Chronic HBV infection, n (%) (percentage of database population 2012-2022)	1,154 (0.01)	2,215 (0.11)	344 (0.16)	2,200 (0.35)	1,285 (0.05)	12,154 (0.04)	19,352
Chronic HCV infection, n (%) (percentage of database population 2012-2022)	1,535 (0.01)	4,623 (0.24)	1,226 (0.59)	4,598 (0.74)	195 (0.01)	12,244 (0.04)	24,421

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

Hospital databases are indicated in green.

12.1.2 Descriptive Data

12.1.2.1 Demographic characteristics of patients with chronic HBV infection

Table 10 provides a comprehensive overview of demographic characteristics of patients diagnosed with chronic HBV infection across databases between 2012 and 2022.

The study population exhibited significant variability in the period covered by prior and future observation across databases. Prior observation time varied notably, with IQVIA DA Germany having the shortest median prior observation of 224 days (IQR: 0 - 1,984) and EBB presenting the longest median previous observation of 4,443 days (IQR: 3,422 - 5,737). The future observation after hepatitis diagnosis also demonstrated considerable diversity, ranging from CPRD GOLD's shortest median follow-up of 816 days (IQR: 349 - 1,759) to EBB's longest median follow-up of 2,029 days (IQR: 794 - 3,152).

The median age of patients diagnosed with chronic HBV infection ranged from 37 (CPRD GOLD) to 53 years (EBB). The age range was broadest in IMASIS, spanning from 0 to 99 years. Age ranges were comparable in CPRD GOLD (0 – 90), IPCI (0 - 90), IQVIA DA Germany (0 - 96) and CHUBX (1 - 95). In contrast, EBB had a slightly narrower age range (13 - 89). In terms of age groups, the age distribution of patients across different databases varied. The majority of patients belonged to age category of 18 to 44 years and 45 to 64 years, with a smaller proportion in <18 and ≥ 65 years age group. More specifically, majority of patients in CHUBX, EBB, IMASIS and IQVIA DA Germany belonged to 45 to 64-year age category (39.7%, 55.2%, 38.5%, 41.6% respectively), while CPRD GOLD and IPCI exhibited substantial representations in the 18 to 44-year category (70.8% and 51.3%, respectively).

In terms of sex distribution across databases, the proportion of males diagnosed with chronic HBV infection was higher than for females, with proportions ranging from 51.5% to 65.7% except for the EBB database where proportion of males was 38.4%. Particularly, IMASIS reported the highest proportion of male patients diagnosed with chronic HBV infection (n=1,445, 65.7%) compared to other databases.

Table 10. Demographic characteristics of patients diagnosed with chronic HBV infection during the study period, per database

	CPRD GOLD UK	CHUBX France	EBB Estonia	IMASIS Spain	IPCI Netherlands	IQVIA DA Germany
Number of patients	1,154	2,215	344	2,200	1,285	12,154
Prior observation (days), Median (IQR)	586 (95 – 2,028)	1,407 (161 – 3,094)	4,443 (3,422 – 5,737)	3,710 (735 – 7,506)	826 (312 – 1,642)	224 (0 – 1,984)
Future observation (days), Median (IQR)	816 (349 – 1,759)	1,319 (479 – 2,554)	2,029 (794 – 3,152)	1,121 (360 – 1,978)	1,425 (605 – 2,445)	851 (169 – 1,793)
Age at index (years), Median (IQR)	37 (30 - 46)	50 (35 - 62)	53 (42 - 61)	50 (39 - 64)	42 (33 - 53)	48 (37 - 59)
Age range (years)	0 - 90	1 - 95	13 - 89	0 - 99	0 - 90	0 - 96
Age group (years), n (%)						
• 1 to 17	19 (1.6)	42 (1.9)	<5	<5	50 (3.9)	158 (1.3)
• 18 to 44	817 (70.8)	837 (37.8)	95 (27.6)	821 (37.3)	659 (51.3)	4,959 (40.8)
• 45 to 64	261 (22.6)	879 (39.7)	190 (55.2)	846 (38.5)	455 (35.4)	5,061 (41.6)
• ≥ 65	55 (4.8)	457 (20.6)	56 (16.3)	529 (24.0)	115 (8.9)	1,970 (16.2)
Sex, n (%)						
• Female	547 (47.4)	964 (43.5)	212 (61.6)	755 (34.3)	623 (48.5)	5,665 (46.6)
• Male	607 (52.6)	1,251 (56.5)	132 (38.4)	1,445 (65.7)	662 (51.5)	6,477 (53.3)
• Missing	0	0	0	0	0	12 (0.1)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, IQR = interquartile range;

Hospital databases are indicated in green.

12.1.2.2 Demographic characteristics of patients with chronic HCV infection

Table 11 provides demographic characteristics of patients diagnosed with chronic HCV infection across databases from 2012 to 2022.

The study population demonstrated notable variability in the prior and future observation across databases. IQVIA DA Germany had the shortest median prior observation time of 66 days (IQR: 0 - 1,714), while IMASIS presented the longest median prior observation time of 5,4941 days (IQR: 1,361 – 8,019). Similarly, IQVIA DA Germany had shortest median follow-up of 601 days (IQR: 100 - 1,810), contrasting with to EBB's longest median follow-up of 2,650 days (IQR: 1,482 - 3,396).

The median age of patients diagnosed with chronic HCV infection ranged from 41 in CPRD GOLD to 54 years in IPCI and CHUBX. The age range was broadest in IQVIA DA Germany, spanning from 0 to 97 years. Age ranges were comparable in CHUBX (3 - 98) and IMASIS (3 - 99), whereas the age range was narrower in CPRD GOLD (2 - 88), EBB (18 - 88) and IPCI (17 - 88). In context of age groups, majority of patients in CHUBX, IMASIS, IPCI and IQVIA DA Germany belonged to 45 to 64-year age category (57.9%, 44%, 60.5%, 46.8% respectively), while CPRD GOLD and EBB exhibited substantial representations in the 18 to 44-year category (60% and 47.1%, respectively).

In terms of sex distribution across databases, the proportion of males diagnosed with chronic HCV infection was higher than for females. The proportions varied, ranging from 58% in IQVIA DA Germany to 68.3% in CPRD GOLD. In contrast, the proportion of male patients diagnosed with of chronic HCV infection in EBB (40%) was lower that the proportion of females.

Table 11. Demographic characteristics of patients diagnosed with chronic HCV infection during the study period, per database

	CPRD GOLD UK	CHUBX France	EBB Estonia	IMASIS Spain	IPCI Netherlands	IQVIA DA Germany
Number of HCV patients	1,535	4,623	1,226	4,598	195	12,244
Prior observation (days), Median (IQR)	1,909 (344 - 4030)	2,432 (335 – 3,276)	3,836 (3,138 – 5,009)	5,494 (1,361 – 8,019)	859 (308 – 1,786)	66 (0 – 1,714)
Future observation (days), Median (IQR)	1,121 (429 – 2,223)	1,572 (449 – 2,904)	2,650 (1,482 – 3,396)	1,052 (284 – 2,171)	1,177 (503 – 2,108)	601 (100 – 1,810)
Age at index (years), Median (IQR)	41 (33 - 50)	54 (47 - 64)	46 (34 - 55)	53 (44 - 69)	54 (46 - 60)	51 (41 - 61)
Age range (years)	2 - 88	3 - 98	18 - 88	3 - 99	17 - 88	0 - 97
Age group (years), n (%)						
• 1 to 17	8 (0.5)	5 (0.1)	0 (0)	8 (0.2)	<5	108 (0.9)
• 18 to 44	921 (60)	794 (17.2)	578 (47.1)	1,209 (26.3)	45 (23.1)	4,069 (33.2)
• 45 to 64	545 (35.5)	2,678 (57.9)	532 (43.4)	2,025 (44)	118 (60.5)	5,730 (46.8)
• ≥ 65	61 (4)	1,146 (24.8)	116 (9.5)	1,356 (29.5)	31 (15.9)	2,326 (19)
Sex, n (%)						
• Female	486 (31.7)	1,680 (36.3)	735 (60)	1,616 (35.2)	76 (39)	5,091 (42)
• Male	1,049 (68.3)	2,943 (63.7)	491 (40)	2,982 (64.9)	119 (61)	7,150 (58)
• Missing	0	0	0	0	0	<5

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HCV = hepatitis C viral infection; IQR = interquartile range.

Hospital databases are indicated in green.

12.1.3 Outcome Data and Main Results

12.1.3.1 Initiation of interferon or antiviral treatment in chronic HBV infection

Table 12 outlines the initiation of interferon and/or specified antivirals in patients diagnosed with chronic HBV infection over the study period, stratified by respective databases. The primary emphasis is on the new use of any therapeutic intervention, encompassing both interferon and antiviral treatments. Furthermore, the analysis delves into therapeutic drug classes, distinguishing between antivirals and interferons individually, as well as providing granularity on drug-specific treatments.

The initiation of any therapeutic intervention including interferons or antiviral treatment in patients diagnosed with chronic HBV infection varied across different databases during the study period. Prescription rates ranged from 2.95% in CPRD GOLD (n=34) to 7.87% in IQVIA DA Germany (n=956) in primary care databases, from 11.73% in IMASIS (n=258) to 13.45% in CHUBX (n=298) in hospital databases to 15.41% in EBB (n=53). A similar pattern was observed when focusing on therapeutic drug classes, particularly antivirals, where initiation rates ranged from 2.86% in CPRD GOLD (n=33) to 7.83% in IQVIA DA Germany (n=952) in primary care datasets, from 11.59% in IMASIS (n=255) to 13.41% in CHUBX (n=297) for hospital databases and biobank. Initiation of interferon treatment was generally low, registering at less than 5% in EBB (n=15, 4.36%), IMASIS (n=11, 0.50%) and IQVIA DA Germany (n=13, 0.11%), with minimal or no users in other databases.

Further exploration into drug-specific treatments for the initiation of treatment in chronic HBV infection revealed distinct trends across countries, with certain drugs being scarcely prescribed or not at all, some showing widespread use, and others being specific to countries. Notably, adefovir, bulevirtide, cepeginterferon, interferon, interferon alfa-2b, peginterferon alfa-2b and peginterferon alfacon-2 demonstrate minimal to no prescription across all countries. In contrast, certain drugs exhibit widespread prescription across multiple countries. Entecavir emerged as one of the most frequently prescribed drugs during treatment initiation, with notable prescription rates in all databases, ranging from 0.52% in CPRD GOLD to 5.91% in IPCI in primary care databases, from 4.6% in CHUBX to 5.41% in IMASIS in hospital databases and 13.37% in EBB. Similarly, the use of tenofovir disoproxil during treatment initiation was scarce in EBB but substantial across other databases. Prescription rates ranged from 2.86% in in CPRD GOLD to 4.86% in IQVIA DA Germany in primary care databases and from 8.23% in IMASIS to 8.98% in CHUBX in hospital databases. The use of lamivudine was low, ranging from 0.86% in IQVIA DA Germany to 1.27% in IMASIS, 1.31% in CHUBX and 1.45% in EBB. Moreover, there are drugs that appear to be database-specific in their usage. Peginterferon alfa-2a treatment was notably prescribed in EBB (4.36%) while scarcely in IMASIS (0.5%) and IQVIA DA Germany (0.12%).

Table 12. Initiation of interferon or any specified antiviral treatment in patients diagnosed with chronic HBV infection, per database

	*	CPRD GOLD UK	CHUBX France	EBB Estonia	IMASIS Spain	IPCI Netherlands	IQVIA DA Germany
Number of eligible patients		1,154	2,215	344	2,200	1,285	12,154
Any Therapeutic intervention							
Interferon/antivirals	n (%)	34 (2.95)	298 (13.45)	53 (15.41)	258 (11.73)	97 (7.55)	956 (7.87)
Therapeutic Drug Class							
Antivirals	n (%)	33 (2.86)	297 (13.41)	46 (13.37)	255 (11.59)	97 (7.55)	952 (7.83)
Interferons	n (%)	<5	<5	15 (4.36)	11 (0.5)	0 (0)	13 (0.11)
Drug-specific treatment							
Adefovir	n (%)	0 (0)	<5	0 (0)	0 (0)	0 (0)	11 (0.09)
Bulevirtide	n (%)	0 (0)	<5	0 (0)	0 (0)	0 (0)	5 (0.04)
Cepeginterferon	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Entecavir	n (%)	6 (0.52)	102 (4.6)	46 (13.37)	119 (5.41)	76 (5.91)	385 (3.17)
Interferon alfa-2a	n (%)	<5	<5	0 (0)	0 (0)	0 (0)	0 (0)
Interferon alfa-2b	n (%)	0 (0)	<5	0 (0)	0 (0)	0 (0)	0 (0)
Lamivudine	n (%)	0 (0)	29 (1.31)	5 (1.45)	28 (1.27)	<5	105 (0.86)
Peginterferon alfa-2a	n (%)	0 (0)	<5	15 (4.36)	11 (0.5)	0 (0)	14 (0.12)
Peginterferon alfa-2b	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5
Peginterferon alfacon-2	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Telbivudine	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0.04)
Tenofovir	n (%)	<5	55 (2.48)	<5	26 (1.18)	14 (1.09)	80 (0.66)
Tenofovir disoproxil	n (%)	33 (2.86)	199 (8.98)	<5	181 (8.23)	38 (2.96)	591 (4.86)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection.

*Number of patients diagnosed with chronic HBV who initiated treatment and the corresponding percentage of those who initiated treatment relative to all patients diagnosed with chronic HBV infection;

Interferon/antivirals = use of interferon or antiviral. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Initiation of interferon or antiviral treatment in chronic HBV infection, stratified by sex

Table 1 in **Appendix IV** provides a comprehensive breakdown of the initiation of interferon or antiviral treatment in patients diagnosed with chronic HBV, stratified by sex. The results revealed notable differences between males and females across various countries with consistent male predominance in the initiation of any therapeutic intervention (interferon/antivirals) across all databases, with the highest frequencies seen in EBB (18.94% males vs. 13.21% in females) and hospital databases CHUBX (16.79% in males vs. 9.13% in females) and IMASIS (13.29% in males vs. 8.74% in females). This pattern was observed when examining therapeutic drug classes or when examining drug-specific treatments. For instance, entecavir exhibited higher initiation rates in males. In primary databases, frequency ranged from 3.84% in males vs. 2.4% in females in IQVIA DA Germany to 7.7% in males vs. 4.01% in females in IPCI. In hospital databases, frequency was in 5.84% in males vs. 3.01% % in females in CHUBX and 5.81% in males vs. 4.64 % in females in IMASIS, while in the biobank (EBB) it was 14.39% in males vs. 12.74% in females. Likewise, initiation of lamivudine, peginterferon alfa-2a, tenofovir and tenofovir disoproxil treatment consistently demonstrated a male predominance across the databases. In contrast a subtle shift is observed in IPCI, where there is a slight predominance of tenofovir disoproxil treatment initiation in females over males (3.2% females vs. 2.7% males).

Initiation of interferon or antiviral treatment in chronic HBV infection, stratified by age

Table 2 in **Appendix IV** provides insights into the initiation pattern of interferon or antiviral treatment in patients diagnosed with chronic HBV over the study period, stratified by age categories. The trend in initiating any therapeutic intervention (interferon/antivirals) displayed considerable variability across different databases. In the CPRD GOLD, there was a consistent increase in the use of interferon or antiviral treatment with age. Specifically, the prescription rate ranged from 2.33% in the 18 to 44 age group to 4.6% in the 45 to 64 age group in CPRD GOLD. Conversely, CHUBX, IPCI and EBB showed varying treatment rates across age groups. CHUBX and IPCI generally had higher prescription frequencies in the 45 to 64 age category, while EBB demonstrated the highest frequency in the ≥65 age category. IMASIS and IQVIA DA Germany, on the other hand, showed a decreasing trend in initiation rates for any therapeutic intervention with increasing age, with the highest frequency in the 1 to 17 age group (11.39% in IQVIA DA Germany) and the lowest in ≥65 age group (9.26% in IMASIS and 5.99% in IQVIA DA Germany).

Similar trend was observed for antiviral treatment alone. In contrast, the initiation of interferons was consistently low, with some databases reporting negligible rates across age categories. Finally, initiation of drug-specific treatment also varied across different database. For instance, hospital database CHUBX and IMASIS and EBB displayed increasing treatment initiation rates across age groups for entecavir, with highest frequency observed in ≥65 age group. However, IQVIA DA Germany showed a decreasing trend and IPCI demonstrated varying rates across age categories, with highest frequency in the 45-64 age group. Detailed results can be assessed through an interactive web-application ("shiny app") at https://data-dev.darwin-eu.org/EUPAS107650-broad/.

Initiation of interferon or antiviral treatment in chronic HBV infection, stratified by calendar year

Table 3 in **Appendix IV** outlines temporal trend in the initiation frequency of any therapeutic intervention in patients diagnosed with chronic HBV at any time across databases from 2012-2022. A general trend of fluctuation and gradual decrease in the frequency of any therapeutic intervention (interferons/antivirals) is observed over the years across most databases.

In CHUBX and IQVIA DA Germany, the frequency of interferon/antiviral treatment initiation showed variability from 2012 (10.81% (n=32) and 3.38% (n=25), respectively) to 2018 (1.53% (n=18) and 1.37% (n=65), respectively) characterized by occasional increases and decreases. However, a distinct shift occurred in 2019, marked by a significant decline in treatment initiation rates in both databases. Specifically, in CHUBX, the frequency decreased from 2.56% in 2019 (n=32) to 1.04% in 2022 (n=13), while in IQVIA DA Germany, it declined from 4.02% in 2019 (n=247) to 1.46% in 2022 (n=105). Likewise, use of interferons/antivirals showed fluctuation in IMASIS with highest frequency of 4.13 in 2012 (n=9) and lowest frequency of 1.46% in 2020 (n=18). In IPCI, the frequency of patients initiating any therapeutic intervention fluctuated over time from 2.01% in 2013 (n=6) to 0.89% in 2022 (n=8), with a peak frequency of 2.4% in 2018 (n=17). However, a notable decline in treatment initiation rates was observed starting from 2020, ranging from 1.51% in 2020 (n=12) to 0.89% in 2022 (n=8). Notably, the results in IPCI are based on limited number of cases (n<20). The frequency of patients initiating treatment over time in CPRD GOLD yielded limited results, due to either the absence of captured exposure or the inability to report counts below 5. In parallel, the assessment of the number of patients initiating treatment in EBB for each calendar year encountered limitations. Despite these constraints, discernible fluctuations in the frequency of treatment initiation were observed in EBB. Specifically, the percentages changed from 4.83% in 2014 (n=7) and 3.41% in 2017 (n=7) to 2.26% in 2019 (n=6), culminating in 2.08% in 2021 (n=7).

All results on initiation of therapeutic drug classes or drug-specific treatment can be found in an interactive web-application ("shiny app") at https://data-dev.darwin-eu.org/EUPAS107650-broad/.

12.1.3.2 Initiation of interferon or antiviral treatment in chronic HCV infection

Table 13 outlines the initiation of interferon and/or specified antivirals in patients diagnosed with chronic HCV infection over the study period, stratified by the respective databases. Similarly, as for chronic HBV infection, the primary emphasis is on the utilization of any therapeutic intervention, encompassing both interferon and antiviral treatments. Furthermore, the analysis delves into therapeutic drug classes, distinguishing between antivirals and interferons individually, as well as providing granularity on drug-specific treatments.

The drug prescription pattern for the initiation of treatment in chronic HCV infection revealed notable variations in the utilization of different treatments across countries. Among the treatments, interferon/antivirals were consistently common and widely prescribed across all countries, with substantial percentages ranging from 4.43% in CPRD GOLD to 11.79% in IPCI in primary care databases, from 3.96% in CHUBX to 21.62% in IMASIS, and 50.65% in EBB. The same pattern was observed when focusing on therapeutic drug classes, particularly antivirals. On the other hand, interferons alone exhibit varying prescription rates across countries, with Estonia having the highest at 14.52%. The use of interferons as a standalone treatment was relatively low or even non-existent in CPRD GOLD, CHUBX, IMASIS, IPCI and IQVIA DA Germany.

Further exploration into drug-specific treatments revealed variations in the initiation of drug-specific treatment across databases. Drugs such as asunaprevir, asunaprevirx, cepeginterferon, coblopasvir, faldaprevir, interferon, interferon alfa-2b and peginterferon alfacon-2 were consistently reported as rarely prescribed or not prescribed at all across databases. On the other hand, certain drugs showed common prescription patterns across countries. For instance, glecaprevir, ledipasvir/sofosbuvir, ribavirin, sofosbuvir, and sofosbuvir/velpatasvir were frequently prescribed, with varying frequencies across databases.

Furthermore, country-specific variations in drug utilization are evident. Dasabuvir, ombitasvir, dasabuvir-ombitasvir-paritaprevir, elbasvir, elbasvir_grazoprevir, peginterferon alfa-2a, peginterferon alfa-2b and telaprevir, showed distinct prescription rates in EBB.

Table 13. Initiation of interferon or any specified antiviral treatment in patients diagnosed with chronic HCV infection, per database

	*	CPRD GOLD UK	CHUBX France	EBB Estonia	IMASIS Spain	IPCI Netherlands	IQVIA DA Germany
Number of eligible patients		1,535	4,623	1,226	4,598	195	12,244
Any Therapeutic intervention							
Interferon/antivirals	n (%)	68 (4.43)	183 (3.96)	621 (50.65)	994 (21.62)	23 (11.79)	979 (8)
Therapeutic Drug Class							
Antivirals	n (%)	68 (4.43)	181 (3.92)	620 (50.57)	993 (21.6)	23 (11.79)	978 (7.99)
Interferons	n (%)	16 (1.04)	19 (0.41)	178 (14.52)	32 (0.7)	0 (0)	108 (0.88)
Drug-specific treatment							
Asunaprevir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asunaprevir / Beclabuvir / Daclatasvir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Boceprevir	n (%)	0 (0)	<5	8 (0.65)	0 (0)	0 (0)	17 (0.14)
Cepeginterferon	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coblopasvir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Daclatasvir	n (%)	5 (0.33)	35 (0.76)	0 (0)	43 (0.94)	7 (3.59)	37 (0.3)
Dasabuvir	n (%)	<5	0 (0)	188 (15.33)	67 (1.46)	<5	28 (0.23)
Dasabuvir / Ombitasvir / Paritaprevir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Elbasvir	n (%)	<5	5 (0.11)	134 (10.93)	54 (1.17)	<5	111 (0.91)
Elbasvir / Grazoprevir	n (%)	<5	5 (0.11)	134 (10.93)	54 (1.17)	<5	111 (0.91)
Faldaprevir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Glecaprevir	n (%)	21 (1.37)	24 (0.52)	203 (16.56)	441 (9.59)	7 (3.59)	312 (2.55)
Grazoprevir	n (%)	<5	5 (0.11)	134 (10.93)	54 (1.17)	<5	111 (0.91)
Interferon alfa-2a	n (%)	11 (0.72)	<5	<5	0 (0)	0 (0)	0 (0)
Interferon alfa-2b	n (%)	<5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ledipasvir / Sofosbuvir	n (%)	6 (0.39)	33 (0.71)	0 (0)	97 (2.11)	6 (3.08)	205 (1.67)
Ombitasvir / paritaprevir / ritonavir	n (%)	<5	0 (0)	188 (15.33)	72 (1.57)	<5	33 (0.27)
Peginterferon alfa-2a	n (%)	<5	16 (0.35)	152 (12.4)	26 (0.57)	0 (0)	88 (0.72)
Peginterferon alfa-2b	n (%)	0 (0)	0 (0)	41 (3.34)	7 (0.15)	0 (0)	25 (0.2)
Peginterferon alfacon-2	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ribavirin	n (%)	20 (1.3)	53 (1.15)	195 (15.91)	101 (2.2)	<5	182 (1.49)
Simeprevir	n (%)	0 (0)	8 (0.17)	11 (0.9)	0 (0)	<5	5 (0.04)
Sofosbuvir	n (%)	31 (2.02)	132 (2.86)	26 (2.12)	531 (11.55)	18 (9.23)	497 (4.06)
Sofosbuvir / Velpatasvir	n (%)	16 (1.04)	54 (1.17)	26 (2.12)	378 (8.22)	<5	200 (1.63)
Sofosbuvir / Velpatasvir / Voxilaprevir	n (%)	<5	0 (0)	0 (0)	18 (0.39)	0 (0)	11 (0.09)
Telaprevir	n (%)	<5	8 (0.17)	16 (1.31)	0 (0)	0 (0)	21 (0.17)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

*Number of patients diagnosed with chronic HCV who initiated treatment and the corresponding percentage of those who initiated treatment relative to all patients diagnosed with chronic HCV infection;

Interferon/antivirals = use of interferon or antiviral. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Initiation of interferon or antiviral treatment in chronic HCV infection, stratified by sex

Table 4 in Appendix IV outlines sex differences in the initiation pattern of any therapeutic intervention in patients diagnosed with chronic HCV across various databases.

The results revealed differences between males and females across various countries and databases. Notably, consistent male predominance in initiation of any therapeutic intervention (interferon/antivirals) was observed across databases. In contrast, a subtle shift was observed in CPRD GOLD, where there is a slight predominance of treatment initiation in females over males (5.35% females vs. 4% males). This pattern was observed when examining antiviral treatment alone. However, sex differences in the initiation of interferons were not pronounced, as frequencies were similar between males and females, or with a slight predominance of females in CHUBX, IMASIS, and IQVIA DA Germany.

When examining drug-specific treatment, certain medications showed sex-specific differences in prescription rates. In CPRD GOLD, IQVIA DA Germany, EBB and IMASIS, the use of specific drugs such as glecaprevir, dasabuvir, elbasvir, grazoprevir, ribavirin, and sofosbuvir demonstrated different prescription patterns between males and females. For instance, the use of glecaprevir was slightly more prevalent in females in CPRD GOLD (1.85% in females vs. 1.14% in males) than in other databases (EBB: 14.97% females vs. 18.94% males; IQVIA DA Germany 2.24% females vs. 2.77% males , CHUBX: 0.3% females vs. 0.65% males and IMASIS: 6.99% in females vs. 11% in males), while ribavirin showed higher utilization in females in CHUBX (1.31% females vs. 1.05% males).

Additionally, there were instances where drug utilization rates were consistently low or negligible across both genders, as observed in the limited prescription of drugs like asunaprevir, asunaprevir-beclabuvir-daclatasvir, cepeginterferon, coblopasvir, faldaprevir, and peginterferon alfacon-2.

Initiation of interferon or antiviral treatment in chronic HCV infection, stratified by age

Table 5 in Appendix IV provides a comprehensive breakdown of the initiation of interferon or antiviral treatment in patients diagnosed with chronic HCV, stratified by age categories. The trend in initiating antivirals/interferon showed variability across different databases. In primary care data CPRD GOLD, IPCI and IQVIA DA Germany, there was a decrease in the use of any of the therapeutic interventions with age. Specifically, the highest prescription frequencies were observed in 18-44 age group. In IPCI, the prescription rate ranged from 15.56% in 18-44 age category (n=7) to 12.71% in 45-64 age category (n=15). Similar pattern was observed in hospital database, IMASIS, where the highest prescription frequencies were found in youngest patients (1-17 age category: 62.5% (n=5)), while the lowest frequencies were seen in oldest patients (≥65 age category: 12.09% (n=164). Conversely, CHUBX and EBB showed an increasing trend from the 1-44 age group to the 45-64 age group, with higher prescription frequencies observed in the 45 to 64 age category, followed by a decrease in prescription frequency in the ≥65 age category. Similar trend was observed for antiviral treatment alone. In contrast, the initiation of interferons was consistently low, with some databases reporting negligible rates across age categories. Finally, initiation of drug-specific treatment also varied across different database. Boceprevir, daclatasvir, dasabuvir, elbasvir, glecaprevir, ledipasvir/sofosbuvir, ombitasvir, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, sofosbuvir, sofosbuvir/velpatasvir, and

telaprevir showed variable prescription rates across age categories, with some drugs having higher proportion in specific age groups.

Initiation of interferon or antiviral treatment in chronic HCV infection, stratified by calendar year

Table 6 in Appendix IV outlines temporal dynamics in incident use of any therapeutic intervention in patients diagnosed with chronic HCV across various databases.

Within CPRD GOLD, CHUBX, EBB, and IQVIA DA Germany, the frequency of patients initiating therapeutic interventions exhibited fluctuations over time, with slight declining trend during the study period. Specifically, in CPRD GOLD, the initiation frequency ranged from 1.32% in 2013 (n=7) to 1% in 2015 (n=7) and from 1.46% in 2017 (n=11) to 0.71% in 2020 (n=5). These results in CPRD GOLD are based on the limited number of cases (n<13). Notably, in CHBUX, the frequency ranged from 1.44% in 2012 (n=16) to 0.24% in 2022 (n=5), while in EBB, it ranged from 11.79% in 2012 (n=46) to 6.68% in 2021 (n=79), reaching its peak at 11.54% in 2016 (n=99). In IMASIS, the frequency started at 0.69% in 2013 (n=7), increasing to 9.48% in 2018 (n=213), and subsequently declining to 4.83% in 2022 (n=103). The analysis of the frequency of patients initiating treatment over time in IPCI yielded limited results, due to either the absence of captured exposure or the inability to report counts below 5. Finally, in IQVIA DA Germany, the initiation frequency fluctuated, decreasing from 2.68% in 2012 (n=35) to 1.53% in 2022 (n=81), with a peak at 3.66% in 2015 (n=137). These findings underscore the dynamic nature of therapeutic initiation patterns in chronic HCV patients.

12.1.3.3 Prevalent use of interferon or antiviral treatment in chronic HBV infection

Table 14 outlines interferon and/or any specified antivirals treatment in patients diagnosed with chronic HBV throughout the study period, stratified by database.

The trends and patterns observed in prevalent use of any therapeutic intervention (interferon/antivirals), drug classes or drug-specific treatment generally mirrored those of incident use. All details, including the number of users and population for each database can be found in **Table 14** and the shiny app (https://data-dev.darwin-eu.org/EUPAS107650-broad/). Briefly, prevalent use of any therapeutic intervention (interferon/antivirals) varied across different databases, ranging from 2.95% in CPRD GOLD (n=34) to 9.73% in IPCI (n=125) in primary care databases, from 12.59% in IMASIS (n=277) to 15.85% in CHUBX (n=351) in hospital databases and 15.41% in EBB (n=53). The similar pattern was observed when focusing on antivirals. Initiation of interferon treatment was generally low, registering at less than 5% in EBB, IMASIS and IQVIA DA Germany, with minimal or no users in other databases.

Table 14. Prevalent use of interferon and/or any specified antivirals treatment in patients diagnosed with chronic HBV throughout the study period, stratified by database.

	*	CPRD GOLD UK	CHUBX France	EBB Estonia	IMASIS Spain	IPCI Netherlands	IQVIA DA Germany
Number of eligible patients		1,154	2,215	344	2,200	1,285	12,154
Any Therapeutic intervention							
Interferon/antivirals	n (%)	34 (2.95)	351 (15.85)	53 (15.41)	277 (12.59)	125 (9.73)	995 (8.19)
Therapeutic Drug Class							
Antivirals	n (%)	33 (2.86)	350 (15.8)	47 (13.66)	277 (12.59)	125 (9.73)	991 (8.15)
Interferons	n (%)	<5	<5	15 (4.36)	12 (0.55)	0 (0)	13 (0.11)
Drug-specific treatment							
Adefovir	n (%)	0 (0)	<5	0 (0)	<5	<5	17 (0.14)
Bulevirtide	n (%)	0 (0)	<5	0 (0)	0 (0)	0 (0)	5 (0.04)
Cepeginterferon	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Entecavir	n (%)	6 (0.52)	122 (5.51)	46 (13.37)	220 (10)	107 (8.33)	442 (3.64)
Interferon alfa-2a	n (%)	<5	<5	0 (0)	0 (0)	0 (0)	0 (0)
Interferon alfa-2b	n (%)	0 (0)	<5	0 (0)	0 (0)	0 (0)	0 (0)
Lamivudine	n (%)	<5	48 (2.17)	5 (1.45)	91 (4.14)	9 (0.7)	145 (1.19)
Peginterferon alfa-2a	n (%)	0 (0)	<5	16 (4.65)	13 (0.59)	<5	14 (0.12)
Peginterferon alfa-2b	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5
Peginterferon alfacon-2	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Telbivudine	n (%)	0 (0)	0 (0)	0 (0)	<5	0 (0)	6 (0.05)
Tenofovir	n (%)	<5	60 (2.71)	<5	30 (1.36)	16 (1.25)	86 (0.71)
Tenofovir disoproxil	n (%)	36 (3.12)	274 (12.37)	<5	381 (17.32)	63 (4.9)	742 (6.1)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

*Number of prevalent users diagnosed with chronic HBV and the corresponding percentage of those relative to all patients diagnosed with chronic HBV infection;

Interferon/antivirals = use of interferon or antiviral. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Prevalent use of interferon or antiviral treatment in chronic HBV infection, stratified by sex

Table 7 in Appendix IV provides a comprehensive overview of prevalent use of interferon or any specified antivirals treatment in patients diagnosed with chronic HBV infection, stratified by sex.

The trends observed in prevalent use of any therapeutic intervention (interferon/antivirals), drug classes or drug-specific treatment in relation to sex, generally mirrored those of incident use. Briefly, the results revealed notable differences between males and females across various countries with consistent male predominance. All details, including the number of users and population for each database can be found in **Table 7** in **Appendix IV** and the shiny app (https://data-dev.darwin-eu.org/EUPAS107650-broad/).

Prevalent use of interferon or antiviral treatment in chronic HBV infection, stratified by age

Table 8 in **Appendix IV** presents a comprehensive overview of prevalent use of interferon or any specified antivirals treatment in patients diagnosed with chronic HBV infection, stratified by age categories.

The results for the prevalent use of any therapeutic intervention (interferon/antivirals), drug classes, or drug-specific treatments aligned with those identified in incident use. For detailed information, including the number of users and population data for each database, please refer to **Table 8** in **Appendix IV** and the Shiny app (https://data-dev.darwin-eu.org/EUPAS107650-broad/).

Prevalent use of interferon or antiviral treatment in chronic HBV infection, stratified by calendar year

Table 9 in Appendix IV outlines temporal trend in the prevalent use of interferon/antiviral in patients diagnosed with chronic HBV across databases from 2012-2022. A general trend of fluctuation and gradual decrease in the frequency of any therapeutic intervention (interferons/antivirals) is observed over the years across most databases. These results mirror those of incident use. For detailed information, including the number of users and population data for each database, please refer to **Table 9** in **Appendix IV** and the Shiny app (https://data-dev.darwin-eu.org/EUPAS107650-broad).

12.1.3.4 Prevalent use of interferon or antiviral treatment in chronic HCV infection

Table 15 presents prevalent use of interferon and/or any specified antivirals in patients diagnosed with chronic HCV, by database.

The trends observed in prevalent use of any therapeutic intervention (interferon/antivirals), drug classes or drug-specific treatment generally mirrored those of incident use. Briefly, prevalent use of any therapeutic intervention (interferon/antivirals) varied across different databases, ranging from 4.5% in IPCI (n=69) to 13.33% in IPCI (n=26) in primary care databases, from 4.07% in CHUBX (n=188) to 22.88% in IMASIS (n=112) and 55.71% in EBB (n=683). The same pattern was observed, with the highest use noticed in EBB, when focusing on therapeutic drug classes, particularly antivirals. Interferons alone exhibit varying prescription rates across countries, with Estonia having the highest at 16.88%. All details, including the number of users and population for each database can be found in **Table 15** and the shiny app https://data-dev.darwin-eu.org/EUPAS107650-broad/).

Table 15. Counts of patients diagnosed with chronic HCV infection who underwent treatment with interferon or any specified antivirals, stratified by database throughout the study period

	*	CPRD GOLD UK	CHUBX France	EBB Estonia	IMASIS Spain	IPCI Netherlands	IQVIA DA Germany
Number of eligible patients		**1,535**	**4,623**	**1,226**	**4,598**	**195**	**12,244**
Any Therapeutic intervention							
Interferon/antivirals	n (%)	69 (4.5)	188 (4.07)	683 (55.71)	1,052 (22.88)	26 (13.33)	1,002 (8.18)
Therapeutic Drug Class							
Antivirals	n (%)	69 (4.5)	186 (4.02)	682 (55.63)	1,053 (22.9)	26 (13.33)	1,001 (8.18)
Interferons	n (%)	16 (1.04)	19 (0.41)	207 (16.88)	35 (0.76)	0 (0)	123 (1)
Drug-specific treatment							
Asunaprevir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asunaprevir / Beclabuvir / Daclatasvir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Boceprevir	n (%)	0 (0)	<5	8 (0.65)	0 (0)	0 (0)	17 (0.14)
Cepeginterferon	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coblopasvir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Daclatasvir	n (%)	5 (0.33)	35 (0.76)	0 (0)	44 (0.96)	7 (3.59)	38 (0.31)
Dasabuvir	n (%)	<5	0 (0)	188 (15.33)	72 (1.57)	<5	28 (0.23)
Dasabuvir / Ombitasvir / Paritaprevir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Elbasvir	n (%)	<5	5 (0.11)	134 (10.93)	54 (1.17)	<5	111 (0.91)
Elbasvir / Grazoprevir	n (%)	<5	5 (0.11)	134 (10.93)	54 (1.17)	<5	111 (0.91)
Faldaprevir	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Glecaprevir	n (%)	21 (1.37)	24 (0.52)	203 (16.56)	444 (9.66)	7 (3.59)	315 (2.57)
Grazoprevir	n (%)	<5	5 (0.11)	134 (10.93)	54 (1.17)	<5	111 (0.91)

	*	CPRD GOLD UK	CHUBX France	EBB Estonia	IMASIS Spain	IPCI Netherlands	IQVIA DA Germany
Number of eligible patients		**1,535**	**4,623**	**1,226**	**4,598**	**195**	**12,244**
Interferon alfa-2ª	n (%)	11 (0.72)	<5	<5	0 (0)	0 (0)	0 (0)
Interferon alfa-2b	n (%)	<5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ledipasvir / Sofosbuvir	n (%)	6 (0.39)	34 (0.74)	0 (0)	100 (2.17)	6 (3.08)	206 (1.68)
Ombitasvir / paritaprevir / ritonavir	n (%)	<5	0 (0)	188 (15.33)	77 (1.67)	<5	33 (0.27)
Peginterferon alfa-2ª	n (%)	<5	16 (0.35)	166 (13.54)	43 (0.94)	0 (0)	108 (0.88)
Peginterferon alfa-2b	n (%)	0 (0)	0 (0)	47 (3.83)	10 (0.22)	0 (0)	28 (0.23)
Peginterferon alfacon-2	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ribavirin	n (%)	20 (1.3)	56 (1.21)	220 (17.94)	144 (3.13)	<5	207 (1.69)
Simeprevir	n (%)	0 (0)	8 (0.17)	11 (0.9)	0 (0)	<5	5 (0.04)
Sofosbuvir	n (%)	31 (2.02)	133 (2.88)	26 (2.12)	545 (11.8)	20 (10.26)	502 (4.1)
Sofosbuvir / Velpatasvir	n (%)	16 (1.04)	54 (1.17)	26 (2.12)	381 (8.29)	5 (2.56)	203 (1.66)
Sofosbuvir / Velpatasvir / Voxilaprevir	n (%)	<5	0 (0)	0 (0)	18 (0.39)	0 (0)	11 (0.09)
Telaprevir	n (%)	<5	8 (0.17)	16 (1.31)	0 (0)	0 (0)	22 (0.18)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

*Number of prevalent users diagnosed with chronic HCV and the corresponding percentage of those relative to all patients diagnosed with chronic HCV infection;

Interferon/antivirals = use of interferon or antiviral. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Prevalent use of interferon or antiviral treatment in chronic HCV infection, stratified by sex

Table 10 in **Appendix IV** presents prevalent use of interferon or any specified antivirals treatment in patients diagnosed with chronic HCV infection, stratified by sex.

Similarly to previous analysis, the trends observed in prevalent use of any therapeutic intervention (interferon/antivirals), drug classes or drug-specific treatment in relation to sex, generally mirrored those of incident use. All details, including the number of users and population for each database can be found in **Table 10** in **Appendix IV** and the shiny app https://data-dev.darwin-eu.org/EUPAS107650-broad/).

Prevalent use of interferon or antiviral treatment in chronic HCV infection, stratified by age

Table 11 in **Appendix IV** outlines prevalent use of interferon or any specified antivirals treatment in patients diagnosed with chronic HCV infection, stratified by age categories.

The results for the prevalent use of any therapeutic intervention (interferon/antivirals), drug classes, or drug-specific treatments aligned with those identified in incident use. For detailed information, including the number of users and population data for each database, please refer to **Table 11** in **Appendix IV** and the Shiny app (https://data-dev.darwin-eu.org/EUPAS107650-broad/).

Prevalent use of interferon or antiviral treatment in chronic HCV infection, stratified by calendar year

Finally, **Table 12 in Appendix IV** illustrates temporal trend in the prevalent use of interferon/antiviral in patients diagnosed with chronic HCV across databases from 2012-2022. A general trend of fluctuation and gradual decrease in the frequency of any therapeutic intervention (interferons/antivirals) is observed over the years across most databases, echoing the trends identified in incident use. For detailed information, including the number of users and population data for each database, please refer to **Table 12** in **Appendix IV** and the Shiny app https://data-dev.darwin-eu.org/EUPAS107650-broad/).

12.2 Patient-level drug utilization

12.2.1 Participants

The number of individuals diagnosed with chronic HBV and HCV infection who initiated treatment with interferon or specified antiviral across different databases from 2012 to 2022 is outlined in **Table 16** and **Table 17**. Briefly, the initiation of any therapeutic intervention either interferons or specific antivirals in patients diagnosed with chronic HBV infection varied across different databases during the study period with treatment initiation rates ranging from 2.95% in CPRD GOLD (n=34), 7.55% in IPCI (n=97) to 7.92% in IQVIA DA Germany (n=963) in primary care databases and from 11.95% in IMASIS (n=263), 13.72% in CHUBX (n=304) to 15.41% in EBB (n=53) in hospital databases and biobank. Similarly, the percentage of patients initiating treatment for chronic HCV infection varied across different databases with initiation rates ranging from 4.43% in CPRD GOLD (n=68), 8.04% in IQVIA DA Germany (n=984) to 11.79% in IPCI (n=23) in primary care databases, from 3.96% in CHUBX (n=183) to 21.62% in IMASIS (n=994) in hospital databases and 50.65% in EBB (n=621).

Table 16. Demographic characteristics of patients initiating treatment for chronic HBV infection during the study period, per database

	CPRD GOLD UK n=1,154	CHUBX France n=2,215	EBB Estonia n=344	IMASIS Spain n=2,200	IPCI Netherlands n=1,285	IQVIA DA Germany n=12,154
Number of patients initiating treatment for chronic HBV, n (%)*	34 (2.95)	304 (13.72)	53 (15.41)	263 (11.95)	97 (7.55)	963 (7.92)
Prior observation (days), Median (IQR)	613 (110 -3,324)	1,668 (112 - 3,012)	4,802 (3,277 -5,831)	2,294 (143 - 6,164)	963 (476 -1,769)	0 (0 -90)
Future observation (days), Median (IQR)	1,466 (584 -2,324)	1,876 (770 - 3,125)	1,760 (697 -3,213)	1,243 (546 - 1,980)	1,960 (1,159 - 3,180)	1,255 (598 - 2,016)
Age at index (years), Median (IQR)	40 (30 - 50)	53 (45 - 64)	55 (42 - 64)	47 (38 - 60)	45 (38 - 54)	45 (34 - 57)
Age range (years)	20 - 81	9 - 91	18 - 77	18 - 89	25 - 76	4 - 88
Age group (years), n (%)*						
• 1 to 17	-	<5	-	-	-	18 (1.9)
• 18 to 44	19 (55.9)	73 (24.0)	15 (28.3)	112 (42.6)	45 (46.4)	450 (46.7)
• 45 to 64	12 (35.3)	157 (51.6)	25 (47.2)	100 (38.0)	45 (46.4)	376 (39.9)
• ≥ 65	<5	73 (24.0)	13 (24.5)	51 (19.4)	7 (7.2)	119 (12.4)
Sex, n (%)*						
• Female	10 (29)	89 (29)	28 (53)	68 (26)	37 (38)	359 (37)
• Male	24 (71)	215 (71)	25 (47)	195 (74)	60 (62)	604 (63)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection; IQR = interquartile range;

*Number of patients diagnosed with chronic HBV who initiated treatment and the corresponding percentage of those who initiated treatment relative to all patients diagnosed with chronic HBV infection;

**Number of patients diagnosed with chronic HBV who initiated treatment and the associated percentage within each category (age, sex), relative to the total number of patients diagnosed with chronic HBV infection who initiated treatment;

Hospital databases are indicated in green.

Table 17. Demographic characteristics of patients initiating treatment for chronic HCV infection during the study period, per database

	CPRD GOLD UK n=1,535	CHUBX France n=4,623	EBB Estonia n=1,226	IMASIS Spain n=4,598	IPCI Netherlands n=195	IQVIA DA Germany n=12,244
Number of patients initiating treatment for chronic HCV, n (%)*	68 (4.43)	183 (3.96)	621 (50.65)	994 (21.62)	23 (11.79)	984 (8.04)
Prior observation (days), Median (IQR)	3,243 (633-6,529)	1,743 (163-2,727)	3,918 (3,184-5,145)	4,309 (831-8,005)	791 (440-1,358)	0 (0-52)
Future observation (days), Median (IQR)	2,079 (1,106-3,065)	2,139 (1,109-3,340)	2,619 (1,416-3,374)	1,702 (868-2,601)	1,661 (681-2,528)	424 (198-1,233)
Age at index (years), Median (IQR)	39 (32-46)	53 (48-60)	48 (36-56)	49 (40-59)	53 (43-59)	48 (39-57)
Age range (years)	24 - 68	24 - 89	18 - 83	6 - 91	30 - 66	16 - 90
Age group (years), n (%)**						
• 1 to 17	-	-	-	5 (0.5)	-	<5
• 18 to 44	48 (70.6)	28 (15.3)	266 (42.8)	356 (35.8)	7 (30.4)	407 (41.4)
• 45 to 64	18 (26.5)	132 (72.1)	302 (48.6)	469 (47.2)	15 (65.2)	468 (47.6)
• ≥ 65	<5	23 (12.6)	53 (8.5)	164 (16.5)	<5	107 (10.9)
Sex, n (%)**						
• Female	26 (38)	49 (27)	369 (59)	311 (31)	8 (35)	375 (38)
• Male	42 (62)	134 (73)	252 (41)	683 (69)	15 (65)	609 (62)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection; IQR = interquartile range;

*Number of patients diagnosed with chronic HCV who initiated treatment and the corresponding percentage of those who initiated treatment relative to all patients diagnosed with chronic HCV infection;

**Number of patients diagnosed with chronic HCV who initiated treatment and the associated percentage within each category (age, sex), relative to the total number of patients diagnosed with chronic HCV infection who initiated treatment;

Hospital databases are indicated in green.

12.2.2 Descriptive Data

12.2.2.1 Demographic characteristics of patients initiating treatment for chronic HBV patients

Demographic characteristics of patients initiating treatment for chronic HBV infection are shown in **Table 16**. The median age ranged from 40 years in CPRD GOLD to 55 years in EBB. In terms of sex distribution, the proportion of males initiating treatment for chronic HBV infection surpassed that of females, ranging from 62% to 74%. Notably, IMASIS reported the highest proportion of male patients initiating treatment (n=195, 74%) among the databases. In contrast, the proportion of males initiating treatment for chronic HBV infection in EBB (47%) was lower that the proportion of females.

12.2.2.2 Demographic characteristics of patients initiating treatment for chronic HCV patients

Demographic characteristics of patients initiating treatment for chronic HCV infection are detailed in **Table 17**. The median age spanned from 39 years in CPRD GOLD to 53 years in CHUBX and IPCI. Predominantly, the patient population comprised males, with proportions varying from 62% in CPRD GOLD and IQVIA DA Germany to 73% in CHUBX. Notably, EBB presented an exception where the proportion of males (41%) was lower than that of females.

12.2.3 Outcome Data and Main Results

12.2.3.1 Characterisation of patients initiating treatment for chronic HBV infection

Characteristics of individuals initiating treatment for chronic HBV infection at the index date and one year prior to index date in terms of comorbidity and in terms of concomitant medications are described in **Table 18 - Table 20**.

Table 18 presents the prevalence of prespecified comorbidities in the study population, revealing considerable variability across databases. Cardiovascular disorders emerged as notably prevalent, with CHUBX reporting 35.53%, IMASIS 26.62%, IPCI 11.34% and IQVIA DA Germany 10.07%. Hypertension also exhibited notable prevalence, with CHUBX reporting 17.76%, IMASIS 8.37%, IPCI 6.19% and IQVIA DA Germany 6.33%. CHUBX had the highest prevalence of cirrhosis (14.14%) and diabetes (14.14%), while IMASIS (8.37% and 6.46%, respectively) and IQVIA DA Germany (5.19% and 3.01%) reported lower prevalence. Alcoholism emerged as notably prevalent in hospital databases, CHUBX (7.89%) and IMASIS (8.75%). Additionally, prevalence of kidney disease ranged from 1.14% in IQVIA DA Germany, 3.62% in CHUBX to 5.32% in IMASIS. Similarly, prevalence of HIV infection ranged from 3.12% in IQVIA DA Germany, 6.91% in CHUBX to 13.69% in IMASIS. It is noteworthy that prevalence data for prespecified conditions in CPRD GOLD, EBB, and IPCI were often either missing or recorded as 0.

Table 18. Prevalence of prespecified comorbidities in patients with chronic HBV infection, at index date and one year prior to index date, per database

		CPRD GOLD UK n=34	CHUBX France n=304	EBB Estonia n=53	IMASIS Spain n=263	IPCI Netherlands n=97	IQVIA DA Germany n=963
Alcoholism	n (%)	0 (0)	24 (7.89)	0 (0)	23 (8.75)	<5	<5
Cardiovascular disorder	n (%)	0 (0)	108 (35.53)	<5	70 (26.62)	11 (11.34)	97 (10.07)
Cirrhosis	n (%)	0 (0)	43 (14.14)	<5	22 (8.37)	0 (0)	50 (5.19)
Diabetes	n (%)	0 (0)	43 (14.14)	<5	17 (6.46)	<5	29 (3.01)
Fatty liver	n (%)	0 (0)	<5	0 (0)	0 (0)	0 (0)	0 (0)
HIV	n (%)	0 (0)	21 (6.91)	0 (0)	36 (13.69)	0 (0)	30 (3.12)
Hypertension	n (%)	0 (0)	54 (17.76)	<5	22 (8.37)	6 (6.19)	61 (6.33)
Kidney disease	n (%)	0 (0)	11 (3.62)	0 (0)	14 (5.32)	0 (0)	11 (1.14)
STD	n (%)	0 (0)	<5	0 (0)	<5	<5	10 (1.04)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection; STD= Sexually Transmitted Disease

Hospital databases are indicated in green.

Table 19 presents the prevalence of top 10 comorbidities in the population of individuals with chronic HBV infection, at index date and one year prior index date.

This table reports disease codes but not aggregated codes for a specific comorbidity of interest. Therefore, large variation in conditions were observed, hypertension (7.22% in IPCI , 8.62% in IQVIA DA Germany, 17.61% in IMASIS, 18.87% in EBB and 25.99% in CHUBX) or blood pressure findings (50% in CPRD GOLD) was the disease code most frequently reported.

Among liver related disorders, cirrhosis of liver was reported among top 10 comorbidities in CHUBX (15.13%) and IQVIA DA Germany (4.98%) and hepatic fibrosis in CHUBX (8.88%). Alcohol dependence was common comorbidity in CPRD GOLD (8.55%) and IMASIS (6.46%).

Other common comorbidities across databases included tobacco dependence syndrome (10.86% in CHUBX and 13.31% in IMASIS) and type 2 diabetes mellitus (3.63% in IQVIA DA Germany, 7.22% in IMASIS and 10.2% in CHUBX). Remarkably, asymptomatic human immunodeficiency virus infection had a high prevalence in IMASIS (17.61%), while hyperlipidaemia was observed in EBB (16.98%) and IMASIS (16.98%).

Table 19. Prevalence of top comorbidities in patients with chronic HBV infection, at index date and one year prior to index date, per database

CPRD GOLD UK n=34		CHUBX France n=304		EBB Estonia n=53		IMASIS Spain n=263		IPCI Netherlands n=97		IQVIA DA Germany n=963	
Comorbidity	n (%)	Comorbidity	n (%)	Comorbidity	n (%)	Comorbidity	n (%)	Comorbidity	n (%)	Comorbidity	n (%)
Blood pressure finding	17 (50)	Essential hypertension	79 (25.99)	Essential hypertension	10 (18.87)	Chronic hepatitis C	39 (14.83)	Fit and well	8 (8.25)	Essential hypertension	83 (8.62)
Exercise grading	5 (14.71)	Chronic hepatitis C	47 (15.46)	Hypertensive heart disease without congestive heart failure	9 (16.98)	Tobacco dependence syndrome	35 (13.31)	Fatigue	8 (8.25)	Acute type B viral hepatitis	70 (7.27)
Finding of pulse rate	5 (14.71)	Cirrhosis of liver	46 (15.13)	Serum cholesterol raised	9 (16.98)	Essential hypertension	33 (12.55)	Finding of region of thorax	7 (7.22)	Cirrhosis of liver	48 (4.98)
NA		Fatigue	38 (12.5)	Sleep disorder	7 (13.21)	Asymptomatic human immunodeficiency virus infection	31 (11.79)	Acute type B viral hepatitis	7 (7.22)	Type 2 diabetes mellitus without complication	35 (3.63)
NA		Tobacco dependence syndrome	33 (10.86)	Anemia in neoplastic disease	7 (13.21)	Hyperlipidemia	23 (8.75)	Essential hypertension	7 (7.22)	Acute upper respiratory infection	29 (3.01)
NA		Type 2 diabetes mellitus	31 (10.2)	Spondylosis	6 (11.32)	Human immunodeficiency virus infection	22 (8.37)	Localized abdominal pain	7 (7.22)	Steatosis of liver	29 (3.01)
NA		Hepatic fibrosis	27 (8.88)	Anemia of chronic disease	6 (11.32)	COVID-19	20 (7.6)	Cough	6 (6.19)	Disease of liver	27 (2.8)
NA		Abdominal pain	27 (8.88)	Nerve root disorder	6 (11.32)	Type 2 diabetes mellitus without complication	19 (7.22)	Dermatophytosis	5 (5.15)	Chronic viral hepatitis B with hepatitis D	27 (2.8)
NA		Hyperkalemia	26 (8.55)	Iron deficiency anemia	6 (11.32)	Alcohol abuse	17 (6.46)	Low back pain	5 (5.15)	Acute bronchitis	26 (2.7)
NA		Alcohol dependence	26 (8.55)	Type 2 diabetes mellitus without complication	5 (9.43)	Acute renal failure syndrome	16 (6.08)	Type 2 diabetes mellitus	5 (5.15)	Illness	25 (2.7)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection; Hospital databases are indicated in green.

Table 20 presents the top 10 prevalent drugs in individuals with chronic hepatitis B, at index date and one year prior to index date, according to the respective database.

Commonly used drugs at index date and one year prior the index date across databases included antibiotic amoxicillin (EBB: 13.21%, CPRD GOLD: 14.71%), analgesics and antipyretics paracetamol (CHUBX: 12.83%, IMASIS: 32.32%), proton-pump inhibitors omeprazole (IPCI: 7.22%, IMASIS: 13.31%, EBB: 15.09%) and non-steroidal anti-inflammatory drug diclofenac (EBB: 9.43%, IPCI: 10.31%). Electrolyte supplement sodium chloride and glucose injectable solution were highly used in CHUBX and IMASIS with prescription rates ranging from 25.99% in CHUBX and 23.95% in IMASIS and 11.84% in CHUBX and 22.01% in IMASIS, respectively. Notably, zopiclone use was high in EBB (18.87%).

Table 20. Top prevalent drugs in patients with chronic HBV infection, at index date and one year prior to index date, per database

CPRD GOLD UK n=34		CHUBX France n=304		EBB Estonia n=53		IMASIS Spain n=263		IPCI Netherlands n=97		IQVIA DA Germany n=963	
Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)
amoxicillin 500 MG Oral Capsule	5 (14.71)	Sodium 9 MG/ML Injectable Solution	79 (25.99)	zopiclone 7.5 MG Oral Tablet	10 (18.87)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	85 (32.32)	diclofenac sodium 50 MG Delayed Release Oral Tablet	10 (10.31)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A	10 (1.04)
NA		acetaminophen 1000 MG Oral Tablet	39 (12.83)	Omeprazole 20 MG Oral Capsule	8 (15.09)	500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	63 (23.95)	metformin hydrochloride 500 MG Oral Tablet	8 (8.25)	pantoprazole 40 MG Oral Tablet [Pantoprazol - 1a Pharma] Box of 100 by 1 A	8 (0.83)
NA		glucose 50 MG/ML Injectable Solution	36 (11.84)	amoxicillin 875 MG / clavulanate 125 MG Oral Tablet	7 (13.21)	2 ML Dexketoprofen 25 MG/ML Injectable Solution	37 (14.07)	omeprazole 20 MG Delayed Release Oral Capsule	7 (7.22)	Aspirin 100 MG Oral Tablet [Ass 1a Pharma] Box of 100 by 1 A	7 (0.73)
NA		acetaminophen 10 MG/ML Injection	34 (11.18)	prednisolone 5 MG Oral Tablet	6 (11.32)	omeprazole 20 MG Delayed Release Oral Capsule	35 (13.31)	omeprazole 40 MG Delayed Release Oral Capsule	6 (6.19)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe	7 (0.73)
NA		Glucose 100 MG/ML / Potassium Chloride 2 MG/ML / Sodium Chloride 4 MG/ML Prefilled Syringe	33 (10.86)	acyclovir 400 MG Oral Tablet	6 (11.32)	dipyrone 400 MG/ML Injectable Solution	33 (12.55)	cetostearyl alcohol	5 (5.15)	torsemide 10 MG Oral Tablet [Torasemid 1a Pharma] Box of 100 by 1 A	7 (0.73)
NA		enoxaparin sodium 100 MG/ML Injectable Solution	23 (7.57)	metoprolol succinate 50 MG Extended Release Oral Tablet	6 (11.32)	Fentanyl 0.05 MG/ML Injectable Solution	24 (9.13)	120 ACTUAT fluticasone 0.0275 MG/ACTUAT Nasal Spray [Avamys]	5 (5.15)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi	7 (0.73)
NA		Potassium Chloride 600 MG Oral Capsule	22 (7.24)	diclofenac sodium 100 MG Oral Tablet	5 (9.43)	5 ML Potassium Chloride 150 MG/ML Injection	24 (9.13)	influenza A virus (H1N1) antigen / influenza A virus (H3N2) antigen / influenza B virus antigen Injectable Suspension	5 (5.15)	Sulfamethoxazole / Trimethoprim Oral Tablet [Cotrim Ratiopharm]	6 (0.62)

CPRD GOLD UK n=34		CHUBX France n=304		EBB Estonia n=53		IMASIS Spain n=263		IPCI Netherlands n=97		IQVIA DA Germany n=963	
Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)
NA		nefopam 10 MG/ML Injectable Solution	20 (6.58)	allopurinol 300 MG Oral Tablet	5 (9.43)	20 ML Propofol 10 MG/ML Injection Box of 5	22 (8.37)	polyethylene glycol 3350 13100 MG / potassium chloride 46.6 MG / sodium bicarbonate 179 MG / sodium chloride 351 MG Powder for Oral Solution	5 (5.15)	Eucalyptol 200 MG Oral Capsule [Soledumeln] Box of 20 by M.C.M.Klosterfrau Vertriebs-Gmbh	5 (0.52)
NA		tramadol hydrochloride 50 MG/ML Injectable Solution	19 (6.25)	methylprednisolone 4 MG Oral Tablet	5 (9.43)	5 ML Midazolam 1 MG/ML Injectable Solution Box of 50	20 (7.6)	petrolatum	5 (5.15)	levothyroxine 0.05 MG Oral Tablet [L Thyrox Hexal] Box of 100 by Novartis	5 (0.52)
NA		esomeprazole 40 MG Delayed Release Oral Tablet	15 (4.93)	clarithromycin 500 MG Oral Tablet	5 (9.43)	Omeprazole 40 MG Injectable Solution Box of 50	20 (7.6)	NA		Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A	10 (1.04)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System;

Hospital databases are indicated in green.

12.2.3.2 Characterisation of patients initiating treatment for chronic HCV infection

Characteristics of individuals initiating treatment for chronic HCV infection at the index date and one year prior to index date in terms of comorbidity and in terms of concomitant medications are described in **Table 21 - Table 23**.

Table 21 presents the prevalence of prespecified comorbidities in the study population, revealing considerable variability across databases. Cardiovascular disorders emerged as notably prevalent, with CHUBX reporting 37.7%, IMASIS 11.37%, EBB 5.31% and IQVIA DA Germany 7.11%. Hypertension was also prevalent across databases, with CHUBX reporting 16.39%, IMASIS 5.73%, while EBB reported 2.74% and IQVIA DA Germany 3.76%. In terms of liver disease, cirrhosis exhibited substantial prevalence in CHUBX (32.24%), IMASIS (6.54%), EBB (1.45%) and IQVIA DA Germany (4.07%). CHUBX had the highest prevalence of alcoholism (19.67%), whereas lower prevalence was observed in IMASIS (7.85%) and IQVIA DA Germany (2.13%).

Prevalence of HIV infection ranged from 1.13% in EBB and 1.52% in IQVIA DA Germany to 7.65% in CHUBX. It is noteworthy that prevalence data for prespecified conditions in CPRD GOLD and IPCI were often either missing or recorded as 0. However, these two databases had a limited number of individuals initiating treatment for chronic HCV infection.

Table 21. Prevalence of prespecified comorbidities in patients with chronic HCV infection, at index date and one year prior to index date, per database

		CPRD GOLD UK n=68	CHUBX France n=183	EBB Estonia n=621	IMASIS Spain n=994	IPCI Netherlands n=23	IQVIA DA Germany n=984
Alcoholism	n (%)	<5	36 (19.67)	<5	78 (7.85)	0 (0)	21 (2.13)
Cardiovascular disorder	n (%)	<5	69 (37.7)	33 (5.31)	113 (11.37)	<5	70 (7.11)
Cirrhosis	n (%)	<5	59 (32.24)	9 (1.45)	65 (6.54)	0 (0)	40 (4.07)
Diabetes	n (%)	0 (0)	15 (8.2)	8 (1.29)	24 (2.41)	<5	28 (2.85)
Fatty liver	n (%)	0 (0)	<5	<5	<5	0 (0)	<5
HIV	n (%)	<5	14 (7.65)	7 (1.13)	51 (5.13)	<5	15 (1.52)
Hypertension	n (%)	0 (0)	30 (16.39)	17 (2.74)	57 (5.73)	<5	37 (3.76)
Kidney disease	n (%)	0 (0)	6 (3.28)	<5	9 (0.91)	0 (0)	<5
STD	n (%)	0 (0)	0 (0)	8 (1.29)	<5	0 (0)	<5

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HCV = hepatitis C viral infection; STD= sexually transmitted disease

Hospital databases are indicated in green.

Table 22 presents the prevalence of top 10 comorbidities in the population of individuals with chronic hepatitis C, at index date and one year prior index date, across databases.

The most common condition included hypertension (IQVIA DA Germany: 4.67% , EBB: 18.36%, IMASIS 9.15% CHUBX 20.22%). Blood pressure finding was most frequently reported in CPRD GOLD (51.47%).

Cirrhosis of liver was another prevalent comorbidity, with varying prevalence across databases: 3.86% in IQVIA DA Germany, 5.53% in IMASIS and 36.61% in CHUBX. Additionally, portal hypertension and esophageal varices without bleeding were commonly reported in CHUBX (14.21% and 11.48%, respectively). It's worth noting that cirrhosis is the most common cause of portal hypertension and varices.

Tobacco dependence syndrome was listed among top comorbidities in CHUBX (19.13%) and IMASIS (10.46%) as well as alcohol dependence/abuse (CHUBX: 16.94%, IMASIS: 5.53%).

Table 22. Prevalence of top comorbidities in patients with chronic HCV infection, at index date and one year prior to index date, per database

CPRD GOLD UK n=68		CHUBX France n=183		EBB Estonia n=621		IMASIS Spain n=994		IPCI Netherlands n=23		IQVIA DA Germany n=984	
Comorbidity	n (%)	Comorbidity	n (%)	Comorbidity	n (%)	Comorbidity	n (%)	Comorbidity	n (%)	Comorbidity	n (%)
Blood pressure finding	35 (51.47)	Cirrhosis of liver	67 (36.61)	Essential hypertension	114 (18.36)	Tobacco dependence syndrome	104 (10.46)	NA	-	Opioid dependence	79 (8.03)
Finding of pulse rate	19 (27.94)	Essential hypertension	37 (20.22)	Acute upper respiratory infection	84 (13.53)	Asymptomatic human immunodeficiency virus infection	101 (10.16)	NA	-	Acute hepatitis C	77 (7.83)
Exercise grading	12 (17.65)	Tobacco dependence syndrome	35 (19.13)	Hypertensive heart disease without congestive heart failure	61 (9.82)	Essential hypertension	91 (9.15)	NA	-	Essential hypertension	46 (4.67)
Depressive disorder	8 (11.76)	Alcohol dependence	31 (16.94)	Joint pain	52 (8.37)	Opioid dependence	66 (6.64)	NA	-	Cirrhosis of liver	38 (3.86)
Anxiety disorder	7 (10.29)	Portal hypertension	26 (14.21)	Nerve root disorder	48 (7.73)	Cirrhosis - non-alcoholic	55 (5.53)	NA	-	Steatosis of liver	27 (2.74)
Respiratory tract infection	6 (8.82)	Localized edema	23 (12.57)	Pain in spine	48 (7.73)	Alcohol abuse	55 (5.53)	NA	-	Chronic viral hepatitis B without delta-agent	24 (2.44)
Misuses drugs	5 (7.35)	Fatigue	21 (11.48)	Acute bronchitis	44 (7.09)	Human immunodeficiency virus infection	53 (5.33)	NA	-	Type 2 diabetes mellitus without complication	24 (2.44)
Drug dependence	5 (7.35)	Esophageal varices without bleeding	21 (11.48)	Sleep disorder	43 (6.92)	Continuous opioid dependence	44 (4.43)	NA	-	Illness	23 (2.34)
NA		Thrombocytopenic disorder	20 (10.93)	Viral disease	43 (6.92)	Drug abuse, continuous	44 (4.43)	NA	-	Disease of liver	21 (2.13)
NA		Elevated level of transaminase and lactic acid dehydrogenase	18 (9.84)	Acute hepatitis C	40 (6.44)	Cannabis abuse	41 (4.12)	NA	-	Harmful pattern of use of nicotine	20 (2.03)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HCV = hepatitis C viral infection; NA – non applicable

Hospital databases are indicated in green.

Table 23 presents the top 10 prevalent drugs in the study population, at index date and one year prior to index date, according to the respective database.

Commonly used drugs at index date and one year prior the index date across databases included amoxicillin (EBB: 4.99%, CPRD GOLD: 13.24%, IMASIS: 6.34%), acetaminophen (CPRD GOLD: 11.76%, CHUBX: 15.85%, IMASIS: 21.33%) and proton-pump inhibitor omeprazole (EBB: 7.89% and CPRD GOLD: 13.24).

Other drugs with prevalence exceeding 20% in at least one database included floxacillin (CPRD GOLD: 22.06%) and electrolyte supplement sodium solution (CHUBX: 22.4%, IMASIS: 16%) and pantoprazole (20.2% in IMASIS).

Table 23. Top prevalent drugs in patients with chronic HCV infection, at index date and one year prior to index date, per database

CPRD GOLD UK n=68		CHUBX France n=183		EBB Estonia n=621		IMASIS Spain n=994		IPCI Netherlands n=23		IQVIA DA Germany n=984	
Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)
floxacillin 500 MG Oral Capsule	15 (22.06)	Sodium 9 MG/ML Injectable Solution	41 (22.4)	clarithromycin 500 MG Oral Tablet	51 (8.21)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	212 (21.33)	NA	-	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A	5 (0.51)
amoxicillin 500 MG Oral Capsule	9 (13.24)	acetaminophen 1000 MG Oral Tablet	29 (15.85)	amoxicillin 875 MG / clavulanate 125 MG Oral Tablet	50 (8.05)	500 ML Sodium Chloride 9 MG/ML Injectable Solution Box of 20	159 (16)	NA	-	NA	-
methadone hydrochloride 1 MG/ML Oral Solution	9 (13.24)	Glucose 100 MG/ML / Potassium Chloride 2 MG/ML / Sodium Chloride 4 MG/ML Prefilled Syringe	25 (13.66)	Omeprazole 20 MG Oral Capsule	49 (7.89)	2 ML Dexketoprofen 25 MG/ML Injectable Solution	105 (10.56)	NA	-	NA	-
omeprazole 20 MG Delayed Release Oral Capsule	9 (13.24)	acetaminophen 10 MG/ML Injection	19 (10.38)	zopiclone 7.5 MG Oral Tablet	40 (6.44)	dipyrone 400 MG/ML Injectable Solution	81 (8.15)	NA	-	NA	-
acetaminophen 500 MG Oral Tablet	8 (11.76)	glucose 50 MG/ML Injectable Solution	16 (8.74)	amoxicillin 500 MG Oral Tablet	31 (4.99)	Fentanyl 0.05 MG/ML Injectable Solution	68 (6.84)	NA	-	NA	-
tramadol hydrochloride 50 MG Oral Capsule	8 (11.76)	oxazepam 50 MG Oral Tablet	14 (7.65)	meloxicam 15 MG Oral Tablet	27 (4.35)	glecaprevir 100 MG / pibrentasvir 40 MG Oral Tablet [Maviret] Box of 84 by Abbvie	67 (6.74)	NA	-	NA	-
mirtazapine 45 MG Oral Tablet	7 (10.29)	enoxaparin sodium 100 MG/ML Injectable Solution	12 (6.56)	chloramphenicol / dexamethasone Ophthalmic Solution	26 (4.19)	Amoxicillin 1000 MG / Clavulanate 200 MG Injection	63 (6.34)	NA	-	NA	-
acetaminophen 500 MG / codeine phosphate 30 MG Oral Tablet	6 (8.82)	nefopam 10 MG/ML Injectable Solution	12 (6.56)	alprazolam 0.5 MG Oral Tablet	25 (4.03)	calcium chloride 0.0014 MEQ/ML / potassium chloride 0.004 MEQ/ML / sodium chloride 0.103 MEQ/ML / sodium lactate 0.028 MEQ/ML Injectable Solution	63 (6.34)	NA	-	NA	-

CPRD GOLD UK n=68		CHUBX France n=183		EBB Estonia n=621		IMASIS Spain n=994		IPCI Netherlands n=23		IQVIA DA Germany n=984	
Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)
Albuterol 0.1 MG/ACTUAT Inhalant Powder [Ventolin Evohaler] by Glaxosmithkline	6 (8.82)	pyridoxine 50 MG/ML Injectable Solution	12 (6.56)	metoprolol succinate 50 MG Extended Release Oral Tablet	25 (4.03)	5 ML Midazolam 1 MG/ML Injectable Solution Box of 50	61 (6.14)	NA	-	NA	-
amitriptyline hydrochloride 50 MG Oral Tablet	6 (8.82)	thiamine 50 MG/ML Injectable Solution	12 (6.56)	nebivolol 5 MG Oral Tablet	25 (4.03)	Diazepam 5 MG Oral Tablet Box of 500	57 (5.73)	NA	-	NA	-

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System;

Hospital databases are indicated in green.

12.3 Population-level descriptive epidemiology

12.3.1 Participants

Table 24 provides the total number of individuals in the study population covered by the primary care databases from January 1, 2012, to December 31, 2022**.** The database populations varied: CPRD GOLD (10,433,005), EBB (209,457), IPCI (2,680,988), and IQVIA DA Germany (33,702,562).

12.3.2 Outcome Data and Main Results

Table 24 provides information on the proportion of patients with chronic HBV and HCV infections in the study population covered by the primary care databases from January 1, 2012, to December 31, 2022.

The proportion of patients with chronic HBV infection is presented as the number of cases and the percentage of the respective primary care database population during the specified period. Across the primary care databases, the proportion ranged from 0.01% in CPRD GOLD to 0.16% in EBB.

Similarly, the proportion of patients with chronic HCV infection is provided in terms of the number of cases and the percentage of the database population from 2012 to 2022. The prevalence varies, with the lowest at 0.01% in CPRD GOLD and IPCI and the highest at 0.59% in EBB.

Table 24. Proportion of individuals with chronic HBV and chronic HCV infection during the study period, per primary care database

	CPRD GOLD UK	EBB Estonia	IPCI Netherlands	IQVIA DA Germany
Database population between 01/01/2012 and 31/12/2022	10,433,005	209,457	2,680,988	33,702,562
Chronic HBV infection, n (%) (percentage of database population 2012-2022)	1,154 (0.01)	344 (0.16)	1,285 (0.05)	12,142 (0.04)
Chronic HCV infection, n (%) (percentage of database population 2012-2022)	1,535 (0.01)	1,226 (0.59)	195 (0.01)	12,241 (0.04)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

Proportion of patients with chronic HBV and HCV infection, stratified by sex

Table 13 in **Appendix IV** shows the proportion of all patients with chronic HBV and HCV infections, stratified by sex, across different primary care databases. In chronic HBV infection, sex-based differences are observed across databases. For instance, in EBB the proportion of male cases was notably higher than females, with percentage of 0.18% compared to 0.15% in females. The proportion of male cases and female cases was comparable in other databases. Similar results were observed in chronic HCV infection. The percentage of male cases was considerably higher than females in EBB and IQVIA DA Germany.

Proportion of patients HBV and HCV infection, stratified by age

Table 14 in Appendix IV provides insights into the proportion of all patients diagnosed with chronic HBV and HCV over the study period, stratified by age categories. In chronic HBV infection, overall, the proportion was low across all age groups in all primary care databases. Slightly higher proportions were observed in 18 to 44 age group in CPRD GOLD (0.02% vs. ≤0.01% in other age categories) and 45 and 64 group in EBB, IPCI and IQVIA DA Germany. In chronic HCV infection, the similar trend was observed. For detailed information, please refer to **Table 14** in Appendix IV and the Shiny app (https://data-dev.darwin-eu.org/EUPAS107650-broad/).

Proportion of patients with chronic HBV and HCV infection, stratified by calendar year

Table 15 in **Appendix IV** outlines the proportions of chronic HBV an HCV infections, over the span of the last 10 years (2012-2022), across various primary care databases.

In chronic HBV infection, overall, the proportion was low across all primary care databases. In CPRD GOLD, the proportion consistently remained low and stable, <0.01% in 2012 and 0.01% in 2022. In other databases, the proportion was also low, however, a slight gradual increase was observed over time. For instance, in EBB, the proportion ranged from 0.03% in 2012 to 0.16% in 2021. The proportion in IPCI and IQVIA DA Germany indicated low proportions from 0.02% and 0.01% in 2012 to 0.06% and 0.08%, respectively.

In chronic HCV infection, overall, the proportion was low across all primary care databases but slightly higher than the proportion for chronic HBV infection. In CPRD GOLD and IPCI, the proportion consistently remained low and stable, while in other databases, a slight increase was observed over time (EBB: 0.19% in 2012 to 0.57% in 2021, IQVIA DA Germany: 0.02% in 2012 to 0.06% in 2022). Detailed results can be found in an interactive web-application ("shiny app") at https://data-dev.darwin-eu.org/EUPAS107650-broad/.

12.4 Other Analysis

n/a

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analyzed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfill the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).
Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

14 DISCUSSION

14.1 Key Results

Population-level drug utilization

In this study, the number of individuals diagnosed with chronic HBV and chronic HCV infection collectively included 19,352 patients diagnosed with chronic HBV infection and 24,421 patients diagnosed with chronic HCV infection across six different databases during between 2012 and 2022. The trends in number of patients diagnosed over time has shown variation over the years across different databases. For chronic HBV, overall, there is a noticeable upward trend in the number of diagnoses in most databases. For chronic HCV, the trend suggests a period of rising diagnoses of chronic HCV followed by a potential plateau or decline in recent years, with some variability among databases.

The median age of patients diagnosed with chronic HBV infection ranged from 37 to 53 years across different databases, while in chronic HCV infection ranged from 41 to 54 years, with the majority of patients being males.

The frequency of interferons or antiviral treatment initiation in patients diagnosed with chronic HBV infection varied across different databases ranging from 2.95% in CPRD GOLD (n=34) to 7.87% in IQVIA DA Germany (n=956) in primary care databases, from 11.73% in IMASIS (n=258) to 13.45% in CHUBX (n=298) in hospital databases to 15.41% in EBB (n=53) during the whole study period. The frequency of interferons or antiviral treatment initiation in chronic HCV infection ranged from 4.43% in CPRD GOLD to 11.79% in IPCI in primary care databases, from 3.96% in CHUBX to 21.62% in IMASIS, and 50.65% in EBB during whole reporting period. In terms of temporal trend, trend of fluctuation and gradual decrease in the frequency of any therapeutic intervention (interferons/antivirals) in chronic HBV and HCV was observed over the years across most databases. The frequencies observed in prevalent use of interferons or antiviral treatment mirrored those of new use for both chronic HBV and chronic HCV infection in each database. Regarding specific drugs used for treatment, the most frequently prescribed medications were entecavir, tenofovir disoproxil, and peginterferon alfa-2a for patients with chronic HBV infection. For chronic HCV infection, the commonly prescribed drugs included glecaprevir, ledipasvir/sofosbuvir, ribavirin, sofosbuvir, and sofosbuvir/velpatasvir.

Patient-level drug utilization

A total of 1,610 patients diagnosed with chronic HBV and 1,978 patients diagnosed with chronic HCV infection, initiated treatment with interferons or antivirals. The mean age of these patients ranged from 40

to 55 years old in chronic HBV and from 39 to 53 years old in chronic HCV, with a predominance of male patients for individuals diagnosed with both infections.

In the cohort with chronic HBV diagnosed at any time during the study period and being treated, comorbidities at the index date and one year prior included hypertension, liver related disorders including cirrhosis of liver and hepatic fibrosis, alcohol dependence, tobacco dependence syndrome and type 2 diabetes mellitus. Frequently prescribed medications encompassed antibiotic amoxicillin, analgesics and antipyretics paracetamol, proton-pump inhibitors omeprazole and non-steroidal anti-inflammatory drug diclofenac, while hospital databases frequently recorded electrolyte supplement sodium chloride and glucose injectable solution.

Turning to patients with chronic HCV infection and being treated, comorbidities at the index date and one year prior included hypertension, cirrhosis of liver, portal hypertension and esophageal varices without bleeding, tobacco dependence syndrome and alcohol dependence/abuse. Frequently prescribed medications mirrored those in the chronic HBV cohort with amoxicillin, paracetamol, and omeprazole being common. Additionally, floxacillin, electrolyte supplement sodium solution, and pantoprazole were among the frequently recorded medications in this cohort.

Population-level descriptive epidemiology

The proportion of chronic HBV infection, during the specified period in the study population covered by the primary databases, ranged from 0.01% (CPRD GOLD) to 0.16% (EBB). Similarly, the proportion of chronic HCV infection varied across databases, with the lowest at 0.01% in CPRD GOLD and IPCI and the highest at 0.59% in EBB.

The examination of proportion per calendar year, over the span of the last 10 years (2012-2022), indicated low proportion of chronic HBV infection across databases. While in some databases, the proportion consistently remained low and stable (CPRD GOLD: <0.01% in 2012 and 0.01% in 2022), in other databases, the proportion was also low, however, a slight gradual increase was observed over time. For instance, in EBB, the proportion ranged from 0.03% in 2012 to 0.16% in 2021. In IPCI and IQVIA DA Germany, the proportion remained low namely from 0.02% and 0.01% in 2012 to 0.06% and 0.08%, respectively.

Similarly, the proportion of chronic HCV infection, over the span of the last 10 years (2012-2022), was low across all databases. In CPRD GOLD and IPCI, the proportion consistently remained low and stable, while in other databases, a slight increase was observed over time (EBB: 0.19% in 2012 to 0.57% in 2021, IQVIA DA Germany: 0.02% in 2012 to 0.06% in 2022). Detailed results can be found in an interactive web-application ("shiny app") (https://data-dev.darwin-eu.org/EUPAS107650-broad/).

14.2 Limitations of the research methods

The study drew insights from routinely collected healthcare data, and it is important to consider several factors that may influence the interpretation of the results.

General limitations:

Drug prescriptions: A recording of a prescription did not mean that the patient took the drug. Therefore, assumptions of actual use were made.

Setting: For this study, we included data from 2 hospital data sources (CHUBX in France and IMASIS in Spain). Results of these databases may not necessarily reflect prescription, dispensation and/or administration in other hospital databases. Similarly, this observation extends to primary health care settings and the corresponding national guidelines for diagnosing, prescribing, and monitoring patients with chronic HBV or HCV infections, taking into account disease staging and medication costs.

Study-specific limitations:

Firstly, the definition of chronic HBV and HCV conditions was primarily reliant on clinical diagnosis, lacking the inclusion of laboratory data and measurements of antigens, which would have provided a more comprehensive characterization.

Secondly, while the antiviral medications investigated are specific to HBV and HCV, it is noteworthy that some antiviral drugs, such as lamivudine or tenofovir, possess broader applications and are utilized for treating various viral infections, including HIV.

Thirdly, antiviral treatments are often only prescribed by specialists in hospitals the data from the primary care databases may not provide a robust estimation of treatment. However, in France for the straightforward cases, patients often receive care from their general practitioner near their residence, while more complex cases involving co-infections, comorbidities, or reinfection are typically managed by a multidisciplinary medical team, potentially at a hospital. Therefore, the hospital database from France might not provide a robust estimation of treatment.

Fourthly, the lack of understanding of local clinical pathways for patients with chronic HBV and HCV infections, makes it challenging to interpret the data captured in each database accurately.

Finally, it is essential to acknowledge that changes in guideline recommendations and standard-of-care practices may have impacted treatment decisions, introducing an additional layer of complexity to the interpretation of our results. Understanding these study-specific limitations is crucial for a nuanced interpretation of our findings in the context of chronic HBV and HCV.

14.3 Interpretation

The demographic characteristics of patients with chronic HBV and HCV infection in this study closely resembled findings from previous studies. In this study, the median age of patients diagnosed with chronic HBV infection ranged from 37 to 53 years across different databases, while in chronic HCV infection ranged from 41 to 54 years, with the majority of patients being males. These results align with demographic characteristics reported through routine surveillance from EU/EEA countries to ECDC.(7, 8)

The study revealed that 2.95% to 7.87% patients with chronic HBV infection in primary care databases and 11.73% to 13.45% in hospital databases and biobank initiated treatment with interferon or antivirals, while prevalent use ranged from 2.95% to 15.85%. These estimates align with estimate reported through routine surveillance from EU/EEA countries to ECDC where proportion of patients with chronic HBV on treatment at the national level for one country was reported to be 11% .(4)

Similarly, for chronic HCV infection, 4.43% to 11.79%% patients initiated treatment in primary care database, 3.96% to 21.62% in hospital database and 50.65% in biobank, with prevalent use ranging from 2.44% to 13.13 These figures, excluding the proportion reported in the biobank, align with estimates reported through routine surveillance from EU/EEA countries to ECDC reporting. The proportion ranged from 2.3% to 16.2%.(4)

Interestingly, the highest frequency of treated patients with chronic HCV was reported in EBB (50.65%) .This finding is consistent with previous literature reporting 47% of patients initiating treatment using both outpatients and inpatients data from all hospitals in Estonia where HCV-infected patients were treated.(17) The figures are attributed to Estonia's national HCV eradication strategy, 100% reimbursement of drugs by health insurance and a high level of awareness among Estonian doctors regarding the issue.

In line with current guidelines, the patients with chronic HBV infection were most frequently treated with entecavir, tenofovir disoproxil and peginterferon alfa-2a.(18) Similarly, in line with the current guidelines, patients with chronic HCV infection in our study were treated with glecaprevir, ledipasvir/sofosbuvir, ribavirin, sofosbuvir, and sofosbuvir/velpatasvir.

When investigating the most prevalent comorbidities at time of treatment initiation in individuals with chronic HBV and chronic HCV infections, certain findings such as cirrhosis of liver stand out for their significant public health implications.(4) When considering differences in comorbidity prevalence between the two infections, it's notable that chronic HCV patients consistently exhibit higher rates of alcoholism compared to chronic HBV patients across databases.

This study reveals a low proportion of patients with chronic HBV infection, with estimates consistently at or below 0.05% in primary care databases and at 0.16% in the biobank (EBB). Similarly, chronic HCV showed low estimates at or below 0.04% in primary care databases and at 0.59% in the biobank (EBB). These findings align with previous literature. In a systematic literature review by Bivegete et al. covering the years 2018 to 2021, the median prevalence of chronic HBV in the general population of EU/EEA countries and the United Kingdom was found to be low, estimated at 0.5%.(19) In a study by Campbell et al., varying prevalence rates were reported across different sources in the UK, ranging from 0.27% to 0.73%, consistent with an estimated antenatal chronic HBV prevalence of <0.5%.(20) Additionally, a study conducted in the Netherlands estimated the prevalence of chronic HBV infection at 0.34% and chronic HCV infection at 0.16%.(21) However, while relatively low, these previously reported proportions in the literature are higher than the ones found in this study (0.01% in IPCI, Netherlands, and 0.01% in CPRD, UK).

In terms of trend over calendar years, proportions remained low which is line with previous findings.(7, 8)

14.4 Generalisability

While our study comprised data from 6 European Countries and covers a wide range of settings (hospital in-patient setting, outpatient specialist settings and primary care databases), findings from this study are not to be generalised to other countries or databases but only reflect the situation in the specific region and setting covered by the respective database.

14.5 Other information

NA

15 CONCLUSION

Patients diagnosed with chronic HBV and HCV infections typically belong to the middle-aged adult demographic, with a male predominance and often presenting with comorbidities such as hypertension and diabetes mellitus. Across various databases (excluding EBB, where nearly half of HCV patients received treatment), fewer than 15% of diagnosed patients underwent treatment with interferon or antiviral medications with large variations between databases. Common treatments included entecavir, tenofovir

disoproxil, and peginterferon alfa-2a for chronic HBV infection, while chronic HCV infection was frequently managed with glecaprevir, ledipasvir/sofosbuvir, ribavirin, sofosbuvir, and sofosbuvir/velpatasvir. The proportion of patients chronic HBV and HCV infections remained low in the study population.

16 REFERENCES

1. United Nations. The Sustainable Development Goals New York: UN; 2015 [Available from: https://sdgs.un.org/goals.
2. World Health Organization. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030 Geneva: WHO; 2022 [Available from: https://iris.who.int/bitstream/handle/10665/360348/9789240053779-eng.pdf?sequence=1.

3. WHO Regional Office for Europe. Regional action plans for ending AIDS and the epidemics of viral hepatitis and sexually transmitted infections 2022–2030 Copenhagen: WHO; 2023 [Available from: https://iris.who.int/bitstream/handle/10665/369243/9789289058957-eng.pdf?sequence=7.
4. European Centre for Disease Prevention and Control. Monitoring of responses to the hepatitis B and C epidemics in EU/EEA countries – 2020 data Stockholm: ECDC; 2022 [Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Monitoring-responses-to-hepatitis-B-and-C-epidemics-2020-data.pdf.
5. WHO. Hepatitis: 354 million people globally live with a hepatitis B or C infection. Geneva: World Health Organization; 2023 July 18, 2023.
6. CDC. Global Viral Hepatitis: Millions of People are Affected. US: Centers for Disease Control and Prevention, Division of Viral Hepatitis NCfH, Viral Hepatitis, STD, and TB Prevention; 2021 July 19, 2021.
7. ECDC. Hepatitis B - Annual Epidemiological Report for 2021. Surveellance Report. Stockholm: European Centre for Disease Prevention and Control; 2022 December 22, 2022.
8. ECDC. Hepatitis C - Annual Epidemiological Report for 2021. Surveillance Report. Stockholm: European Centre for Disease Prevention and Control; 2022 December 2022.
9. Tripathi N, Mousa OY. Hepatitis B. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Omar Mousa declares no relevant financial relationships with ineligible companies.: StatPearls Publishing

Copyright © 2023, StatPearls Publishing LLC.; 2023.
10. Basit H, Tyagi I, Koirala J. Hepatitis C. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Isha Tyagi declares no relevant financial relationships with ineligible companies. Disclosure: Janak Koirala declares no relevant financial relationships with ineligible companies.: StatPearls Publishing

Copyright © 2023, StatPearls Publishing LLC.; 2023.
11. WHO. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. Geneva: World Health Organization, Global HIV HaSTIP; 2016 17 May 2016. Report No.: WHO/HIV/2016.06 Contract No.: WHO/HIV/2016.06.
12. Palmaro A, Gauthier M, Conte C, Grosclaude P, Despas F, Lapeyre-Mestre M. Identifying multiple myeloma patients using data from the French health insurance databases: Validation using a cancer registry. Medicine (Baltimore). 2017;96(12):e6189.
13. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.
14. Planas Domingo J, Gallen Castillo M, Malats Riera N, Porta Serra M, Guasch Jordan I, Cardona Hernandez T, et al. [Tumors registered in Hospital del Mar (Barcelona). Descriptive analysis from 1978 to 1986]. Rev Clin Esp. 1988;183(4):175-9.

15. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med. 1999;38(4-5):339-44.
16. al GIe. Diagnostics for OMOP Common Data Model Drug Records: Package 'DrugExposureDiagnostics'. Version 0.4.1. 2023 [Available from: https://cran.r-project.org/web//packages//DrugExposureDiagnostics/DrugExposureDiagnostics.pdf.
17. Mansberg K, Kull K, Salupere R, Prukk T, Margus B, Kariis T, et al. A Population-Based Surveillance Study on the Epidemiology of Hepatitis C in Estonia. Medicina (Kaunas). 2018;54(1).
18. Jeng W, Lok A. Should Treatment Indications for Chronic Hepatitis B Be Expanded? Clin Gastroenterol Hepatol 2021;19(10):2006-14.
19. Bivegete S MA, Trickey A, Thornton Z, Scanlan B, Lim AG, Nerlander L, Fraser H, Walker JG, Hickman M, Vickerman P, Johnson H, Duffell E, Brooks-Pollock E, Christensen H. Estimates of hepatitis B virus prevalence among general population and key risk groups in EU/EEA/UK countries: a systematic review. . Euro Surveill 2023.
20. Campbell C WT, Burrow R, Mandal S, Hippisley-Cox J, Barnes E, Matthews PC. Estimating the epidemiology of chronic Hepatitis B Virus (HBV) infection in the UK: what do we know and what are we missing? Wellcome Open Res. 2023;7:203.
21. Koopsen J, van Steenbergen JE, Richardus JH, Prins M, Op de Coul ELM, Croes EA, et al. Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population. Epidemiol Infect. 2019;147:e147.

17 ANNEXES

17.1 Appendix I: Concept sets for conditions of interest

Final chronic HBV and HCV code list is specified through a set of concepts outlined in **Table 1** and **Table 2**.

Table 1. Code list for chronic HBV infection

Concept Name	Concept ID	Concept Code
Chronic active type B viral hepatitis	4173584	50167007
Chronic aggressive type B viral hepatitis	4009793	1116000
Chronic hepatitis B co-occurrent with hepatitis C and hepatitis D	3654685	838380002
Chronic persistent type B viral hepatitis	4296554	38662009
Chronic type B viral hepatitis	194574	61977001
Chronic viral hepatitis B with hepatitis D	192240	235869004
Chronic viral hepatitis B without delta-agent	439674	186639003
Cirrhosis of liver due to hepatitis B	45772057	103611000119102
Hepatic coma due to chronic hepatitis B	4308946	424340000
Hepatic coma due to chronic hepatitis B with delta agent	46270152	153091000119109
Occult chronic type B viral hepatitis	37017654	713966008
Hepatitis B carrier	4340379	235871004
Hepatitis D superinfection of hepatitis B carrier	197493	235865005

Table 2. Code list for chronic HCV infection

Concept Name	Concept ID	Concept Code
Chronic active hepatitis C	45769525	708198006
Chronic hepatitis C	198964	128302006
Chronic hepatitis C caused by Hepatitis C virus genotype 1	35625141	768127002
Chronic hepatitis C caused by Hepatitis C virus genotype 1a	35625296	768289009
Chronic hepatitis C caused by Hepatitis C virus genotype 1b	35625295	768288001
Chronic hepatitis C caused by Hepatitis C virus genotype 2	35625139	768125005
Chronic hepatitis C caused by Hepatitis C virus genotype 3	35625040	768006009
Chronic hepatitis C caused by Hepatitis C virus genotype 4	35625140	768126006
Chronic hepatitis C caused by hepatitis C virus genotype 5	35624867	767810006
Chronic hepatitis C caused by hepatitis C virus genotype 6	35624866	767809001
Chronic hepatitis C co-occurrent with human immunodeficiency virus infection	3654682	838377003
Chronic hepatitis C with stage 2 fibrosis	45766656	703866000
Chronic hepatitis C with stage 3 fibrosis	45757726	347891000119103
Chronic viral hepatitis C with hepatic coma	763021	435101000124104
Cirrhosis of liver due to chronic hepatitis C	43531723	831000119103
Hepatic coma due to chronic hepatitis C	46270142	146371000119104
Hepatitis C carrier	4340380	235872006

Concept Name	Concept ID	Concept Code
Reactivation of hepatitis C viral hepatitis	45773146	702969000

17.2 Appendix II: Concept sets for exposure of interest

Medication code list is specified through a set of concepts outlined in **Table 3** including all descendants of specified concepts.

Table 3. Code list for drugs of interest

Concept Name	Concept ID	Code
Peginterferon		
Cepeginterferon alfa-2b	45893501	L03AB14
Peginterferon -α-2a	1714165	120608
Peginterferon -α-2b	1797155	253453
Peginterferon alfacon-2	36851449	OMOP5169066
Interferon alfa-2a	1379969	5879
interferon alfa-2b	1380068	5880
Antivirals for treatment of HCV infections		
Ribavirin	1762711	9344
Telaprevir	40239330	1102261
Boceprevir	40238770	1102129
Faldaprevir	36854917	OMOP5172534
Simeprevir	44785086	1482790
Asunaprevir	46233931	1652103
Daclatasvir	46221696	1606218
Sofosbuvir	44785094	1484911
Dasabuvir	45892558	1597381
Elbasvir	35606465	1734628
Grazoprevir	35606467	1734630
Coblopasvir	36852943	OMOP5170559
Sofosbuvir and ledipasvir	36248545, 36248546, 37497233, 37497234, 37497235, 43135174, 43157331, 44082734, 45775026, 45775030	2204094, 1591941, OMOP450086, 1591940, 2204093, 1591939, 2204096, 1591946, OMOP1077365, OMOP450087
Dasabuvir, ombitasvir, paritaprevir and ritonavir	2937842, 2937843, 2937992, 2937994, 36897515, 36897543, 36897682, 36897763, 36898056, 36898068, 40220769, 40220795, 40220796, 40220797, 40221116, 42731574, 42731594, 42731595,	OMOP1115234, OMOP1115234, 1802212, OMOP1090675, OMOP1040464, OMOP1062535, 1802216, OMOP1107063, OMOP1045641, 1802213, 1597387, 1802214, OMOP573412, OMOP2728902, 1597388, OMOP2809924, OMOP2809955, 1802215, OMOP573247, OMOP5154527, OMOP5154666, OMOP2809898,

Concept Name	Concept ID	Code
	42731648, 42731691, 43298018, 43298279, 43298296, 43298357, 43298482, 43298529, 43522495, 43522777, 43522783, 43522786, 43522791, 43522795, 43522809, 43522840, 43522868, 44045833, 44051010, 44067904, 44096044, 44112432, 44120603, 45892214, 45893034	OMOP2724176, OMOP2728995, OMOP2722662, OMOP2731397, OMOP5154526, OMOP5154665, OMOP998131, OMOP1003227, OMOP1007158, OMOP995034, OMOP573249, OMOP573024, OMOP2809892, OMOP2809983, OMOP1001185, OMOP992279, OMOP573376, OMOP573035, OMOP2809610, OMOP2809901, OMOP2809906, OMOP2809910
Ombitasvir, paritaprevir and ritonavir	2937842, 2937843, 2937992, 2937994, 21051386, 21061185, 21061186, 21080806, 21110299, 21139717, 21149567, 35770020, 36897515, 36897543, 36897682, 36897763, 36898056, 36898068, 40220769, 40220795, 40220796, 40220797, 40221116, 40853055, 42731574, 42731594, 42731595, 42731648, 42731691,	1597377, 1659653, OMOP343894, OMOP1115234, OMOP4689614, 1802212, OMOP482196, OMOP548051, OMOP1090675, OMOP482197, 1597379, 1659652 OMOP343895, OMOP4689613, 1659656, OMOP343898, OMOP548052, OMOP4689612, OMOP482198, OMOP548053, OMOP343899, OMOP482200, OMOP1040464, OMOP1044468, OMOP1062535, 1802216, OMOP343897, OMOP1107063, OMOP343900, OMOP2771481, OMOP343901, OMOP482199,

Concept Name	Concept ID	Code
	42963128, 42963129, 42963130, 43138759, 43171802, 43182791, 43182792, 43193751, 43204732, 43204733, 43262883, 43268384, 43268385, 43298018, 43298279, 43298296, 43298357, 43298482, 43298529, 43522495, 43522777, 43522783, 43522786, 43522791, 43522795, 43522809, 43522840, 43522868, 44045833, 44049837, 44051010, 44067904, 44096044, 44112432, 44120603, 44170968, 45892214, 45892556, 45892557, 45893034, 46275632, 46275633, 46275634	OMOP1045641, 1802213, OMOP2051017, OMOP482201, OMOP3047691, 1597387, 1802214, OMOP482202, OMOP573412, OMOP2728902, 1597388, OMOP2809924, OMOP2809955, 1802215, OMOP573247, OMOP5154527, OMOP5154666, OMOP2809898, OMOP2724176, OMOP2728995, OMOP2722662, OMOP2731397, OMOP5154526, OMOP5154665, OMOP998131, OMOP1003227, OMOP1007158, OMOP995034, OMOP573249, OMOP573024, OMOP2809892, OMOP2809983, OMOP1001185, OMOP992279, OMOP573376, OMOP573035, OMOP2809610, OMOP2809901, OMOP2809906, OMOP2809910
Elbasvir and grazoprevir	35409127, 35411280, 35411858, 35411999, 35412079, 35412798, 35413011, 35606469, 35606470,	1734634, 1734639, OMOP1145584, 1734636, 1734638, OMOP1146383, 1734642, OMOP1145664, OMOP1146596, OMOP1109866, OMOP4983810, OMOP2801809,

Concept Name	Concept ID	Code
	35606472, 35606473, 35606474, 36058205, 36058206, 36263604, 36787812, 40745016, 43514694, 43514786, 44115235	OMOP2801901, OMOP1144865, OMOP3114479, OMOP4712174, OMOP1142712, OMOP4983809, OMOP1145443, OMOP4776076
Sofosbuvir and velpatasvir	702125, 702126, 702128, 702129, 702130, 702131, 793745, 793746, 793748, 793749, 793752,1537209, 1537210, 1537211, 1830554, 1830555, 35407752, 35408164, 35410230, 35410850, 35411344, 35412005, 35412137, 35898123, 35898124, 35898125, 35898126, 36249208, 36249209, 36249211, 36249212, 36249215, 36257335, 36261059, 36274850, 36788696, 36788697, 36788698, 36788699, 36788700, 36788701, 36788702, 37499475, 37499476, 37499477, 40747949, 40747950, 40747951, 40747952,44100855	2584195, 1799210, 2584198, 1939327, 1799215, 1939332, 2559845, 2559846, 2584196, 2584200, OMOP1145590, 2288814, 2288815, 1799212, 1799214, 2559847, 2584199, 2584201, OMOP1141749,2288816, OMOP4776954, 1799218, OMOP4776953, 1939329, 1939331, OMOP1145722, 1939335, OMOP1141337, OMOP5042364, OMOP1095486, OMOP5042365, OMOP3125725, OMOP5042363, OMOP4776952, OMOP3108210, OMOP1144929, OMOP5042362, OMOP4776950, OMOP3111934, OMOP4709291, OMOP5155808, OMOP1144435, OMOP4709290, OMOP1143815, OMOP4709292, OMOP4776951, OMOP4709293, OMOP5155807, OMOP4776949, OMOP4776948

Concept Name	Concept ID	Code
Sofosbuvir, velpatasvir and voxilaprevir	793745, 793749, 36788702, 36788701, 793746, 793748, 793752, 36788700, 36788698, 40747951, 40747952, 40747950, 36788699, 40747949, 1830554, 36788697, 36788696	1939327, 1939332, OMOP4776954, OMOP4776953, 1939329, 1939331, 1939335, OMOP4776952, OMOP4776950, OMOP4709291, OMOP4709290, OMOP4709292, OMOP4776951, OMOP4709293, OMOP5155807, OMOP4776949, OMOP4776948
Glecaprevir and pibrentasvir	1537158, 793862, 1537161, 793866, 40743709, 36787555, 36787554	2557905, 1940701, 2557908 1940706, OMOP4713338, OMOP4775820, OMOP4775819
Daclatasvir, asunaprevir and beclabuvir	35142393, 35161682	OMOP4799505, OMOP4818648
Antivirals for treatment of HBV infections		
Adefovir dipivoxil	40133589, 35862150	636214, OMOP5018321
Entecavir	1711246	306266
Telbivudine	1758392	474128
Tenofovir alafenamide	35605546	1721603
Tenofovir disoproxil fumarate	1710281	300195
Lamivudine	1704183	68244
Bulevirtide	36042920	OMOP5047741

17.3 Appendix III: Concept definitions for baseline characteristics (comorbidities)

Table 4. Code list for clinical observation/conditions

Concept Name	Concept ID	Concept Code
Liver cirrhosis	4064161	19943007
Alcoholic fatty liver	193256	50325005
Human immunodeficiency virus infection	439727	86406008
Sexually transmitted disease	440647	8098009
Diabetes mellitus	200687, 201254, 201826, 318712, 376065, 377821, 435216, 443729, 443731, 443732, 443733, 42538169	46635009, 44054006, 420279001, 422099009, 421326000, 422014003, 421893009, 421365002, 422166005, 739681000, 421468001, 420868002
Cardiovascular disease	134057	49601007
Hypertension	320128	59621000
Chronic kidney disease (CKD)	46271022	709044004
Alcoholism	4218106	7200002

17.4 Appendix IV: Supplemental Tables

Table 1. Initiation of interferon or any specified antivirals in patients diagnosed with chronic HBV infection, stratified by sex

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Number of eligible subjects		547	607	964	1,251	212	132	755	1,445	623	662	5,665	6,477
Any Therapeutic intervention													
Interferon/antivirals	n (%)	10 (1.83)	24 (3.95)	88 (9.13)	210 (16.79)	28 (13.21)	25 (18.94)	66 (8.74)	192 (13.29)	37 (5.94)	60 (9.06)	357 (6.3)	599 (9.25)
Therapeutic Drug Class													
Antivirals	n (%)	10 (1.83)	23 (3.79)	87 (9.02)	210 (16.79)	26 (12.26)	20 (15.15)	65 (8.61%)	190 (13.15)	37 (5.94)	60 (9.06)	356 (6.28)	596 (9.2)
Interferons	n (%)	0 (0)	<5	<5	<5	6 (2.83)	9 (6.82)	<5	7 (0.48)	0 (0)	0 (0)	5 (0.09)	8 (0.12)
Drug-specific treatment													
Adefovir	n (%)	0 (0)	0 (0)	<5	<5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5	8 (0.12)
Bulevirtide	n (%)	0 (0)	0 (0)	<5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5	<5
Cepeginterferon	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Entecavir	n (%)	<5	<5	29 (3.01)	73 (5.84)	27 (12.74)	19 (14.39)	35 (4.64)	84 (5.81)	25 (4.01)	51 (7.7)	136 (2.4)	249 (3.84)

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Interferon alfa-2a	n (%)	0 (0)	<5	<5	<5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interferon alfa-2b	n (%)	0 (0)	0 (0)	0 (0)	<5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lamivudine	n (%)	0 (0)	0 (0)	<5	25 (2)	<5	<5	7 (0.93)	21 (1.45)	0 (0)	<5	40 (0.71)	65 (1)
Peginterferon alfa-2a	n (%)	0 (0)	0 (0)	<5	0 (0)	6 (2.83)	9 (6.82)	<5	7 (0.48)	0 (0)	0 (0)	5 (0.09)	9 (0.14)
Peginterferon alfa-2b	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5	<5
Peginterferon alfacon-2	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Telbivudine	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<5	<5
Tenofovir	n (%)	<5	0 (0)	14 (1.45)	41 (3.28)	<5	0 (0)	<5	22 (1.52)	5 (0.8)	9 (1.36)	25 (0.44)	55 (0.85)
Tenofovir disoproxil	n (%)	11 (2.01)	22 (3.62)	61 (6.33)	138 (11.03)	<5	0 (0)	46 (6.09)	135 (9.34)	20 (3.21)	18 (2.72)	227 (4.01)	364 (5.62)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection; IQR = interquartile range;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 2. Initiation of treatment with interferon or any specified antivirals in patients diagnosed with chronic HBV infection, stratified by age

		CPRD GOLD UK				CHUBX France				EBB Estonia*			IMASIS Spain*			IPCI Netherlands				IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	18-44	45-64	≥65	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Number of eligible subjects		19	817	261	55	42	837	879	457	95	190	56	821	846	529	50	659	455	115	158	4,959	5,061	1,970
Any Therapeutic intervention																							
Interferon/antivirals	n (%)	0 (0)	19 (2.33)	12 (4.6)	<5	<5	73 (8.72)	152 (17.29)	72 (15.75)	15 (15.79)	25 (13.16)	13 (23.21)	110 (13.4)	99 (11.7)	49 (9.26)	0 (0)	45 (6.83)	45 (9.89)	7 (6.09)	18 (11.39)	446 (8.99)	374 (7.39)	118 (5.99)
Therapeutic Drug class																							
Antivirals	n (%)	0	18 (2.2)	12 (4.6)	<5	0	73 (8.72)	152 (17.29)	72 (15.75)	9 (9.47)	24 (12.63)	13 (23.21)	107 (13.03)	99 (11.7)	49 (9.26)	0	45 (6.83)	45 (9.89)	7 (6.09)	18 (11.39)	446 (8.99)	370 (7.31)	118 (5.99)
Interferons	n (%)	0	<5	0	0	<5	<5	<5	0	9 (9.47)	<5	<5	8 (0.97)	<5	0	0	0	0	0	0	7 (0.14)	6 (0.12)	0
Drug-specific treatment																							
Adefovir	n (%)	0	0	0	0	0	0	<5	<5	0	0	0	0	0	0	0	0	0	0	0	6 (0.12)	<5	<5
Bulevirtide	n (%)	0	0	0	0	0	0	<5	0	0	0	0	0	0	0	0	0	0	0	0	<5	<5	0
Cepeginterferon	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Entecavir	n (%)	0	<5	<5	<5	0	20 (2.39)	50 (5.69)	32 (7)	10 (10.53)	23 (12.11)	13 (23.21)	38 (4.63)	48 (5.27)	33 (6.24)	0	28 (4.25)	39 (8.57)	9 (7.83)	<5	172 (3.47)	151 (2.98)	58 (2.94)
Interferon alfa-2a	n (%)	0	<5	0	0	<5	<5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Interferon alfa-2b	n (%)	0	0	0	0	0	0	<5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lamivudine	n (%)	0	0	0	0	0	<5	19 (2.16)	6 (1.31)	<5	<5	<5	6 (0.73)	19 (2.25)	<5	0	<5	<5	0	0	44 (0.89)	47 (0.93)	14 (0.71)

		CPRD GOLD UK				CHUBX France				EBB Estonia*			IMASIS Spain*			IPCI Netherlands				IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	18-44	45-64	≥65	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Peginterferon alfa-2a	n (%)	0	0	0	0	<5	0	0	0	9 (9.47)	<5	<5	8 (0.97)	<5	0	0	0	0	0	0	7 (0.14)	7 (0.14)	0
Peginterferon alfa-2b	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<5	<5	0
Peginterferon alfacon-2	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Telbivudine	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<5	<5	0
Tenofovir	n (%)	0	<5	0	0	0	14 (1.67)	32 (3.64)	9 (1.97)	0	<5	0	15 (1.83)	10 (1.18)	<5	0	6 (0.91)	6 (1.32)	<5	0	33 (0.67)	30 (0.59)	17 (0.86)
Tenofovir disoproxil	n (%)	0	20 (2.45)	10 (3.83)	<5	0	56 (6.69)	103 (11.72)	40 (8.75)	<5	0	0	91 (11.08)	64 (7.57)	26 (4.91)	0	23 (3.49)	14 (3.08)	<5	14 (8.86)	296 (5.97)	223 (4.41)	58 (2.94)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection; IQR = interquartile range.

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

*Age category 1-17, which contains <5 patients, has been excluded from the table.

Hospital databases are indicated in green.

Table 3. Initiation of treatment with interferon or any specified antivirals in patients diagnosed with chronic HBV infection, stratified by calendar year

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
	Year	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)
Any Therapeutic intervention													
Interferons/Antivirals	2012	208	NA (NA)	296	32 (10.81)	73	NA (NA)	218	9 (4.13)	169	NA (NA)	740	25 (3.38)
Interferons/Antivirals	2013	362	6 (1.66)	487	21 (4.31)	108	NA (NA)	385	15 (3.9)	298	6 (2.01)	1306	30 (2.3)
Interferons/Antivirals	2014	510	NA (NA)	649	32 (4.93)	145	7 (4.83)	512	22 (4.3)	367	5 (1.36)	1897	47 (2.48)
Interferons/Antivirals	2015	533	NA (NA)	796	35 (4.4)	164	NA (NA)	602	22 (3.65)	451	9 (2)	2448	67 (2.74)
Interferons/Antivirals	2016	454	NA (NA)	951	35 (3.68)	183	NA (NA)	696	17 (2.44)	536	9 (1.68)	3317	56 (1.69)
Interferons/Antivirals	2017	470	NA (NA)	1063	36 (3.39)	205	7 (3.41)	781	16 (2.05)	634	8 (1.26)	4130	66 (1.6)
Interferons/Antivirals	2018	457	NA (NA)	1174	18 (1.53)	236	NA (NA)	1089	32 (2.94)	709	17 (2.4)	4743	65 (1.37)
Interferons/Antivirals	2019	456	NA (NA)	1250	32 (2.56)	265	6 (2.26)	1216	42 (3.45)	766	9 (1.17)	6146	247 (4.02)
Interferons/Antivirals	2020	430	NA (NA)	1266	23 (1.82)	305	10 (3.28)	1232	18 (1.46)	797	12 (1.51)	6651	154 (2.32)
Interferons/Antivirals	2021	388	NA (NA)	1291	21 (1.63)	336	7 (2.08)	1230	37 (3.01)	861	11 (1.28)	6969	94 (1.35)
Interferons/Antivirals	2022	324	5 (1.54)	1256	13 (1.04)			1247	28 (2.25)	897	8 (0.89)	7197	105 (1.46)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection; I

Interferon/antivirals = use of interferon or antivirals. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 4. Initiation of treatment with interferon or any specified antivirals in patients diagnosed with chronic HCV infection, stratified by sex

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Number of eligible subjects		486	1,049	1,680	2,943	735	491	1,616	2,982	76	119	5,091	7,150
Any Therapeutic intervention													
Interferon/antivirals	n (%)	26 (5.35)	42 (4)	49 (2.92)	134 (4.55)	369 (50.2)	252 (51.32)	311 (19.29)	683 (22.9)	8 (10.53)	15 (12.61)	372 (7.31)	607 (8.49)
Therapeutic Drug Class													
Antivirals	n (%)	26 (5.35)	42 (4)	49 (2.92)	132 (4.49)	368 (50.07)	252 (51.32)	310 (19.18)	683 (22.9)	8 (10.53)	15 (12.61)	371 (7.29)	607 (8.49)
Interferons	n (%)	<5	12 (1.14)	7 (0.42)	12 (0.41)	101 (13.74)	77 (15.68)	12 (0.74)	20 (0.67)	0	0	45 (0.88)	63 (0.88)
Drug-specific treatment													
Asunaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Asunaprevir / Beclabuvir / Daclatasvir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Boceprevir	n (%)	0	0	0	<5	6 (0.82)	<5	0	0	0	0	5 (0.1)	12 (0.17)
Cepeginterferon	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Coblopasvir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Daclatasvir	n (%)	<5	<5	<5	31 (1.05)	0	0	15 (0.93)	28 (0.94)	<5	<5	9 (0.18)	28 (0.39)
Dasabuvir	n (%)	<5	<5	0	0	117 (15.92)	71 (14.46)	34 (2.1)	33 (1.11)	<5	<5	10 (0.2)	18 (0.25)
Dasabuvir / Ombitasvir / Paritaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Elbasvir	n (%)	<5	0	<5	<5	85 (11.56)	49 (9.98)	22 (1.36)	32 (1.07)	<5	0	45 (0.88)	66 (0.92)
Elbasvir / Grazoprevir	n (%)	<5	0	<5	<5	85 (11.56)	49 (9.98)	22 (1.36)	32 (1.07)	<5	0	45 (0.88)	66 (0.92)
Faldaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Glecaprevir	n (%)	9 (1.85)	12 (1.14)	5 (0.3)	19 (0.65)	110 (14.97)	93 (18.94)	113 (6.99)	328 (11)	<5	<5	114 (2.24)	198 (2.77)
Grazoprevir	n (%)	<5	0	<5	<5	85 (11.56)	49 (9.98)	22 (1.36)	32 (1.07)	<5	0	45 (0.88)	66 (0.92)
Interferon alfa-2a	n (%)	<5	8 (0.76)	<5	<5	<5	0	0	0	0	0	0	0
Interferon alfa-2b	n (%)	<5	<5	0	0	0	0	0	0	0	0	0	0
Ledipasvir / Sofosbuvir	n (%)	<5	<5	5 (0.3)	28 (0.95)	0	0	37 (2.29)	60 (2.01)	<5	<5	95 (1.87)	110 (1.54)
Ombitasvir / paritaprevir / ritonavir	n (%)	<5	<5	0	0	117 (15.92)	71 (14.46)	35 (2.17)	37 (1.24)	<5	<5	11 (0.22)	22 (0.31)
Peginterferon alfa-2a	n (%)	0	<5	6 (0.36)	10 (0.34)	89 (12.11)	63 (12.83)	10 (0.62)	16 (0.54)	0	0	40 (0.79)	48 (0.67)

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Peginterferon alfa-2b	n (%)	0	0	0	0	22 (2.99)	19 (3.87)	<5	5 (0.17)	0	0	9 (0.18)	16 (0.22)
Peginterferon alfacon-2	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Ribavirin	n (%)	<5	16 (1.53)	22 (1.31)	31 (1.05)	109 (14.83)	86 (17.52)	29 (1.79)	72 (2.41)	<5	<5	69 (1.36)	113 (1.58)
Simeprevir	n (%)	0	0	<5	6 (0.2)	7 (0.95)	<5	0	0	0	<5	<5	<5
Sofosbuvir	n (%)	11 (2.26)	20 (1.91)	27 (1.61)	105 (3.57)	16 (2.18)	10 (2.04)	174 (10.77)	357 (11.97)	6 (7.89)	12 (10.08)	192 (3.77)	305 (4.27)
Sofosbuvir / Velpatasvir	n (%)	6 (1.23)	10 (0.95)	12 (0.71)	42 (1.43)	16 (2.18)	10 (2.04)	115 (7.120	263 (8.82)	0	<5	69 (1.36)	131 (1.83)
Sofosbuvir / Velpatasvir / Voxilaprevir	n (%)	<5	<5	0	0	0	0	<5	14 (0.47)	0	0	6 (0.12)	5 (0.07)
Telaprevir	n (%)	0	<5	<5	5 (0.17)	11 (1.5)	5 (1.02)	0	0	0	0	7 (0.14)	14 (0.2)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 5. Initiation of treatment with interferon or any specified antivirals in patients diagnosed with chronic HCV infection, stratified by age

		CPRD GOLD UK				CHUBX France				EBB Estonia*			IMASIS Spain				IPCI Netherlands*			IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	18-44	45-64	≥65	1-17	18-44	45-64	≥65	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Number of eligible subjects		8	921	545	61	5	794	2,678	1,146	578	532	116	8	1,209	2,025	1,356	45	118	31	108	4,069	5,730	2,326
Any Therapeutic intervention																							
Interferon/antivirals	n (%)	0	48 (5.21)	18 (3.3)	<5	0	28 (3.53)	132 (4.93)	23 (2.01)	266 (46.02)	302 (56.77)	53 (45.69)	5 (62.5)	356 (29.45)	469 (23.16)	164 (12.09)	7 (15.56)	15 (12.71)	<5	<5	405 (9.95)	466 (8.13)	106 (4.56)
Therapeutic Drug class																							
Antivirals	n (%)	0	48 (5.21)	18 (3.3)	<5	0	27 (3.4)	131 (4.89)	23 (2.01)	265 (45.85)	302 (56.77)	53 (45.69)	5 (62.5)	356 (29.45)	468 (23.11)	164 (12.09)	7 (15.56)	15 (12.71)	<5	<5	404 (9.93)	466 (8.13)	106 (4.56)
Interferons	n (%)	0	13 (1.41)	<5	0	0	<5	13 (0.49)	<5	102 (17.65)	73 (13.72)	<5	<5	6 (0.5)	22 (1.09)	0	0	0	0	<5	65 (1.6)	38 (0.66)	<5
Drug-specific treatment																							
Asunaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Asunaprevir / Beclabuvir / Daclatasvir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Boceprevir	n (%)	0	0	0	0	0	0	<5	0	<5	6 (1.13)	0	0	0	0	0	0	0	0	<5	7 (0.17)	8 (0.14)	<5
Cepeginterferon	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Coblopasvir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Daclatasvir	n (%)	0	<5	<5	0	0	<5	28 (1.05)	<5	0	0	0	0	17 (1.41)	23 (1.14)	<5	<5	<5	0	0	19 (0.47)	18 (0.31)	0
Dasabuvir	n (%)	0	<5	<5	0	0	0	0	0	52 (9)	122 (22.93)	14 (12.07)	0	9 (0.74)	24 (1.19)	34 (2.51)	<5	<5	0	0	10 (0.25)	13 (0.23)	5 (0.21)
Dasabuvir / Ombitasvir / Paritaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

		CPRD GOLD UK				CHUBX France				EBB Estonia*			IMASIS Spain				IPCI Netherlands*			IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	18-44	45-64	≥65	1-17	18-44	45-64	≥65	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Elbasvir	n (%)	0	<5	0	0	0	<5	<5	<5	50 (8.65)	65 (12.22)	19 (16.38)	0	11 (0.91)	31 (1.53)	12 (0.88)	0	0	<5	0	30 (0.74)	61 (1.06)	20 (0.86)
Elbasvir / Grazoprevir	n (%)	0	<5	0	0	0	<5	<5	<5	50 (8.65)	65 (12.22)	19 (16.38)	0	11 (0.91)	31 (1.53)	12 (0.88)	0	0	<5	0	30 (0.74)	61 (1.06)	20 (0.86)
Faldaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Glecaprevi	n (%)	0	16 (1.74)	<5	<5	0	7 (0.88)	12 (0.45)	5 (0.44)	93 (16.09)	93 (17.48)	17 (14.66)	<5	185 (15.3)	209 (10.32)	46 (3.39)	0	<5	<5	0	130 (3.19)	150 (2.62)	32 (1.38)
Grazoprevir	n (%)	0	<5	0	0	0	<5	<5	<5	50 (8.65)	65 (12.22)	19 (16.38)	0	185 (15.3)	209 (10.32)	46 (3.39)	0	0	<5	0	30 (0.74)	61 (1.06)	20 (0.86)
Interferon alfa-2a	n (%)	0	9 (0.98)	<5	0	0	<5	<5	0	<5	0	0	0	0	0	0	0	0	0	0	0	0	0
Interferon alfa-2b	n (%)	0	<5	<5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ledipasvir / Sofosbuvir	n (%)	0	<5	<5	0	0	6 (0.76)	24 (0.9)	<5	0	0	0	0	21 (1.74)	48 (2.37)	28 (2.06)	<5	<5	<5	<5	74 (1.82)	101 (1.76)	29 (1.25)
Ombitasvir / paritaprevir / ritonavir	n (%)	0	<5	<5	0	0	0	0	0	52 (9)	122 (22.93)	14 (12.07)	0	11 (0.91)	27 (1.33)	34 (2.51)	<5	<5	0	0	14 (0.34)	14 (0.24)	5 (0.21)
Peginterferon alfa-2a	n (%)	0	<5	0	0	0	<5	11 (0.41)	<5	82 (14.19)	68 (12.78)	<5	0	6 (0.5)	20 (0.99)	0	0	0	0	0	56 (1.38)	30 (0.52)	<5
Peginterferon alfa-2b	n (%)	0	0	0	0	0	0	0	0	24 (4.15)	16 (3.01)	<5	<5	0	<5	0	0	0	0	<5	12 (0.29)	10 (0.17)	<5
Peginterferon alfacon-2	n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ribavirin	n (%)	0	13 (1.41)	7 (1.28)	0	0	5 (0.63)	42 (1.57)	6 (0.52)	108 (18.69)	84 (15.79)	<5	<5	20 (1.65)	58 (2.86)	19 (1.4)	<5	<5	0	<5	87 (2.14)	81 (1.41)	13 (0.56)
Simeprevir	n (%)	0	0	0	0	0	<5	6 (0.22)	<5	<5	8 (1.5)	0	0	0	0	0	0	<5	0	0	<5	<5	0
Sofosbuvir	n (%)	0	19 (2.06)	12 (2.2)	0	0	19 (2.39)	99 (3.7)	14 (1.22)	11 (1.9)	12 (2.26)	<5	0	170 (14.06)	263 (12.99)	98 (7.23)	6 (13.33)	11 (9.32)	<5	<5	199 (4.89)	243 (4.24)	54 (2.32)
Sofosbuvir / Velpatasvir	n (%)	0	8 (0.87)	8 (1.47)	0	0	11 (1.39)	38 (1.42)	5 (0.44)	11 (1.9)	12 (2.26)	<5	0	131 (10.84)	187 (9.23)	60 (4.42)	<5	<5	0	0	88 (2.16)	92 (1.61)	20 (0.86)
Sofosbuvir / Velpatasvir / Voxilaprevir	n (%)	0	<5	<5	0	0	0	0	0	0	0	0	0	6 (0.5)	10 (0.49)	<5	0	0	0	0	<5	6 (0.1)	<5

		CPRD GOLD UK				CHUBX France				EBB Estonia*			IMASIS Spain				IPCI Netherlands*			IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	18-44	45-64	≥65	1-17	18-44	45-64	≥65	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Telaprevir	n (%)	0	<5	<5	0	0	<5	7 (0.26)	0	5 (0.87)	10 (1.88)	<5	0	0	0	0	0	0	0	0	8 (0.2)	11 (0.19)	<5

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HCV = hepatitis C viral infection; IQR = interquartile range.

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

*Age category 1-17, which contains <5 patients, has been excluded from the table.

Hospital databases are indicated in green.

Table 6. Initiation of treatment with interferon or any specified antivirals in patients diagnosed with chronic HCV infection, stratified by calendar year

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
	Year	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)
Any Therapeutic intervention													
Interferons/Antivirals	2012	268	0	1,112	16 (1.44)	390	46 (11.79)	667	NA (NA)	-	0 (NA)	1,306	35 (2.68)
Interferons/Antivirals	2013	530	7 (1.32)	1,630	18 (1.1)	546	47 (8.61)	1,020	7 (0.69)	-	0 (NA)	2,233	39 (1.75)
Interferons/Antivirals	2014	670	5 (0.75)	1,974	21 (1.06)	658	34 (5.17)	1,266	15 (1.18)	18	0	2,874	50 (1.74)
Interferons/Antivirals	2015	701	7 (1)	2,283	17 (0.74)	750	33 (4.4)	1,463	60 (4.1)	48	5 (10.42)	3,743	137 (3.66)
Interferons/Antivirals	2016	738	NA (NA)	2,562	21 (0.82)	858	99 (11.54)	1,821	75 (4.12)	75	6 (8)	4,312	97 (2.25)
Interferons/Antivirals	2017	751	11 (1.46)	2,696	24 (0.89)	928	67 (7.22)	1,997	99 (4.96)	93	NA (NA)	4,678	113 (2.42)
Interferons/Antivirals	2018	759	12 (1.58)	2,753	25 (0.91)	1,005	83 (8.26)	2,248	213 (9.48))	102	NA (NA)	4,885	81 (1.66)
Interferons/Antivirals	2019	772	11 (1.42)	2,703	21 (0.78)	1,075	78 (7.26)	2,371	184 (7.76)	109	0	5,340	125 (2.34)
Interferons/Antivirals	2020	706	5 (0.71)	2,545	9 (0.35)	1,141	55 (4.82)	2,288	134 (5.86)	121	NA (NA)	5,361	118 (2.2)
Interferons/Antivirals	2021	677	NA (NA)	2,358	6 (0.25)	1,182	79 (6.68)	2,234	100 (4.48)	137	NA (NA)	5,325	103 (1.93)
Interferons/Antivirals	2022	567	NA (NA)	2,101	5 (0.24)			2,134	103 (4.83)	133	NA (NA)	5,282	81 (1.53)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HCV = hepatitis C viral infection;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 7. Prevalent use of interferon or any specified antivirals treatment in patients diagnosed with chronic HBV infection, stratified by sex

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Number of eligible subjects		547	607	964	1,251	212	132	755	1,445	623	662	5,665	6,477
Any Therapeutic intervention													
Interferon/antivirals	n (%)	10 (1.83)	24 (3.95)	101 (10.48)	250 (19.98)	28 (13.21)	25 (18.94)	72 (9.54)	205 (14.19)	45 (7.22)	80 (12.08)	371 (6.55)	624 (9.63)
Therapeutic Drug Class													
Antivirals	n (%)	10 (1.83)	23 (3.79)	100 (10.37)	250 (19.98)	27 (12.74)	20 (15.15)	71 (9.4)	206 (14.26)	45 (7.22)	80 (12.08)	370 (6.53)	621 (9.59)
Interferons	n (%)	0	<5	<5	<5	6 (2.83)	9 (6.82)	5 (0.66)	7 (0.48)	0	0	5 (0.09)	8 (0.12)
Drug-specific treatment													
Adefovir	n (%)	0	0	<5	<5	0	0	0	<5	0	<5	<5	13 (0.2)
Bulevirtide	n (%)	0	0	<5	0	0	0	0	0	0	0	<5	<5
Cepeginterferon	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Entecavir	n (%)	<5	<5	38 (3.94)	84 (6.71)	27 (12.74)	19 (14.39)	59 (7.81)	161 (11.14)	35 (5.62)	72 (10.88)	150 (2.65)	291 (4.49)
Interferon alfa-2a	n (%)	0	<5	<5	<5	0	0	0	0	0	0	0	0
Interferon alfa-2b	n (%)	0	0	0	<5	0	0	0	0	0	0	0	0
Lamivudine	n (%)	<5	<5	11 (1.14)	37 (2.96)	<5	<5	24 (3.18)	67 (4.64)	<5	6 (0.91)	52 (0.92)	93 (1.44)
Peginterferon alfa-2a	n (%)	0	0	<5	0	6 (2.83)	10 (7.58)	5 (0.66)	8 (0.55)	0	<5	5 (0.09)	9 (0.14)
Peginterferon alfa-2b	n (%)	0	0	0	0	0	0	0	0	0	0	<5	<5
Peginterferon alfacon-2	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Telbivudine	n (%)	0	0	0	0	0	0	<5	<5	0	0	<5	<5
Tenofovir	n (%)	<5	0	15 (1.56)	45 (3.6)	<5	0	<5	26 (1.8)	5 (0.8)	11 (1.66)	25 (0.44)	61 (0.94)
Tenofovir disoproxil	n (%)	12 (2.19)	24 (3.95)	79 (8.2)	195 (15.59)	<5	0	105 (13.91)	276 (19.1)	29 (4.65)	34 (5.14)	274 (4.84)	468 (7.23)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 8. Treatment with interferon or any specified antivirals in patients diagnosed with chronic HBV infection, stratified by age

		CPRD GOLD UK				CHUBX France				EBB Estonia				IMASIS Spain				IPCI Netherlands				IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Number of eligible subjects		19	817	261	55	42	837	879	457	<5	95	190	56	<5	821	846	529	50	659	455	115	158	4,959	5,061	1,970
Any Therapeutic intervention																									
Interferon/antivirals	n (%)	0	19 (2.33)	12 (4.6)	<5	<5	80 (9.56)	186 (21.16)	84 (18.38)	NA	15 (15.79)	25 (13.16)	13 (23.21)	NA	119 (14.49)	109 (12.88)	49 (9.26)	<5	62 (9.41)	53 (11.65)	8 (6.96)	18 (11.39)	462 (9.32)	391 (7.73)	124 (6.29)
Therapeutic Drug class																									
Antivirals	n (%)	0	18 (2.2)	12 (4.6)	<5	0	80 (9.56)	186 (21.16)	84 (18.38)	NA	10 (10.53)	24 (12.63)	13 (23.21)	NA	118 (14.37)	110 (13)	49 (9.26)	<5	62 (9.41)	53 (11.65)	8 (6.96)	18 (11.39)	462 (9.32)	387 (7.65)	124 (6.29)
Interferons	n (%)	0	<5	0	0	<5	<5	<5	0	NA	9 (9.47)	<5	<5	NA	9 (1.1)	<5	0	0	0	0	0	0	7 (0.14)	6 (0.12)	0
Drug-specific treatment																									
Adefovir	n (%)	0	0	0	0	0	0	<5	<5	NA	0	0	0	NA	0	0	0	0	<5	0	0	0	8 (0.16)	5 (0.1)	<5
Bulevirtide	n (%)	0	0	0	0	0	0	<5	0	NA	0	0	0	NA	0	0	0	0	0	0	0	0	<5	<5	0
Cepeginterferon	n (%)	0	0	0	0	0	0	0	0	NA	0	0	0	NA	0	0	0	0	0	0	0	0	0	0	0
Entecavir	n (%)	0	<5	<5	<5	0	24 (2.87)	62 (7.05)	36 (7.88)	NA	10 (10.53)	23 (12.11)	13 (23.21)	NA	62 (7.55)	91 (10.76)	67 (12.67)	<5	41 (6.22)	51 (11.21)	14 (12.17)	5 (3.16)	189 (3.81)	180 (3.56)	68 (3.45)
Interferon alfa-2a	n (%)	0	<5	0	0	<5	<5	0	0	NA	0	0	0	NA	0	0	0	0	0	0	0	0	0	0	0
Interferon alfa-2b	n (%)	0	0	0	0	0	0	<5	0	NA	0	0	0	NA	0	0	0	0	0	0	0	0	0	0	0
Lamivudine	n (%)	0	<5	<5	0	0	<5	33 (3.75)	11 (2.41)	NA	<5	<5	<5	NA	21 (2.56)	60 (7.09)	10 (1.89)	<5	<5	<5	<5	0	48 (0.97)	72 (1.42)	25 (1.27)

		CPRD GOLD UK				CHUBX France				EBB Estonia				IMASIS Spain				IPCI Netherlands				IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Peginterferon alfa-2a	n (%)	0	0	0	0	<5	0	0	0	NA	10 (10.53)	<5	<5	NA	9 (1.1)	<5	0	0	<5	0	0	0	7 (0.14)	7 (0.14)	0
Peginterferon alfa-2b	n (%)	0	0	0	0	0	0	0	0	NA	0	0	0	NA	0	0	0	0	0	0	0	0	<5	<5	0
Peginterferon alfacon-2	n (%)	0	0	0	0	0	0	0	0	NA	0	0	0	NA	0	0	0	0	0	0	0	0	0	0	0
Telbivudine	n (%)	0	0	0	0	0	0	0	0	NA	0	0	0	NA	<5	<5	0	0	0	0	0	0	<5	<5	0
Tenofovir	n (%)	0	<5	0	0	0	15 (1.79)	34 (3.87)	11 (2.41)	NA	0	<5	0	NA	16 (1.95)	13 (1.54)	<5	<5	7 (1.06)	6 (1.32)	<5	0	34 (0.69)	33 (0.65)	19 (0.96)
Tenofovir disoproxil	n (%)	0	21 (2.57)	12 (4.6)	<5	0	68 (8.12)	143 (16.27)	63 (13.79)	NA	<5	0	0	NA	183 (22.29)	150 (17.73)	48 (9.07)	0	37 (5.61)	25 (5.49)	<5	14 (8.86)	360 (7.26)	296 (5.85)	72 (3.65)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 9. Prevalent use of interferon or any specified antivirals in patients diagnosed with chronic HBV infection, stratified by calendar year

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
	Year	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)
Any Therapeutic intervention													
Interferons/Antivirals	2012	208	NA (NA)	296	50 (16.89)	73	NA (NA)	218	18 (8.26)	169	10 (5.92)	740	59 (7.97)
Interferons/Antivirals	2013	362	6 (1.66)	487	29 (5.95)	108	NA (NA)	385	16 (4.16)	298	12 (4.03)	1306	31 (2.37)
Interferons/Antivirals	2014	510	NA (NA)	649	40 (6.16)	145	7 (4.83)	512	26 (5.08)	367	9 (2.45)	1897	47 (2.48)
Interferons/Antivirals	2015	533	NA (NA)	796	38 (4.77)	164	NA (NA)	602	23 (3.82)	451	9 (2)	2448	70 (2.86)
Interferons/Antivirals	2016	454	NA (NA)	951	41 (4.31)	183	NA (NA)	696	18 (2.59)	536	10 (1.87)	3317	56 (1.69)
Interferons/Antivirals	2017	470	NA (NA)	1063	40 (3.76)	205	7 (3.41)	781	17 (2.18)	634	10 (1.58)	4130	66 (1.6)
Interferons/Antivirals	2018	457	NA (NA)	1174	22 (1.87)	236	NA (NA)	1089	32 (2.94)	709	20 (2.82)	4743	66 (1.39)
Interferons/Antivirals	2019	456	NA (NA)	1250	34 (2.72)	265	6 (2.26)	1216	42 (3.45)	766	9 (1.17)	6146	247 (4.02)
Interferons/Antivirals	2020	430	NA (NA)	1266	23 (1.82)	305	10 (3.28)	1232	19 (1.54)	797	14 (1.76)	6651	154 (2.32)
Interferons/Antivirals	2021	388	NA (NA)	1291	21 (1.63)	336	7 (2.08)	1230	38 (3.09)	861	13 (1.51)	6969	94 (1.35)
Interferons/Antivirals	2022	324	5 (1.54)	1256	13 (1.04)			1247	28 (2.25)	897	9 (1)	7197	105 (1.46)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HBV = hepatitis B viral infection;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 10. Prevalent us of interferon or any specified antivirals in patients diagnosed with chronic HCV infection, stratified by sex

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Number of eligible subjects		486	1,049	1,680	2,943	735	491	1,616	2,982	76	119	5,091	7,150
Any Therapeutic intervention													
Interferon/antivirals	n (%)	26 (5.35)	43 (4.1)	49 (2.92)	139 (4.72)	407 (55.37)	276 (56.21)	331 (20.48)	721 (24.18)	10 (13.16)	16 (13.45)	381 (7.48)	621 (8.69)
Therapeutic Drug Class													
Antivirals	n (%)	26 (5.35)	43 (4.1)	49 (2.92)	137 (4.66)	406 (55.24)	276 (56.21)	332 (20.54)	721 (24.18)	10 (13.16)	16 (13.45)	381 (7.48)	620 (8.67)
Interferons	n (%)	<5	12 (1.14)	7 (0.42)	12 (0.41)	119 (16.19)	88 (17.92)	14 (0.87)	21 (0.7)	0	0	50 (0.98)	73 (1.02)
Drug-specific treatment													
Asunaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Asunaprevir / Beclabuvir / Daclatasvir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Boceprevir	n (%)	0	0	0	<5	6 (0.82)	<5	0	0	0	0	5 (0.1)	12 (0.17)
Cepeginterferon	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Coblopasvir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Daclatasvir	n (%)	<5	<5	<5	31 (1.05)	0	0	15 (0.93)	29 (0.97)	<5	<5	9 (0.18)	29 (0.41)
Dasabuvir	n (%)	<5	<5	0	0	117 (15.92)	71 (14.46)	37 (2.29)	35 (1.17)	<5	<5	10 (0.2)	18 (0.25)
Dasabuvir / Ombitasvir / Paritaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Elbasvir	n (%)	<5	0	<5	<5	85 (11.56)	49 (9.98)	22 (1.36)	32 (1.07)	<5	0	45 (0.88)	66 (0.92)
Elbasvir / Grazoprevir	n (%)	<5	0	<5	<5	85 (11.56)	49 (9.98)	22 (1.36)	32 (1.07)	<5	0	45 (0.88)	66 (0.92)
Faldaprevir	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Glecaprevir	n (%)	9 (1.85)	12 (1.14)	5 (0.3)	19 (0.65)	110 (14.97)	93 (18.94)	113 (6.99)	331 (11.1)	<5	<5	116 (2.28)	199 (2.78)
Grazoprevir	n (%)	<5	0	<5	<5	85 (11.56)	49 (9.98)	22 (1.36)	32 (1.07)	<5	0	45 (0.88)	66 (0.92)
Interferon alfa-2a	n (%)	<5	8 (0.76)	<5	<5	<5	0	0	0	0	0	0	0
Interferon alfa-2b	n (%)	<5	<5	0	0	0	0	0	0	0	0	0	0
Ledipasvir / Sofosbuvir	n (%)	<5	<5	5 (0.3)	29 (0.99)	0	0	37 (2.29)	63 (2.11)	<5	<5	95 (1.87)	111 (1.55)
Ombitasvir / paritaprevir / ritonavir	n (%)	<5	<5	0	0	117 (15.92)	71 (14.46)	38 (2.35)	39 (1.31)	<5	<5	11 (0.22)	22 (0.31)
Peginterferon alfa-2a	n (%)	0	<5	6 (0.36)	10 (0.34)	98 (13.33)	68 (13.85)	15 (0.93)	28 (0.94)	0	0	45 (0.88)	63 (0.88)

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Peginterferon alfa-2b	n (%)	0	0	0	0	24 (3.27)	23 (4.68)	<5	7 (0.23)	0	0	10 (0.2)	18 (0.25)
Peginterferon alfacon-2	n (%)	0	0	0	0	0	0	0	0	0	0	0	0
Ribavirin	n (%)	<5	16 (1.53)	22 (1.31)	34 (1.16)	125 (17.01)	95 (19.35)	40 (2.48)	104 (3.49)	<5	<5	77 (1.51)	130 (1.82)
Simeprevir	n (%)	0	0	<5	6 (0.2)	7 (0.95)	<5	0	0	0	<5	<5	<5
Sofosbuvir	n (%)	11 (2.26)	20 (1.91)	27 (1.61)	106 (3.6)	16 (2.18)	10 (2.04)	176 (10.89)	369 (12.37)	7 (9.21)	13 (10.92)	193 (3.79)	309 (4.32)
Sofosbuvir / Velpatasvir	n (%)	6 (1.23)	10 (0.95)	12 (0.71)	42 (1.43)	16 (2.18)	10 (2.04)	115 (7.12)	266 (8.92)	<5	<5	70 (1.37)	133 (1.86)
Sofosbuvir / Velpatasvir / Voxilaprevir	n (%)	<5	<5	0	0	0	0	<5	14 (0.47)	0	0	6 (0.12)	5 (0.07)
Telaprevir	n (%)	0	<5	<5	5 (0.17)	11 (1.5)	5 (1.02)	0	0	0	0	7 (0.14)	15 (0.21)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HCV = hepatitis C viral infection;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 11. Prevalent use of interferon or any specified antivirals in patients diagnosed with chronic HCV infection, stratified by age

		CPRD GOLD UK				CHUBX France				EBB Estonia				IMASIS Spain				IPCI Netherlands				IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Number of eligible subjects		8	921	545	61	5	794	2,678	1,146	-	578	532	116	8	1,209	2,025	1,356	<5	45	118	31	108	4,069	5,730	2,326
Any Therapeutic intervention																									
Interferon/antivirals	n (%)	0	48 (5.21)	19 (3.49)	<5	0	29 (3.65)	136 (5.08)	23 (2.01)		291 (50.35)	338 (63.53)	54 (46.55)	5 (62.5)	360 (29.78)	513 (25.33)	174 (12.83)	NA	7 (15.56)	17 (14.41)	<5	<5	412 (10.13)	479 (8.36)	109 (4.69)
																		NA							
Therapeutic Drug class																		NA							
Antivirals	n (%)	0	48 (5.21)	19 (3.49)	<5	0	28 (3.53)	135 (5.04)	23 (2.01)		290 (50.17)	338 (63.53)	54 (46.55)	5 (62.5)	360 (29.78)	514 (25.38)	174 (12.83)	NA	7 (15.56)	17 (14.41)	<5	<5	412 (10.13)	479 (8.36)	108 (4.64)
Interferons	n (%)	0	13 (1.41)	<5	0	0	<5	13 (0.49)	<5		114 (19.72)	90 (16.92)	<5	<5	7 (0.58)	24 (1.19)	0	NA	0	0	0	<5	69 (1.7)	46 (0.8)	7 (0.3)
																		NA							
Drug-specific treatment																		NA							
Asunaprevir	n (%)	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Asunaprevir / Beclabuvir / Daclatasvir	n (%)	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Boceprevir	n (%)	0	0	0	0	0	0	<5	0		<5	6 (1.13)	0	0	0	0	0	NA	0	0	0	<5	7 (0.17)	8 (0.14)	<5
Cepeginterferon	n (%)	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Coblopasvir	n (%)	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Daclatasvir	n (%)	0	<5	<5	0	0	<5	28 (1.05)	<5		0	0	0	0	18 (1.49)	23 (1.14)	<5	NA	<5	<5	0	0	20 (0.49)	18 (0.31)	0
Dasabuvir	n (%)	0	<5	<5	0	0	0	0	0		52 (9)	122 (22.93)	14 (12.07)	0	10 (0.83)	26 (1.28)	36 (2.65)	NA	<5	<5	0	0	10 (0.25)	13 (0.23)	5 (0.21)

		CPRD GOLD UK				CHUBX France				EBB Estonia				IMASIS Spain				IPCI Netherlands				IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Dasabuvir / Ombitasvir / Paritaprevir	n (%)	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Elbasvir	n (%)	0	<5	0	0	0	<5	<5	<5		50 (8.65)	65 (12.22)	19 (16.38)	0	11 (0.91)	31 (1.53)	12 (0.38)	NA	0	0	<5	0	30 (0.74)	61 (1.06)	20 (0.86)
Elbasvir / Grazoprevir	n (%)	0	<5	0	0	0	<5	<5	<5		50 (8.65)	65 (12.22)	19 (16.38)	0	11 (0.91)	31 (1.53)	12 (0.88)	NA	0	0	<5	0	30 (0.74)	61 (1.06)	20 (0.86)
Faldaprevir	n (%)	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Glecaprevir	n (%)	0	16 (1.74)	<5	<5	0	7 (0.88)	12 (0.45)	5 (0.44)		93 (16.09)	93 (17.48)	17 (14.66)	0	186 (15.38)	211 (10.42)	46 (3.39)	NA	0	<5	<5	0	131 (3.22)	151 (2.64)	33 (1.42)
Grazoprevir	n (%)	0	<5	0	0	0	<5	<5	<5		50 (8.65)	65 (12.22)	19 (16.38)	0	11 (0.91)	31 (1.53)	12 (0.88)	NA	0	0	<5	0	30 (0.74)	61 (1.06)	20 (0.86)
Interferon alfa-2a	n (%)	0	9 (0.98)	<5	0	0	<5	<5	0		<5	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Interferon alfa-2b	n (%)	0	<5	<5	0	0	0	0	0		0	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Ledipasvir / Sofosbuvir	n (%)	0	<5	<5	0	0	6 (0.76)	25 (0.93)	<5		0	0	0	0	21 (1.74)	49 (2.42)	30 (2.21)	NA	<5	<5	<5	<5	74 (1.82)	102 (1.78)	29 (1.25)
Ombitasvir / paritaprevir / ritonavir	n (%)	0	<5	<5	0	0	0	0	0		52 (9)	122 (22.93)	14 (12.07)	0	12 (0.99)	29 (1.43)	36 (2.65)	NA	<5	<5	0	0	14 (0.34)	14 (0.24)	5 (0.21)
Peginterferon alfa-2a	n (%)	0	<5	0	0	0	<5	11 (0.41)	<5		90 (15.57)	74 (13.91)	<5	0	10 (0.83)	33 (1.63)	0	NA	0	0	0	0	64 (1.57)	41 (0.72)	<5
Peginterferon alfa-2b	n (%)	0	0	0	0	0	0	0	0		27 (4.67)	19 (3.57)	<5	5 (62.5)	<5	<5	<5	NA	0	0	0	<5	12 (0.29)	11 (0.19)	<5
Peginterferon alfacon-2	n (%)	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	NA	0	0	0	0	0	0	0
Ribavirin	n (%)	0	13 (1.41)	7 (1.28)	0	0	5 (0.63)	45 (1.68)	6 (0.52)		118 (20.42)	99 (18.61)	<5	5 (62.5)	27 (2.23)	87 (4.3)	25 (1.84)	NA	<5	<5	0	<5	97 (2.38)	93 (1.62)	16 (0.69)
Simeprevir	n (%)	0	0	0	0	0	<5	6 (0.22)	<5		<5	8 (1.5)	0	0	0	0	0	NA	0	<5	0	0	<5	<5	0
Sofosbuvir	n (%)	0	19 (2.06)	12 (2.2)	0	0	19 (2.39)	100 (3.73)	14 (1.22)		11 (1.9)	12 (2.26)	<5	0	172 (14.23)	268 (13.23)	105 (7.74)	NA	6 (13.33)	13 (11.02)	<5	<5	200 (4.92)	247 (4.31)	54 (2.32)

		CPRD GOLD UK				CHUBX France				EBB Estonia				IMASIS Spain				IPCI Netherlands				IQVIA DA Germany			
		1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65	1-17	18-44	45-64	≥65
Sofosbuvir / Velpatasvir	n (%)	0	8 (0.87)	8 (1.47)	0	0	11 (1.39)	38 (1.42)	5 (0.44)		11 (1.9)	12 (2.26)	<5	0	131 (10.84)	189 (9.33)	61 (4.5)	NA	<5	<5	0	0	88 (2.16)	95 (1.66)	20 (0.86)
Sofosbuvir / Velpatasvir / Voxilaprevir	n (%)	0	<5	<5	0	0	0	0	0		0	0	0	0	6 (0.5)	10 (0.49)	<5	NA	0	0	0	0	<5	6 (0.1)	<5
Telaprevir	n (%)	0	<5	<5	0	0	<5	7 (0.26)	0		5 (0.87)	10 (1.88)	<5	0	0	0	0	NA	0	0	0	0	8 (0.2)	12 (0.21)	<5

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HCV = hepatitis C viral infection;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 12. Prevalent use of interferon or any specified antivirals in patients diagnosed with chronic HCV infection, stratified by calendar year

		CPRD GOLD UK		CHUBX France		EBB Estonia		IMASIS Spain		IPCI Netherlands		IQVIA DA Germany	
	Year	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)	Population	N (%)
Any Therapeutic intervention													
Interferons/Antivirals	2012	268	0	1,112	18 (1.62)	390	65 (16.67)	667	6 (0.9)		0 (NA)	1,306	48 (3.68)
Interferons/Antivirals	2013	530	8 (1.51)	1,630	18 (1.1)	546	47 (8.61)	1,020	8 (0.78)		0 (NA)	2,233	40 (1.79)
Interferons/Antivirals	2014	670	5 (0.75)	1,974	22 (1.11)	658	39 (5.93)	1,266	16 (1.26)	18	0	2,874	50 (1.74)
Interferons/Antivirals	2015	701	7 (1)	2,283	17 (0.74)	750	37 (4.93)	1,463	73 (4.99)	48	5 (10.42)	3,743	140 (3.74)
Interferons/Antivirals	2016	738	NA (NA)	2,562	21 (0.82)	858	110 (12.82)	1,821	80 (4.39)	75	8 (10.67)	4,312	99 (2.3)
Interferons/Antivirals	2017	751	11 (1.46)	2,696	25 (0.93)	928	76 (8.19)	1,997	106 (5.31)	93	NA (NA)	4,678	114 (2.44)
Interferons/Antivirals	2018	759	12 (1.58)	2,753	26 (0.94)	1005	92 (9.15)	2,248	229 (10.19)	102	NA (NA)	4,885	81 (1.66)
Interferons/Antivirals	2019	772	11 (1.42)	2,703	21 (0.78)	1,075	81 (7.53)	2,371	192 (8.1)	109	0	5,340	126 (2.36)
Interferons/Antivirals	2020	706	5 (0.71)	2,545	9 (0.35)	1,141	56 (4.91)	2,288	135 (5.9)	121	NA (NA)	5,361	120 (2.24)
Interferons/Antivirals	2021	677	NA (NA)	2,358	6 (0.25)	1,182	80 (6.77)	2,234	102 (4.57)	137	NA (NA)	5,325	103 (1.93)
Interferons/Antivirals	2022	567	NA (NA)	2,101	5 (0.24)	-	-	2,134	105 (4.92))	133	NA (NA)	5,282	81 (1.53)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, CHUBX = Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System, HCV = hepatitis C viral infection;

Interferon/antivirals = use of interferon or antivirals. Drug-specific treatment refers to exposure to any specific interferon and /or antivirals. NB: The subjects contributing to the use pattern analysis are not mutually exclusive. Some use patterns might have been obscured if the number of observations is <5.

Hospital databases are indicated in green.

Table 13. Proportion of all patients with chronic HBV and HCV infection, stratified by sex

	CPRD GOLD UK		EBB Estonia		IPCI Netherlands		IQVIA DA Germany	
Sex	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)
Chronic HBV infection								
Females	5,317,892	547 (0.01)	137,218	212 (0.15)	1,371,812	623 (0.05)	15,043,857	5,665 (0.03)
Males	5,115,113	607 (0.01)	72,239	132 (0.18)	1,309,176	662 (0.05)	18,658,705	6,477 (0.04)
Chronic HCV infection								
Females	5,317,892	486 (0.01)	137,218	735 (0.54)	1,371,812	76 (0.01)	18,658,705	5,091 (0.03)
Males	5,115,113	1,049 (0.02)	72,239	491 (0.68)	1,309,176	119 (0.01)	15,043,857	7,150 (0.05)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

Table 14. Proportion of all patients with HBV and HCV infection, stratified by age

	CPRD GOLD UK		EBB Estonia		IPCI Netherlands		IQVIA DA Germany	
Age categories	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)
Chronic HBV infection								
1 to 17	2,350,892	21 (<0.01)	13,857	-	617,788	56 (0.01)	4,788,108	163 (<0.01)
18 to 44	4,683,082	829 (0.02)	126,491	98 (0.08)	1,140,116	669 (0.06)	12,044,439	5,011 (0.04)
45 to 64	2,940,239	358 (0.01)	100,458	230 (0.23)	823,528	605 (0.07)	10,992,185	5,833 (0.05)
≥ 65	2,029,058	69 (<0.01)	43,807	88 (0.2)	552,073	185 (0.03)	8,511,426	2,582 (0.03)
Chronic HCV infection								
1 to 17	2,350,892	8 (<0.01)	13,857	0	617,788		4,788,108	115 (<0.01)
18 to 44	4,683,082	923 (0.02)	126,491	578 (0.46)	1,140,116	46 (<0.01)	12,044,439	4,094 (0.03)
45 to 64	2,940,239	702 (0.02)	100,458	662 (0.66)	823,528	131 (0.02)	10,992,185	6,465 (0.06)
≥ 65	2,029,058	107 (0.01)	43,807	209 (0.48)	552,073	50 (0.01)	8,511,426	2,960 (0.03)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, HBV = hepatitis B viral infection; HCV = hepatitis C viral infection;

Some use patterns might have been obscured if the number of observations is <5.

Table 15. Proportion of all patients with HBV and HCV infection, stratified by calendar year

	CPRD GOLD UK		EBB Estonia		IPCI Netherlands		IQVIA DA Germany	
Calendar Year	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)	Population	Cases (%)
Chronic HBV infection								
2012	7,182,065	208 (0)	209,457	73 (0.03)	1,002,428	169 (0.02)	8,368,655	740 (0.01)
2013	7,096,932	362 (0.01)	209,147	108 (0.05)	1,045,462	298 (0.03)	9,058,126	1,306 (0.01)
2014	6,745,640	510 (0.01)	208,819	145 (0.07)	1,098,382	367 (0.03)	9,639,958	1,897 (0.02)
2015	6,114,133	533 (0.01)	208,477	164 (0.08)	1,235,166	451 (0.04)	10,135,689	2,448 (0.02)
2016	5,229,767	454 (0.01)	208,136	183 (0.09)	1,289,210	536 (0.04)	10,883,456	3,317 (0.03)
2017	4,715,584	470 (0.01)	207,761	205 (0.1)	1,337,941	634 (0.05)	11,377,340	4,130 (0.04)
2018	4,401,658	457 (0.01)	207,420	236 (0.11)	1,335,348	709 (0.05)	11,427,406	4,743 (0.04)
2019	4,252,032	456 (0.01)	207,016	265 (0.13)	1,421,434	766 (0.05)	11,691,795	6,146 (0.05)
2020	3,975,589	430 (0.01)	206,489	305 (0.15)	1,482,341	797 (0.05)	11,440,351	6,651 (0.06)
2021	3,645,908	388 (0.01)	205,860	336 (0.16)	1,537,227	861 (0.06)	11,360,116	6,969 (0.06)
2022	3,333,306	324 (0.01)	-	-	1,509,800	897 (0.06)	9,561,099	7,197 (0.08)
Chronic HCV infection								
2012	7,182,065	268 (0)	209,457	390 (0.19)	1,002,428	-	8,368,655	1,306 (0.02)
2013	7,096,932	530 (0.01)	209,147	546 (0.26)	1,045,462	-	9,058,126	2,233 (0.02)
2014	6,745,640	670 (0.01)	208,819	658 (0.32)	1,098,382	18 (0)	9,639,958	2,874 (0.03)
2015	6,114,133	701 (0.01)	208,477	750 (0.36)	1,235,166	48 (0)	10,135,689	3,743 (0.04)
2016	5,229,767	738 (0.01)	208,136	858 (0.41)	1,289,210	75 (0.01)	10,883,456	4,312 (0.04)
2017	4,715,584	751 (0.02)	207,761	928 (0.45)	1,337,941	93 (0.01)	11,377,340	4,678 (0.04)
2018	4,401,658	759 (0.02)	207,420	1,005 (0.48)	1,335,348	102 (0.01)	11,427,406	4,885 (0.04)
2019	4,252,032	772 (0.02)	207,016	1,075 (0.52)	1,421,434	109 (0.01)	11,691,795	5,340 (0.05)
2020	3,975,589	706 (0.02)	206,489	1,141 (0.55)	1,482,341	121 (0.01)	11,440,351	5,361 (0.05)
2021	3,645,908	677 (0.02)	205,860	1,182 (0.57)	1,537,227	137 (0.01)	11,360,116	5,325 (0.05)
2022	3,333,306	567 (0.02)			1,509,800	133 (0.01)	9,561,099	5,282 (0.06)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, IPCI = Integrated Primary Care Information Project, DA = Disease Analyzer, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection;

Some use patterns might have been obscured if the number of observations is <5.