HepCare

Hepatitis C antiviral Therapy Registry

A joint study organized by the European Society for Antiviral Research among European participants

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Contents

Confirmed Study participants

Anders Sönnenborg, *Karolinska Institute; Sweden*

Anne Boerekamps, *Erasmus Medical Centre; the Netherlands*

Anne Wensing, *University Medical Centre Utrecht; the Netherlands*

Bart Rijnders, *Erasmus Medical Centre; the Netherlands*

Brendan Healy, *Public health wales microbiology Cardiff; United Kingdom*

Carole Seguin-Devaux, *Luxembourg institute of health; Luxembourg*

Clive Loveday, *ICVC charitable trust; United Kingdom*

Dominique Salmon, *Hopital Cochin; France*

Federico García, *Hospital Universitario San Cecilio, Spain*

Ana Belén Pérez, *Hospital Universitario San Cecilio, Spain*

Francesca Ceccherini-Silberstein, *University of Rome Tor Vergata, Italy*

Joop Arends, *University Medical Centre Utrecht; The Netherlands*

Karen Steenhuisen, *Bernhoven hospital; the Netherlands*

Katherine Stene Johansen, *Norwegian institute of Public Health; Norway*

Maja Lunar, *University of Ljubljana & Slovenia AIDS reference; Slovenia*

Mark Claassen, *Rijstate Arnhem; The Netherlands*

Mario Poljak, *University of Ljubljana & Slovenia AIDS reference; Slovenia*

Murat Sayan, *Kocaeli University & Medical Faculty; Turkey*

Oana Sandulescu, *Carol Davila University of Medicine and Pharmacy, Romania*

Orna Mor, *Virology laboratory and national HIV reference laboratory; Israel*

Pjotr Zabek, *Hospital for infectious diseases Warschauw; Poland*

Rafael Usubillaga, *Hospital Cochin, France*

Tomasz Dyda, *Hospital for infectious diseases Warschauw; Poland*

Ton Dofferhoff, *CWZ Nijmegen & University Medical Centre Nijmegen; The Netherlands*

Tulay Yalcinkaya, *Turkisch national public health institution; Turkey*

Valentina Svicher, *University Rome tor Vergata; Italy*

Valeria Cento, *University Rome tor Vergata; Italy*

Organizing structure

Coordinating committee

Annemarie Wensing MD, PhD

Carlo Federico Perno, MD, PhD

Carole Devaux, MD,PhD

Charles Boucher, MD, PhD

Federico Garcia, PhD

Francesca Ceccherini-Silberstein, PhD

Joop Arends, MD, PhD

Study coordinators

Stephanie Popping, MD; S.Popping@erasmusmc.nl

Valeria Cento, PhD; Valeriacento@gmail.com

Federico Garcia, PhD; fegarcia@ugr.es

Antoinet van Kessel; A.vankessel-4@umcutrecht.nl

Statistical analysist

David van de Vijver, PhD; D.vandevijver@erasmusmc.nl

Background

Around 170 million people worldwide are infected with Hepatitis C (HCV). HCV treatment radically changed with the introduction of Direct-Acting Antivirals (DAA). A more than 90% sustained virological response (SVR) is gained with second-generation DAAS[1]. Despite high SVR, virological failure can occur often caused by the selection of resistance associated amino acids (RASs).

There are two different forms of RAS. Those that are due to natural occurring nucleotide changes, the polymorphisms, and the ones that emerges under the pressure of DAA. As an illustration, the Q80K is a polymorphism that is common in patients with a GT1a infection. This RAS is transmittable and can jeopardize treatment with Simeprevir [2-5]. The natural frequency of polymorphism differs between, HCV Geno- and subtypes, geographic region and method of sequencing.

The risk of developing RAS during DAA treatment depends on host- and virus-related factors, the properties of the drugs used and the treatment strategies applied[6-8]. RAS that develop during treatment can occur in all three protein regions, NS3, NS5A and NS5B. The persistence of RASs differs between these regions, for instance the RASs in NS3A persist for months, whereas NS5A RASs can linger for years[9-11]. Considering the fact that some RASs can give cross-resistance within the same drug class, this limits re-treatment options[8,12,13].

In randomized controlled trial most patients respond well to combinations of DAA[14]. However, patients enrolled in clinical trials do not reflect the real patient population encountered in routine practice. Since the recent availability of DAAs, there are a limited amount of real life studies. Since SVR rates in real-world settings are comparable with clinical trials[15], resistance data available provides a small sample size. Furthermore, there is no standardization over methods. The heterogeneity of the data makes it difficult to interpreter data for clinical decision making. Therefore we established HEPCARE, a European surveillance project for HCV resistance.

Study aim and objectives

The aim of HEPCARE is to provide a European surveillance for DAA resistance. HEPCARE is a combined European dataset including HCV sequences linked to patient demographics, clinical and virological information. We aim for a bigger sample size than individual studies to perform in-depth data analyses and create more knowledge about antiviral resistance.

Objectives

- Primary objectives
  - Analyze the mutational patterns associated with virological failure to DAA regimens in real-life
  - Provide knowledge about clinically significant RASs detected at DAA failure
  - Assess the frequency of complex/multiclass resistance patterns jeopardizing retreatment option
  - Contribute to a correct interpretation of HCV resistance testing at DAA-failure
- Secondary objectives
  - Assess prevalence of natural RASs in Europe and their impact on DAA-failure.

Methods

Study design

Observational multi-center study

Inclusion criteria

- Men or women > 18 years old
- PCR confirmed HCV infection
- Sequence available
    - preferably Baseline and Failure
- Receiving DAA therapy
- Treatment outcome available

Study population

The population includes all men/woman > 18 years old who received DAA therapy across multiple clinical sites within Europe. The datasets contains patient's characteristics, clinical data, viral load measurements and viral genotyping results. A full specification of the dataset is available in the supplement. (**Dataset information**)

Data collection

Each contributing partner who agreed with the data sharing agreement will gather and upload their data. Data can be submitted, using an online form available at http://hepvir.crp-sante.lu/, on a per-patient basis in the Hepcare database. Access codes will be distributed on demand by one of our study coordinators. Forms for batch uploading are available and can be requested and sent to our study coordinators. All data will be stored on the HEPVIR server at Luxembourg institute of Health (Strassen, Luxembourg). Submitted datasets can only be accessed by members of the coordinating committee and study coordinators. In addition, individual submitters can access, review and withdraw their submitted data at any time prior to analysis.

Confidentiality of records

Partners are responsible for assuring anonymity of their patients. Patients should not be identified by name or submitted data, or during verbal communications. Patients are allocated a study number, with which only the submitter can identify the patient. In addition only the year of birth, and not the date, will be recorded

Ethical approval

This registry will only include data that are already available. Patients will not be approached to obtain additional samples or information. The data must be submitted by the submitter under a local medical or human research ethics committee approved protocol arranged by the submitter. Please contact one of our study coordinators to request if local ethical approval is already obtained.

Data analysis and reports

Hepcare depends on the data that will become available. A sample size analysis is therefore not feasible. Since the prevalence of RAS is different per RAS and genotype different numbers of samples are needed. To show an indication of the number of samples needed by a certain prevalence of the RAS and varying between precision we used the following formula. The results of this calculation are displayed in table 1.

$$n = \frac{Z \pm \rho\,(1 - \rho)}{D^2}$$

n = sample size
Z = 1.96 (95% confidence interval)
ρ = prevalence of mutation
D = precision of confidence interval

Prevalence RAS	Precision confidence interval 0.01	0.02	0.03	0.04	0.05
1%	381	NA	NA	NA	NA
3%	1118	280	125	70	45
5%	1825	457	203	115	73
10%	3458	865	385	217	139
20%	6147	1537	683	385	246
30%	8068	2017	897	505	323
40%	9220	2305	1025	577	369

Table 1. NA = not applicable

Note: the table shows the number of participants that are required to show a particular prevalence at a pre-defined precision. For example, with the estimated number of uploaded baseline sequences for the next two years (N > 1000, see table 1.) we can already identify a RAS with a prevalence of 10% with a 95% CI from 8-12%.

Longitudinal data

If multiple resistance analyses have been performed on different samples of an individual patient, these should be considered as separate entries. Thus each with concurrent serological and clinical data coupled to the genotypic analysis draw date.

Drug resistance

Assessment of the impact of drug resistance on therapy response will be performed by using web-based resistance interpretation algorithms[16].

Governance

The ESAR-HEPVIR database will contain all data submitted to HepCare. Submission of data to the HepCare database does not affect original ownership of data. The owner of the data reserves the time right to review or withdraw summited data at any time prior to submission of the final manuscript. Permission of the submitters will be requested for any new analysis that is not described in the objectives of this protocol. No transfer of a center's data will be performed without a written consent of the submitter. Primary analysis will be the patterns of resistance in relation to the genotype and drug regimens used. Secondary analysis may be done in the future but permission needs to be obtained from all principal investigators.

Publication of data

Data of the study will be published using the ESAR authorship rules.

Guidelines for authorship

Criteria for Inclusion as Authors in Conference Abstracts and Journal Articles Deriving from Use of HEPCARE Data

A. Proponent and collaborators

1) The proponent of a work (internal or external to HEPCARE) who, in addition to carrying out the scientific idea, will give the input for the analysis and write the abstract of any congressional communication and the first draft of the manuscript is entitled to the first name.
2) Proposer's collaborators (maximum 2, in the case of collaborators belonging to the same center of the proposer, maximum 3 in the case of multi-center collaborators) are entitled to the second/last name and to the third name, agreeing the position with the proposer .
3) The author of the statistical analysis, if additional to the group of 3 or 4 proposer and collaborators, has the right to the second or last name, with priority of choice compared to the first collaborator of the proposer.
4) A further author may be added during a review of a paper, if the specific reviewer's comments require skills that are deemed to be found outside of the proposing group. In this case, the addition of the new collaborator may be decided by the proposing group, provided

5) that such addition is compatible with the maximum number of authors allowed by the journal.
6) The proposer has the right to change his/her collaborators in a research project resulting from an approved proposal, and to add additional contributors if the maximum number of authors was not reached at the time of submitting the request.
7) The proposer has to notify all the representatives of the centers contributing to the project of the state of progress of the work derived from the proposal. Any submission of abstracts or papers derived from the proposal must be communicated at least one week in advance of the actual submission, so that any co-authors can comment.

B. Role of the Scientific Committee

8) Among the members of the scientific committee, only those who have actually contributed substantially to the proposal (design, analysis, writing of the manuscript) are entitled be coauthors, in a position proportionate to the given contribution. In the absence of such a contribution, the simple revision of the study proposal as a member of the Scientific Committee does not give any right to be included among the authors of the publication.

C. Representatives of HEPCARE centers

9) The HEPCARE centers contributing with valid data will have the name of a representative, according to the rotation mechanism described in the next point [9], until reaching the maximum number of authors allowed by the Journal or congress in consideration. In the absence of a precise indication on maximum authors' number, for international publications will apply the limit of a total 15 authors. The center's representative to be included as co-author has to be indicated by the center's referent. The center's referent has the right to select his/her representative co-author according to the criteria he considers appropriate.
10) The rotation criteria for the inclusion of centers representatives contributing to publication are set out as follows:
    a. The number of centers that will have their own referent among the authors of the paper/abstract will be given by the difference between the maximum number of names allowed under point [8] and the number of authors from [1-4]. In any case, a minimum of 5 centers not represented in points [1-4] must be included among the authors of each publication.
    b. The priority of inclusion for centers that have given their consent to the specific study will be obtained on the basis of the percentage of useful cases provided on the total of cases used for the study itself. Depending on the number established under (a) above, a representative for each of the highest priority centers will be included among the authors.
    c. In order to protect the position of centers that can provide data on a limited number of patients, each center whose representative does not join the authors of a specific study, while allowing the use of their data, keeps the score calculated according to the previous paragraph [b] and the sum for subsequent studies. The cumulative score is reset only when the center arrives to place its representative among the authors of the paper/abstract.

d. In case of multiple publications derived from a single data request, the same representatives of the centers are kept among coauthors.

11) All center referrals will be included in all papers as "HEPCARE Collaborative Group" in the appendix.

Supplement:

1) Dataset information

<u>Mandatory Identification</u> - Unique patient ID number - Center - Abstractor initials	 *Open field* *Open field* *Open field*
<u>Mandatory demographics</u> - Year of birth - Gender	 *YEAR* *M/F/transsexual*
<u>Optional demographics</u> - Country of birth - Region of residence	 *countries* *regions*
<u>Mandatory clinical</u> - Route of infection - Co-infection HIV - Co-infection HBV - Cirrhosis - Liver status METAVIR -Diagnostic tool liver status - Previous HCV therapy - Date start current therapy - Date stop current therapy - - Specification of HCV therapy - Discontinuation of HCV treatment -Outcome HCV treatment - Viral rebound	 *Unknown,[Blood ,bloodproducts, organs and tissue], Hemodialysis, IDU, MSM, Mother-to-child, [Occupational exposure - needle injuries],[non-occupational exposures incl. sticks, bites, tattoo piercing], [sexual transmission –heterosexual] , other* *Yes/no/unknown* *Yes/no/unknown* *Yes/no/unknown* *Missing data , F0, F1, F2, F3, F4 compensated, F4 decompensated* *Missing data, biopsy, fibroscan, clinical, seromarker* *Missing data, Yes but no DAAs, Yes but with first generation DAAs, yes with second generation DAAs, No* *Missing data/ MM/year* *Missing data / MM/Year* *Drop down menu* *No treatment discontinuation, protocol, adverse events, drop-out, death, unknown reason* *Missing data, SVR, relapse, breakthrough, non-responder, null-responder, partial-responder, reinfection, compliance , discontinuation* *Date*
<u>Optional clinical</u> - CD4 start HCV therapy - CD4 failure HCV therapy - Date start previous HCV therapy - Past HCV treatment duration	 *Open field* *Open field* *MM/Year* *8/12/18/24/48 weeks*

- Date stop previous HCV therapy	*MM/Year*
- Outcome past HCV treatment	*Missing data, SVR, relapse, breakthrough, non-responder, null-responder, partial-responder, reinfection, compliance , discontinuation*
- Liver status MELD/CTP	*Multiple choice*
- Date last fibro assessment	*MM/Year*
- Date stop current HCV therapy	*MM/Year*
-Hepatocellular carcinoma	*Yes/No*
- Date HCC diagnosis	*MM/Year*
Mandatory virological	
- HCV genotype	*1a, 1b, 2,3,4,5,6,7, mixed and undetermined*
- Test for HCV genotype	*Missing data/ direct sequencing / inno-lipa, Real time PCR*
- Date genotyping	*- MM/Year*
- Baseline viral load	*Missing data / Open field*
- Draw date viral load	*Missing data/ MM/year*
- Viral load under therapy	*Open field – Missing data*
- Viral load draw date (at week no)	*Open field – Missing data/ week no.*
- Sequence at failure	*Open field*
- Sequence identifier	*Open field*
- Sequence date	*Missing data, MM/Year*
- Sequence method	*Missing data, in-house sanger sequencing, in house ultradeep sequencing*
	Missing data/ NS3/ NS5A/ NS5B
	Illumine, Pyro, ..
	Baseline/Failure
- Gene	*Yes/No*
- Ultradeep sequencing method	
- Type	
- Next gen sequencing available	
Optional virological	
- HCV RNA assay	*Missing data, Amplicor HCV monitor, Cobas Amplicor HCV monitor, Versant HCV RNA, Cx HCV RNA, SuperQuant*

More information you can find in the metadataset file

2) Definitions and data entry

Unique patient ID number: applies only for the submitter

IDU: injecting drug user

MSM: men-who-have-sex-with-men

Protocol – treatment discontinuation: stop when patient was supposed to stop

Specification of treatment: please contact one of our study coordinators if the required direct-acting antiviral is not on our list

Previous HCV treatment: please identify previous HCV treatment
Reinfection: confirmed reinfection with sequence; different HCV genotype if only baseline sequence is available. Cave: baseline genotyping errors or mixed infections

Relapse: Patient who had an undetectable HCV level after 12 weeks or after completion of treatment but whose virus rebounded after they completed HCV treatment.

Breakthrough: the on-treatment presence of detectable HCV RNA on 2 consecutive serum tests conducted after a previous on-treatment serum test showed an undetectable level of HCV RNA with a real-time quantitative PCR or similarly sensitive test. The HCV RNA level must be at least 100 IU/mL on the second positive serum test.

Non-responder: also referred to as treatment failure. A patient who does not have a undetectable SVR-12 or, if they stay on treatment for 24 weeks, does not have a 2-log drop in HCV viral load or undetectable viral load during therapy.

Null-responder: patient who achieves little or no decrease in HCV viral load during HCV treatment

Partial-responder: A patient who experiences at least a 2-log decrease in HCV viral load during HCV treatment

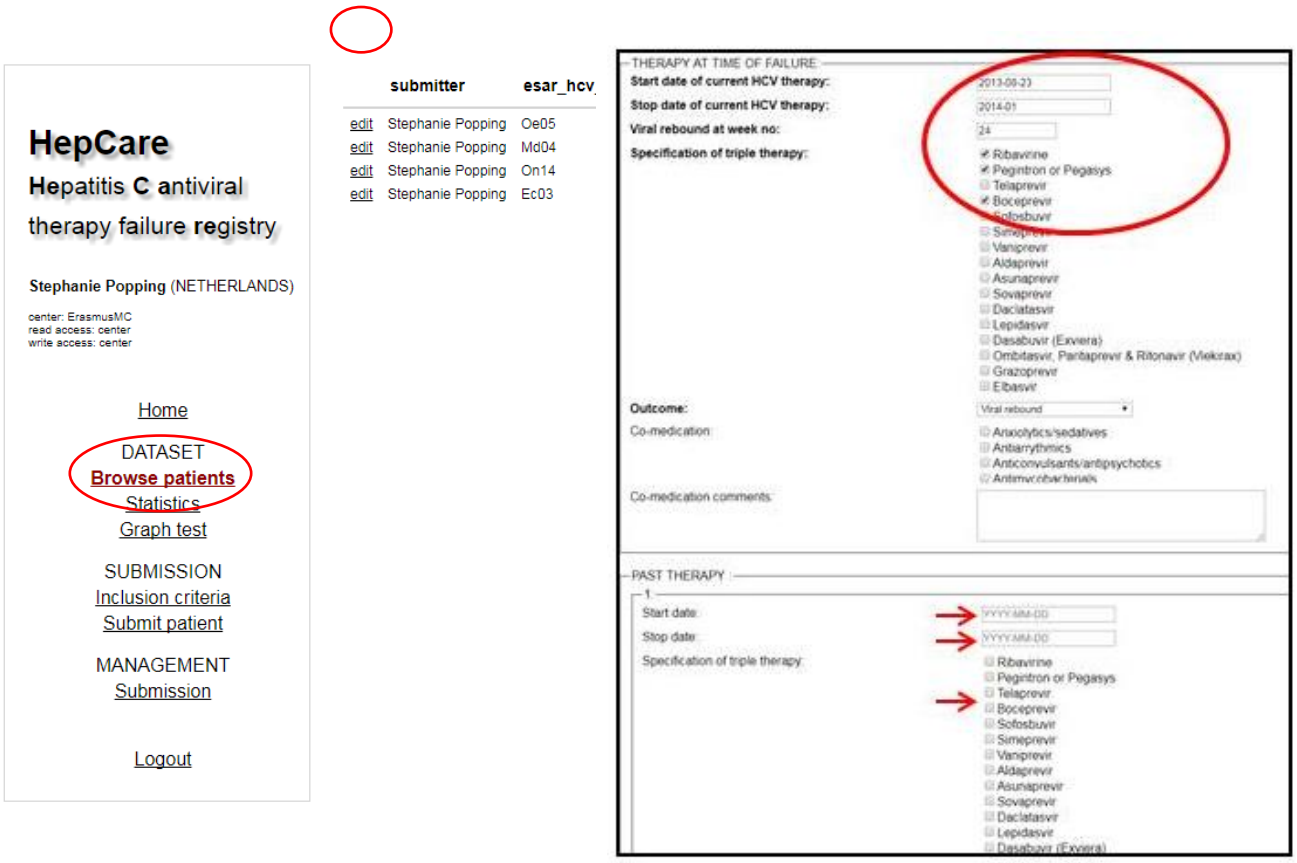
Consensus sequence: Hepcare collects only the consensus sequences, with a >15% cut-off. If you have UDS available and you want to upload a consensus sequence, please contact one of our study coordinators to discuss the method

Which method should be used for the consensus sequence?

TBA

What to do if a patients that, is already uploaded in the Hepcare database, receives retreatment?

If a patient is already included in the database and recently received retreatment you can edit this same file. This is to avoid duplicates. Please go to the patients file by click “Browser patients” and click “edit” for the patient you want to edit. Now remove the “Current therapy and sequence” towards the “Past therapy and sequence” and add the current retreatment regimen into the “Current therapy” field



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