# The need for a European hepatitis C programme monitoring resistance to direct-acting antiviral agents in real life to eliminate hepatitis C

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## Abstract

The World Health Organization (WHO) has declared that hepatitis C virus (HCV) should be eliminated as a public health threat. A key recommendation to reach this elimination goal, is to reduce new infections by 90% and liver-related mortality by 65%. Highly effective direct-acting antiviral agents (DAA) play a major role in this elimination. Unfortunately, DAA treatment fails approximately 2.5–5% of patients, often in the presence of resistance-associated substitutions (RAS). This could eventually lead to a total number of 1.8–3.6 million first-line DAA failures. RAS may jeopardise the elimination goals for several reasons; most importantly, virus transmission and infection progression will continue. More data are required to handle RAS adequately and identify mutational patterns causing resistance. Currently, sample sizes are small, data are scattered and methods heterogenic. Collaboration is therefore key and a European collaboration, such as HEPCARE, should provide a solution.

Keywords: hepatitis C, direct-acting antivirals, resistance, resistance-associated substitutions, elimination

Currently, it is estimated that 71 million people are living with hepatitis C (HCV) worldwide. The World Health Organization (WHO) has declared that HCV could be eliminated as a public health threat by 2030. A key recommendation to reach this elimination goal, is to reduce new infections by 90% and HCV-related liver mortality by 65% [1].

Different strategies can be used to reduce HCV transmission, for example blood screening, injection safety, and harm-reduction programmes. In Europe, blood screening and injection safety have already led to substantially reduced rates of HCV transmission [2,3]. The introduction of direct-acting antivirals (DAA), however, seems a more promising tool to reach elimination. DAAs provide excellent treatment owing to high cure rates and limited side-effects [4]. Moreover, DAAs can be used as a treatment-as-prevention tool opening the possibility for micro-elimination among subpopulations such as men who have sex with men [5–8].

Although DAAs have changed the field of HCV, not all patients achieve a sustained virological response (SVR). Unfortunately, in real-life data treatment with DAAs fails in approximately 2.5–5% of patients and this may often occur in the presence of resistance-associated substitutions (RAS) [9–12]. RAS exist in different forms. The polymorphisms, which are naturally occurring nucleotide changes, and the RAS emerge under the pressure of DAA treatment. The frequency of polymorphisms differs between geno- and subtypes, geographical region and method of sequencing [13] and several elements can influence the emergence of RAS during treatment: viral factors (genotype and fitness of the resistance population); host factors (cirrhosis, previous DAA failure, and IL-28B non-CC); and treatment factors (duration of treatment, adherence, and addition of ribavirin) [14,15].

Virological failure due to RAS is uncommon. However, owing to the wide distribution and further upscaling of DAAs, it is likely that a significant number of patients will experience virological failure. As an illustration, DAA treatment of 71 million people with HCV could result in approximately 1.8–3.6 million first-line DAA treatment failures [1,16].

There are different reasons why resistance needs addressing in order to reach the elimination goals. First, when virological suppression is not obtained HCV is still transmittable. Furthermore, HCV disease will still progress towards development of cirrhosis and possible hepatocellular carcinoma. Second, resistance will add more steps to the cascade of care, in which optimisation is already needed. An RAS leading to resistance requires adequate monitoring and re-treatment after failure, which are two further steps in the cascade of care. This will be a tremendous challenge for certain subgroups, such as people who inject drugs. These subgroups are already difficult to identify and diagnose, let alone follow up for resistance monitoring.

Third, guidelines still contain low-quality and limited real-life data regarding re-treatment strategies. This might lead to treatment failure and patients who are extremely difficult to cure. In addition, resistance testing is performed only in 70% of those individuals whose treatment has failed. Moreover, re-treatment is often not tailored to these results or patients do not receive the recommended second-line treatment [17].

Finally, costs are still a roadblock towards elimination. DAA prices are a restriction in providing full reimbursement [18–21]. As an example, in some countries in Europe, DAA are restricted based on fibrosis stage and co-infection status for first line-DAA treatment. Additionally, not all DAA combinations are reimbursed. The most commonly used and reimbursed DAAs are ombitasvir/paritaprevir/ritonavir + dasabuvir (in 94% of the countries) and sofosbuvir/ledipasvir (in 89% of the countries) [18]. Sofosbuvir/velpatasvir with ribavirin is only reimbursed in 83% of the countries.

Europe currently accounts for an estimated 3.2 million chronic HCV infections [16,22]. Approximately 5% (0.4–5.6%) of this population is treated and 4% are actually cured [22]. In the forthcoming years

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a further scale-up of DAA use is expected, as more awareness and strategies towards HCV elimination are created to achieve the WHO elimination goals [1]. In order to reduce incidence and mortality, disease progression and transmission must be avoided. Therefore, it is of utmost importance to prevent RAS from emerging and handle the existing polymorphisms adequately.

Additional knowledge, based on real-life data is needed in a timely manner. Mutational patterns leading to virological failure need to be identified to tailor first-line DAA treatment. Moreover, additional knowledge is required to identify whether newer antiretroviral regimens are necessary, based on the current mutational patterns leading to virological failure.

Currently, it is difficult to identify these mutational patterns and to provide the necessary information regarding re-treatment. Most European real-life resistance data come from studies with small sample sizes and are scattered among different countries and laboratories. Clinical data often provide the commonly seen genotypes and provide no data on uncommon geno- and subtypes. In addition, available data from clinical trials are selected based on favourable patient characteristics and standardisation methods. Additionally, re-treatment options are becoming scarce, since pharmaceutical companies have stopped the development of newer DAAs [23].

There are clinical-trials that have assessed the efficacy of re-treatment strategies. SVR rates between 86% and 100% were achieved with newer regimens, such as sofosbuvir/velpatasvir combined with ribavirin, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir [24–26]. However, limited real-life data are available on the results of re-treatment options.

In the past, HIV researchers and clinicians experienced similar obstacles in interpreting resistance data. To address this problem, miscellaneous antiretroviral resistance surveillance databases were established and which have provided data aggregation combined with clinical information [27,28]. Common HIV resistance databases are the Stanford HIV database (HIVDB), EuResist, and SPREAD by the European Society for Translational Antiviral Research (ESAR) [29,30].

Currently, HEPCARE is the only large international collaboration within Europe combining different national surveillance programmes in one central database. HEPCARE is established by ESAR, which has years of experience with HIV resistance surveillance (the SPREAD programme). The advantage of one central database, compared to separate studies and other cohorts, is that data are no longer fragmented over different centres. The heterogeneity of resistance reporting has made interpretation challenging and has significantly hampered the use of this information in guiding clinical decision-making. HEPCARE provides a standardisation of methods that ensures an easier analysis of data and provides insights into circulating resistance patterns as compared to separated cohorts. HEPCARE provides a larger sample size compared to separate study sites and combines data from 18 European countries and two large national cohorts. It is important to monitor resistance and its spread so that action can be taken when necessary.

HEPCARE will store baseline sequences, enabling a thorough interpretation of viral resistance profiles when treatment fails, as well as identifying previously undescribed RAS associated with treatment failure. By collecting these sequences and storing data, HEPCARE will also become a reference database to compare data between different study sites.

In order to reach the WHO 2030 elimination goals, virological failure is an obstacle that needs to be addressed. Virological failure will complicate elimination by requiring different, newer and longer DAA regimens that may not be readily accessible. Furthermore, it will lead to a group of difficult-to-treat patients who still experiencing the problems of chronic HCV and who could still transmit the virus.

## Conclusion

Tailoring of re-treatment strategies according to resistance profile can prevent multiclass resistance. As with HIV, drug resistance databases provide comprehensive information correlating RAS with clinical outcomes of antiviral treatment. A large-scale international collaboration will deliver real-life data needed to provide this essential comprehensive information. HEPCARE is a suitable initiative as a European-framed network, fulfils the need for larger sample sizes, a resistance reference database and an HCV surveillance tool. This initiative, therefore, will significantly contribute in providing the best HCV treatment strategy for patients.

## Acknowledgements

### Conflicts of interest

SP reports funding from Gilead Sciences. VC reports personal fees for advisory boards and/or sponsored lectures from AbbVie, Bristol-Myers Squibb, MSD, and Janssen-Cilag. FG reports personal fees for advisory boards and/or sponsored lectures from AbbVie, Gilead, MSD, and Roche Diagnostics. FCS reports personal fees from Gilead Sciences, Bristol-Myers Squibb, AbbVie, Roche Diagnostics, Janssen-Cilag, Abbott Molecular, ViiV Healthcare; grants and personal fees from MSD. CSD received educational grants from Gilead and Janssen. DV and CB report grants from Gilead Sciences, MSD, ViiV Healthcare and Janssen.

### Funding

No financial support was received for the writing of this article.

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