

# Retrieval and re-evaluation of previously diagnosed chronic hepatitis C infections lost to medical follow-up in the Netherlands

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# Retrieval and re-evaluation of previously diagnosed chronic hepatitis C infections lost to medical follow-up in the Netherlands

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**Objectives** Many individuals previously diagnosed with chronic hepatitis C virus (HCV) infection are likely to be lost to medical follow-up and, therefore, remain untreated despite new highly effective drug treatment, direct acting antivirals. We aim to identify and retrieve these chronic HCV-infected individuals to re-evaluate them and offer treatment.

**Methods** Possible chronic HCV infections were identified from test results of the medical microbiological laboratory, notifications to the public health service, and the hospital registries over the past 15 years were checked in South Limburg, the Netherlands. Individuals were contacted based on the physician–patient relationship of the gastroenterologist or microbiologist (retrieval). Individuals were informed about the new treatment options, offered an HCV-RNA test, and if still positive, referred to the gastroenterologist for treatment (re-evaluation).

**Results** In total, 689 individuals with a positive anti-HCV test in the past were identified, 308 (45%) were eligible for retrieval, 90 (29%) of them were retrieved, 34 (38%) of those retrieved were re-evaluated, 19 (56%) of those tested were HCV-RNA positive, and 12 (63%) of these individuals were offered treatment.

**Conclusion** During every step of the retrieval chain, many patients were lost. Nevertheless, with substantial effort, we were able to identify, retrieve, and positively re-evaluate a limited number of individuals with a possible chronic HCV infection who were lost to medical follow-up (19 patients). With this case-finding approach, we were able to prevent potential severe complications in these patients and contribute to a small step in the eradication of HCV in the Netherlands. *Eur J Gastroenterol Hepatol* 32: 851–856

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## Introduction

The WHO estimates that there are 71 million chronic hepatitis C virus (HCV) infections worldwide [1]. In 2015, 720 000 deaths from cirrhosis and 470 000 deaths from hepatocellular carcinoma (HCC) were estimated globally [2]. Approximately 15–30% of people with a chronic HCV infection will develop cirrhosis within 20 years [3]. Hepatitis B virus (HBV) and HCV infections are the predominant causes of HCC worldwide [4]. HCV infections are generally asymptomatic; therefore, many infections remain undetected or are diagnosed at a late stage leading to liver damage and further transmission.

Since the introduction of direct acting antivirals (DAAs), the treatment for HCV has been greatly improved, with cure rates up to 100% and negligible side effects from DAA therapy [5–7]. In the Netherlands, an estimated 23 000 individuals have been infected with HCV [8] and about 300 people died annually between 2002 and 2015 from causes linked to HCV infection [9]. These deaths are to a large extent avoidable, as the highly effective DAAs are readily available and reimbursed by health insurance for all HCV-infected individuals regardless of the stage of liver fibrosis [10].

The introduction of DAAs has led to a shift in focus from how to treat HCV patients to how to identify undiagnosed HCV patients. To prevent severe complications and further transmission, the elimination of HCV infection is crucial in infected individuals. At the individual level, the primary goal of HCV therapy is a sustained virologic response (SVR), defined as undetectable HCV RNA 12 or 24 weeks after completing treatment [11]. An SVR stops further progression of liver disease, lowers the risk of HCC, and reduces mortality [12,13]. At the public health level, the WHO sets a goal to eliminate HCV worldwide, including achieving a 90% diagnosis rate of all individuals chronically infected with HCV by 2030 [14].

To avoid a diagnostic burn-out, the stage where no more newly identified HCV diagnoses are available for treatment, case finding strategies should be improved [15]. However, developing strategies to identify HCV patients have been challenging. Some high-risk groups are relatively easy to reach and screen, such as individuals receiving methadone

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**Keywords:** case-finding, chronic hepatitis C, direct acting antivirals, disease eradication, hepatitis C virus, public health, retrieval

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treatment who have previously used intravenous drugs or HIV-infected individuals receiving medical care [16–19]. Other risk groups such as occasional drug users or migrants are more difficult to target [20,21]. Birth cohort screening, as recommended in the United States [22], has been applied in two identified hotspots in the Netherlands to detect hidden HCV infections. However, this approach had a limited diagnostic yield [23]. To provide adequate HCV treatment, it is essential to capture all persons who are infected with HCV, including those who are hidden or hard-to-reach in the general population [24]. However, the required approval from the Ministry of Health, Welfare and Sports is a barrier for implementing screening projects outside case finding in primary care [25].

In addition to HCV case finding in high-risk groups, the Dutch Health Council recommendation is to focus on the retrieval of individuals who are chronically infected with HCV but currently are not in care [25]. In the Netherlands, estimates of individuals diagnosed with HCV in the past who are lost to medical follow-up and go untreated varies from 14 to 64% [26–30]. Individuals were not completely followed up for several reasons, such as the individual being unable to start treatment because of psycho-social problems or drug/alcohol abuse, they did not attend follow-up appointments, or they did not complete treatment because of side effects. As the spontaneous clearance of chronic HCV infection is relatively rare [31], retrieval of these individuals could have a substantial clinical impact. Several retrieval projects have been implemented and showed the possibility to retrieve a proportion of these individuals and retain them in care [27–30]. To our knowledge, no retrieval study has been implemented in South Limburg, in the Netherlands, despite the high proportion of intravenous drug users and the historically high prevalence of HCV infection among this population [17,32].

In this study, we aimed to identify and retrieve individuals with a previously diagnosed chronic HCV infection who were lost to medical follow-up, and additionally, identify individuals with a possible chronic HCV infection, to re-evaluate them and offer antiviral treatment.

## Methods

The aim of our project was to identify and retrieve individuals with a previously diagnosed chronic HCV infection who were lost to medical follow-up, and additionally, identify individuals with a possible chronic HCV infection in South Limburg, to re-evaluate them and offer antiviral treatment. We assessed the number of individuals in total, identified individuals who were eligible for retrieval, retrieved those individuals, and re-evaluated and offered treatment as the main outcomes of the study.

1. Total: the number of individuals with a possible chronic HCV infection in the past with a previous positive anti-HCV test
2. Identified individuals eligible for retrieval:
  - a. The number and percentage of individuals with a chronic HCV infection, previously anti-HCV and HCV-RNA positive, who were lost to medical follow-up
  - b. The number and percentage of individuals with a possible chronic HCV infection, previously

anti-HCV positive but without an HCV-RNA test result

3. Retrieved: the number and percentage of individuals we were able to contact
4. Re-evaluated: the number and percentage of individuals we were able to test
5. Offered treatment: the number and percentage of individuals who were offered treatment after retrieval and re-evaluation

### Identification of individuals eligible for retrieval

The public health service South Limburg and the Zuyderland Medical Centre, a large secondary hospital in South Limburg, collaborated to identify all potentially eligible individuals with a previous positive anti-HCV test between January 2002 and February 2016. Individuals were identified through test results from the regional medical microbiological laboratory and notifications at the public health service received over the past 15 years, and these were checked in the hospital registry. The region of study had a population of ~400 000 individuals.

Of all identified individuals the following were excluded: (1) those who were deceased, (2) those who had cleared the infection as determined by an HCV-RNA negative test result, (3) those already successfully treated, that is, SVR, and (4) those currently in the care of a gastroenterologist for chronic HCV. This resulted in two groups who were eligible for retrieval: (1) individuals with a chronic HCV infection, previously anti-HCV and HCV-RNA positive, who were lost to medical follow-up and (2) individuals with a possible chronic HCV infection, previously anti-HCV positive but without an HCV-RNA test result.

### Retrieval, re-evaluation, and treatment

Before the actual retrieval of individuals, all general practitioners (GPs) in the region were informed by a letter about the retrieval project and via information-leaflets on a yearly regional conference for GPs. After the identification of individuals eligible for retrieval, individuals were contacted based on the physician–patient relationship of the gastroenterologist or microbiologist. In line with the Medical Treatment Agreement Act, individuals were contacted by a gastroenterology specialist nurse. If the individual was not known at the gastroenterology department, the individual was contacted after a public health nurse received consent from their GP.

The contacted individuals were informed about the new treatment options and our retrieval project. Individuals were invited for re-evaluation including a free PCR test for HCV-RNA at the Zuyderland Medical Centre or at the Public Health Service South Limburg. Patients were screened for the presence of the six types of HCV-RNA with an automated real-time quantitative reverse transcription, the Xpert HCV viral load assay (Cepheid Benelux, Apeldoorn, the Netherlands).

All tested individuals were informed about their test results. When individuals tested positive for HCV-RNA, they were referred to a gastroenterologist for medical evaluation and for antiviral treatment consideration. Medical evaluation consisted of a medical history and physical examination, blood tests including liver enzymes and liver function, fibroscan (FibroScan 430 Mini, Echosens,

Paris, France), and an abdominal ultrasound. After a full medical evaluation, treatment options were discussed and therapy with DAAs was started when individuals wanted treatment and when there was an absence of contraindications for DAAs. An antiviral treatment regimen was chosen according to the latest international and Dutch guidelines [10,11]. If cirrhosis occurred, the individuals were included for regular follow-ups to screen for HCC and other cirrhosis-related complications.

**Statistical analyses and outcomes**

Results were analysed using descriptive statistics in SPSS 21 (IBM Statistics, New York, USA) and Excel 2010 (Microsoft, Redmond, USA).

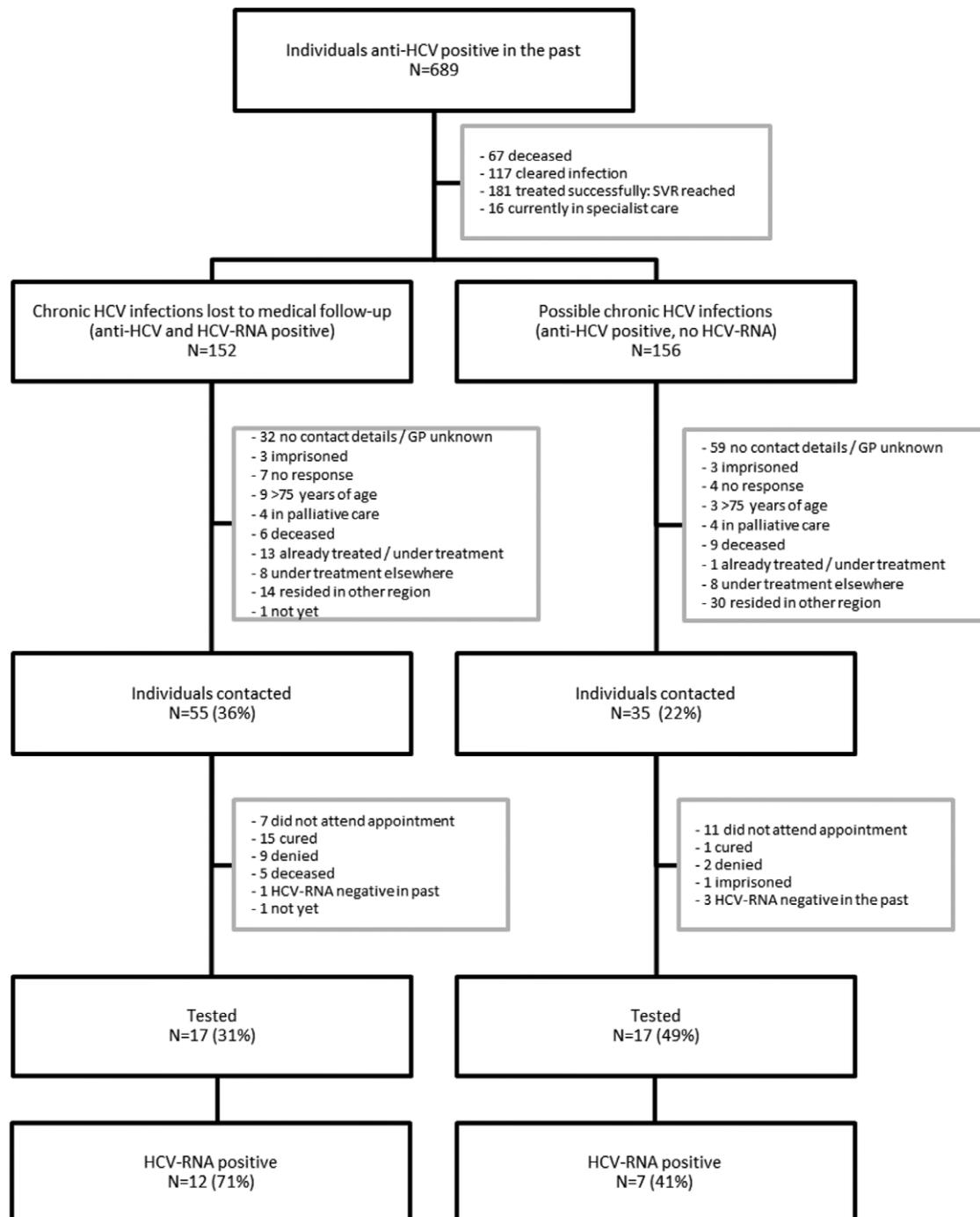
**Ethical approval**

This study was approved by the medical ethics committee of Zuyderland Medical Center and Zuyd Hogeschool (METCZ20190075).

**Results**

**Identification of individuals eligible for retrieval**

A total of 689 individuals were identified with a previous positive anti-HCV test in the past 15 years, as illustrated in Fig. 1. We excluded 55% (n = 381) as they were deceased, had a confirmed spontaneously cleared infection, were already treated successfully, or are currently in



**Fig. 1.** Flowchart on the identification, retrieval, and re-evaluation of individuals who were anti-HCV positive in the past. HCV, hepatitis C virus.

the care of a gastroenterologist for chronic HCV. Of the remaining 308 individuals, a total of 152 individuals had a chronic HCV infection and had been lost to medical follow-up. These individuals were previously lost to medical follow-up as they had denied treatment ( $n = 15$ ) or had contraindications for treatment ( $n = 21$ ), did not attend follow-up appointments ( $n = 37$ ), test results were not followed up ( $n = 46$ ), or no SVR was reached ( $n = 33$ ). Next, 156 individuals had tested anti-HCV positive in the past but without confirmation by HCV-RNA test, these individuals were defined as having a possible chronic HCV infection.

### Retrieval, re-evaluation, and treatment

Of the 152 individuals with a chronic HCV infection who were initially lost to medical follow-up, 64% ( $n = 97$ ) were not contacted and retrieved. Some were impossible to retrieve as their contact details, place of residence or GP were unknown, as they were imprisoned or repeatedly did not answer our phone calls. Individuals >75 years of age and individuals in palliative care were not eligible for retrieval, as treatment was not indicated for these individuals. In addition, some individuals had died, were already treated/currently under treatment, were treated/currently undergoing treatment in another hepatitis centre, or they resided outside the region and thus were not invited for re-evaluation. The exact numbers and reasons of individuals not contacted and retrieved are depicted in Fig. 1. Therefore, 36% ( $n = 55$ ) of the individuals with a chronic HCV infection who were lost to medical follow-up were contacted for re-evaluation. Of these individuals, 31% ( $n = 17$ ) were invited and tested, as some did not attend the appointment for blood testing, had already cured the infection or were currently undergoing treatment, denied to be tested, were deceased or had a negative HCV-RNA test in the past. In the end, 71% ( $n = 12$ ) had a positive HCV-RNA test.

Of the 156 individuals with a possible chronic HCV infection (anti-HCV positive without HCV-RNA confirmation), 78% ( $n = 121$ ) were not contacted and retrieved. In some of the individuals, their GP was unknown. Reasons for not contacting the GP were as follows: the individual was imprisoned or >75 years of age. Reasons for not inviting an individual for re-evaluation were as follows: they were not registered at the former general practice anymore, they did not respond to phone calls and letters, they were in palliative care, they were deceased, had already been treated/currently undergoing treatment (elsewhere) or lived outside our region. The exact numbers and reasons for individuals not being contacted and retrieved are depicted in Fig. 1. Therefore, 22% ( $n = 35$ ) of the individuals with a possible chronic HCV infection were contacted for re-evaluation. Of these invited individuals 49% ( $n = 17$ ) were tested, as some did not attend the appointment for blood testing, had already cured the infection, had denied blood testing, were imprisoned or had a negative HCV-RNA test in the past. In the end, 41% ( $n = 7$ ) had a positive HCV-RNA test.

In total, 45% ( $n = 308$ ) of the individuals with a positive anti-HCV in the past were eligible for retrieval, 29% ( $n = 90$ ) of them were retrieved, 38% ( $n = 34$ ) of those retrieved were re-evaluated, and 56% ( $n = 19$ ) of those

tested were HCV-RNA positive. In other words, of all the individuals who were eligible for retrieval ( $n = 308$ ), 6% had a current chronic HCV infection.

See Table 1 for the characteristics of the individuals with a current chronic HCV infection and the outcome of re-evaluation ( $n = 19$ ). In those who were re-evaluated the reasons for the previous loss of medical follow-up were as follows: no HCV-RNA confirmation (37%,  $n = 7/19$ ), they had contraindications for treatment (37%,  $n = 7/19$ ), they did not attend follow-up appointments (16%,  $n = 3/19$ ), or they did not follow-up on test results (11%,  $n = 2/19$ ). Of the 19 individuals with a current chronic HCV infection, 26% had already progressed to a severe fibrosis stage (F3-F4). The re-evaluation resulted in an adequate treatment regimen in 63% ( $n = 12/19$ ) of those still infected with HCV, resulting in 58% ( $n = 11$ ) being cured after DAA therapy and 5% ( $n = 1$ ) having DAA therapy planned. The prescribed treatment was either a combination of glecaprevir/pibrentasvir ( $n = 10$ ) or sofosbuvir/velpatasvir ( $n = 2$ ). Of the seven remaining patients, three had not had the follow-up appointment yet, one died before the scheduled treatment had started, two had denied treatment, and one had a severely low expected compliance.

### Discussion

The aim of our project was to identify and retrieve individuals with a previously diagnosed (possible) chronic HCV infection who were lost to medical follow-up, in order to re-evaluate them and offer treatment. In total, 45% ( $n = 308$ ) of the individuals with a positive anti-HCV test in the

**Table 1.** Characteristics of individuals with a current chronic hepatitis C infection and the outcome of re-evaluation

|  | N = 19  |
|--|---------|
| Sex, n (%)   |         |
| Male   | 12 (63) |
| Female   | 7 (37)  |
| Age in years, mean (SD)                            | 56 (5)  |
| HCV genotype, n (%)                                |         |
| 1 (not specified)                                  | 2 (11)  |
| 1a   | 5 (26)  |
| 1b   | 6 (32)  |
| 2b   | 1 (5)   |
| 3a   | 4 (21)  |
| Unknown  | 1 (5)   |
| Fibrosis stage, n (%)                              |         |
| F0-F1  | 5 (26)  |
| F2   | 4 (21)  |
| F3   | 1 (5)   |
| F4   | 4 (21)  |
| Unknown  | 5 (26)  |
| Transmission route, n (%)                          |         |
| Intravenous drug use                               | 10 (53) |
| Unsafe blood products                              | 2 (11)  |
| Unsafe tattooing                                   | 1 (5)   |
| Unsafe sexual activities                           | 1 (5)   |
| Shared use of razor blades                         | 1 (5)   |
| Unknown  | 4 (21)  |
| Outcome of re-evaluation, n (%)                    |         |
| Cured after DAA therapy                            | 11 (58) |
| No follow-up appointment yet                       | 3 (16)  |
| Denied treatment                                   | 2 (11)  |
| DAA therapy planned                                | 1 (5)   |
| Deceased before treatment started                  | 1 (5)   |
| No treatment as severe low compliance was expected | 1 (5)   |

DAA, direct acting antivirals; HCV, hepatitis C virus.

past were eligible for retrieval, 29% (n = 90) of them were retrieved, 38% (n = 34) of those retrieved were re-evaluated, and 56% (n = 19) of those tested were HCV-RNA positive. During every step of the retrieval chain many patients were lost. Nevertheless, with substantial effort, we were able to identify, retrieve, re-evaluate, and treat a limited number of individuals with a possible chronic HCV infection who were lost to medical follow-up. With this case-finding approach, we were able to prevent potential severe complications in these patients, helped reduce further transmission, and contributed to a small step in the eradication of HCV in the Netherlands.

A total of 308 individuals with a positive anti-HCV test result in the past were eligible for retrieval. This means that almost half (45%) of all previously anti-HCV positive-tested individuals were lost to medical follow-up or had no confirmation with an HCV-RNA test. This emphasizes the importance of HCV testing guidelines, adequate referrals, and follow-ups in the diagnosis and treatment of HCV. The expanded obligation to notify individuals of both acute and chronic HCV infection diagnoses (as implemented at the start of 2019 in the Netherlands) could improve the current HCV cascade of care.

Overall, 6% of individuals who were eligible for retrieval (19/308) could be identified, retrieved, and positively re-evaluated. This result is either equivalent to or exceeds the results of most previous retrieval projects in the Netherlands (0–5%) [27–30]. The retrieval project in Utrecht was able to retrieve more individuals than previous projects (42/819) [30]. In contrast to our project, they were able to update individual's contact details using the Basic Register of Persons. Furthermore, our retrieval study identified more cases when compared to case finding strategies that focused on testing high risk groups hidden in the general Dutch population (0–12 chronic HBV and HCV cases detected per project) [23,33–35]. In contrast, case finding strategies that focus on first generation migrants seem to detect even more infections with 2–92 HBV and HCV cases diagnosed per project [36–46].

In comparison to other retrieval studies, the strength of our study was that it was nurse-coordinated, we contacted the individuals directly by phone instead of by letter (with the permission of the primary treating physician) and we offered the blood testing free of charge. We did this to remove cost barriers that prevent individuals getting tested and to increase the test uptake. Furthermore, the high proportion of intravenous drug users and the HCV prevalence among them was historically very high in our region of study [17,32]. This is a possible explanation for the large number of individuals that could be identified, retrieved, and positively re-evaluated in our study.

Moreover, the re-evaluation resulted in an adequate treatment regimen in 63% of those still infected with HCV and 26% of those still infected had already progressed to a severe fibrosis stage (F3–F4). This indicates the importance and the clinical impact of our retrieval project on the effective eradication of HCV infection in the general population.

Although the issue of chronic HCV patients lost to medical follow-up is not unique to our country, no retrieval studies have been reported outside the Netherlands. Regional retrieval projects are not recommended for other

low endemic countries, as it is time-consuming, needs well-organised hepatitis care, and it needs extra budgeting. Before implementing retrieval projects in other countries, future studies on cost-effectiveness would be necessary to evaluate the current studies contribution to the elimination of HCV in the Netherlands. In the Netherlands, a national three-year program started in 2018, with the goal to retrieve 4000 patients and offer treatment to 1000 patients [47]. In determining future directions for HCV elimination, healthcare professionals should consider focusing case finding more on screening first generation migrants.

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## Conflicts of interest

There are no conflicts of interest.

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