BACKGROUND

The global hepatitis C virus (HCV) epidemic stimulated the World Health Organization (WHO) to develop viral hepatitis elimination targets in 2016. An estimated 71 million people worldwide were infected by HCV in 2015. Thus, the WHO set the target of a 90% reduction in new infections and a 65% reduction in viral hepatitis-related mortality by 2030 as compared to 2015. These are ambitious but feasible goals, since we have ample tools at hand to curtail the current HCV epidemic. The diagnosis of active HCV can be readily made, by means of sample analysis in a central facility or through point-of-care testing. Direct-acting antivirals (DAAs) cure the infection in ≥95% of cases. Pangenotypic DAAs can be used in all patients with only a few barriers such as potential drug-drug interactions or presence of (decompensated) cirrhosis. Most countries have assessed their specific HCV population and the availability of tools in their countries and subsequently developed national hepatitis plans in line with the WHO elimination targets.

HCV elimination according to the WHO goals can be achieved in various ways, which ideally should be incorporated in a multifaceted approach. We can focus on prevention, by developing a vaccine or by increasing awareness and educating groups at risk of transmission of the virus. Secondly, we can develop or augment existing screening strategies, in order to diagnose more patients.
Lastly, we can treat as many infected patients as possible. Since the development of highly effective and tolerable DAAs, HCV elimination projects have primarily focused on prevention and screening, since treatment was not seen as a problem anymore. However, ensuring treatment for all diagnosed patients remains a problem to this day.

Loss to follow-up (LTFU) prevents patients from receiving the care they need to be cured of their infection. The extent of this problem remains unclear, especially in the DAA era. In order to grasp the scope of the LTFU problem, one needs to understand the HCV care cascade and how patients move through its phases. This review aims to assess published literature on LTFU in the HCV cascade of care during the DAA era and will provide an overview of issues and possible solutions.

2 | CONCEPT OF LOSS TO FOLLOW-UP

Different definitions for LTFU are used in the literature, since patients become lost to follow-up for various reasons. For example, they may have moved house, emigrated, died or been imprisoned. Many times, the reason for LTFU cannot be ascertained as contact with the patient cannot be established. Retrospective observational studies often do not provide a specific definition or use nonattendance to any appointment as a definition. Some of these studies mention death separately and do not include this as a reason for LTFU. Other studies that reviewed ever-diagnosed patients defined LTFU as patients who never or not recently had an appointment with an HCV specialist. Intervventional studies aiming to improve the cascade of care also do not give a definition or define LTFU as nonattendance anywhere in the care cascade, often separating death from the LTFU group.

There may be a lesson to be learned on defining LTFU from studies in other fields of medicine. Previously mentioned HCV studies did not take time into account when defining LTFU. Prospective studies defined LTFU as nonattendance at the end of their study period, which varied greatly among studies. Retrospective studies defined LTFU as nonattendance since their last visit up to study initiation. HIV studies have investigated LTFU extensively and showed that the way you define LTFU greatly influences your LTFU outcomes. In addition, these studies have demonstrated different ways to determine the ideal timeframe to classify someone as LTFU, that is x days after last clinic visit. When different studies use different definitions, it is virtually impossible to compare care cascades and combine results. However, since this is the case for the HCV studies assessed in this review, we chose a pragmatic approach that suits the illustrative purpose of this review. We define LTFU as nonattendance to any appointment in the care cascade at any time since their last visit. Patients who had died were not included in the definition of LTFU.

3 | THE HCV CARE CASCADE

In order to grasp the magnitude of the LTFU problem in chronic HCV patients, we must first understand the HCV care cascade. Reviewing published literature on this subject shows that definitions of the care cascade vary with each paper. However, efforts to come up with an unambiguous description of the HCV care cascade have been made. In 2018, the WHO established a monitoring framework that includes 10 core indicators addressing prevention, diagnosis, treatment and mortality. The WHO states that four of the 10 core indicators should be used for cascade of care reporting: the number of patients infected, diagnosed, treated and cured. Recently, a study group comprised of clinical, epidemiological and public health experts from Australia, Europe and North America have proposed a clarified and slightly extended care continuum. Their Consensus HCV Cascade of Care (CHCoC) is based on the WHO indicators, a review of published literature on HCV care continuums and on methodological issues in HIV cascade of care monitoring. It can be divided into four key steps (the four WHO indicators) and three supplementary steps: (a) estimated HCV prevalence; (b) diagnosed with

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**FIGURE 1** Hepatitis C care cascade. Step 1: HCV prevalence; step 2: diagnosed with chronic HCV; step 3: linked to care; step 4: liver disease assessed; step 5: started on treatment; step 6: achieved SVR; step 7: accessed chronic post-SVR care. Figure freely adapted with permission from Safreed-Harmon et al. HCV, hepatitis C virus; LTFU, lost to follow-up; SVR, sustained virological response
chronic HCV; (c) linked to HCV care; (d) liver disease assessed; (e) started on treatment in (year); (f) achieved sustained virological response (SVR) in (year); and (g) accessed chronic post-SVR care. The authors provided pragmatic definitions for the four key steps, which stakeholders can use to report on elimination progress. Understandably, by increasing the number of steps in the care cascade, the chances of being lost from care also increase. LTFU is seen as a major problem, because it remains unclear whether the patient is cured or not. Liver disease in these patients may progress, and they may even contribute to HCV transmission if they still exhibit certain risk behaviour. When reviewing the literature published on HCV care cascades in the DAA era and their LTFU rates, we used the CHCoC to report our findings (see Figure 1). And overview and characteristics of the included studies in this review can be found in Table 1.

4 | LTFU DURING DIAGNOSTIC ASSESSMENT (CHCOC STEP 2)

The first step in diagnosing chronic HCV is the determination of presence of HCV antibodies. However, the key step in confirming the diagnosis of chronic HCV is determining HCV RNA (or HCV core antigen when RNA assays are not available or not affordable). In many countries, HCV RNA is not tested automatically after receiving a positive antibody test result. This two-step diagnosis provides the first opportunity for patients to become LTFU. Two retrospective, observational studies have shown that approximately 72% of their anti-HCV-positive populations were tested for HCV RNA. This percentage is generally higher in interventional studies aiming to improve the cascade of care, often done in community-based settings: 67%-100% (median 90%). However, some studies have shown that only 7% of anti-HCV-positive people receive confirmatory testing. Reasons for this vary and are often unreported, but might be due to LTFU. One study confirmed that 32% of anti-HCV-positive people were LTFU before receiving an RNA test.

Reflex testing, where the laboratory automatically tests for HCV RNA or HCV core antigen when the antibody test proves to be positive, improves this step in the cascade of care.

5 | LTFU BEFORE LINKAGE TO HCV CARE (CHCOC STEP 3)

When someone has tested positive for HCV RNA, referral to an HCV specialist for further evaluation should follow. However, attendance to this follow-up visit is only reported in 27%-91% (median 68%) of cases. People who inject(ed) drugs (PWID), a well-known hard to reach population, attend in 36%-65% of cases (median 50%). In HIV/HCV-coinfected patients, attendance seems to be higher with 25%-95% (median 90%). Generally speaking, attendance is higher for those under decentralized care. Reasons for absence are difficult to assess; however, some studies confirm LTFU in 26%-100% (median 84%) of absentee. Several diagnostic procedures are available to grade and stage liver disease. Where liver biopsy was standard of care in the past, nowadays noninvasive methods are largely preferred. Liver fibrosis may be quantified by using serological panels, such as the widely used FIB-4 (using the patient’s age, platelet count, AST and ALT levels) or APRI score (using AST levels, the AST upper limit of normal and platelet count), or by using transient elastography. Almost all studies in the DAA era employ noninvasive ways to assess liver disease severity. When looking at people who have had their first visit after being diagnosed or referred, fibrosis was assessed with the APRI score in 52%-99% (median 87%) and with FibroScan in 59%-100% (median 79%). Studies which used other noninvasive measures or did not report which measures were used, reported assessment in 48%-95% (median 88%) of attendees. LTFU may contribute to this suboptimal assessment rate and should be addressed.

7 | LTFU BEFORE INITIATING TREATMENT (CHCOC STEP 5)

Even in the era of highly effective DAAs, treatment initiation rates are low. LTFU proves to be a large contributor to this problem. Retrospective studies have shown that only 12%-77% (median 29%) of patients diagnosed or engaged in care during the DAA era initiated treatment after being diagnosed with chronic HCV. Interventional studies aimed to improve the care cascade show that this rate can increase to 16%-100% (median 73%). Studies in the HIV field show similar results, with 36%-91% (median 90%) initiating treatment in retrospective studies and 25%-100% (median 80%) in interventional studies. However, the treatment rate remains suboptimal in PWID with only 20%-90% (median 53%) initiating treatment. Generally, treatment initiation rates are higher in decentralized settings, both in PWID and non-PWID populations. Reasons for poor treatment initiation rates vary. Unfortunately, many countries still experience restrictions in who can and cannot be treated with DAAs. This problem may especially apply to studies from the first stages of the DAA era. Other reasons for poor treatment initiation rates may be comorbidities or perceived lack of compliance. However, LTFU contributes to a large extent to these poor rates. Studies showed that LTFU is the reason for nontreatment in 0%-67% (median 33%) of cases.
**TABLE 1** Characteristics of studies included in review on the HCV care cascade in mixed populations, people who inject(ed) drugs and HIV/HCV-coinfected patients.

| Referencesa | Country | Summary | CHCoC step 2: HCV RNA not assessed in anti-HCV positive patients | CHCoC step 3: absence at follow-up appointment after diagnosis/ referral | CHCoC step 4: liver disease not assessed in diagnosed/ attendees | CHCoC step 5: treatment not initiated in attendees | CHCoC step 6: LTFU during or after treatment | Intention to treat sustained virological responseb |
|-------------|---------|---------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Zucker, 20181 | USA | Retrospective analysis of anti-HCV positive patients in academic hospital diagnosed in DAA era, using an electronic medical record algorithm | 28% | 73%c | 70% | | | 39% |
| Assoumou, 20202 | USA | Retrospective analysis of multicentre FQHC cohort | 27% | 48% (APRI) | 88% | | | 31% |
| Al-Khazraji, 20203 | USA | Retrospective analysis of HCV positive patients in academic hospital diagnosed in DAA era who are eligible for treatment (RNA-positive and no comorbidities with short life expectancy) | | | | 80% (67% of these were confirmed LTFU) | | 5.3% |
| Moore, 20184 | USA | Retrospective analysis of microbiology database (mandated reporting of positive HCV tests) | | | | | 48% | 65% |
| Nguyen, 20175 | USA | Retrospective analysis of RNA-positive patients seen in academic clinic in the DAA era | | | | | 23% (24% of these were confirmed LTFU) | | 89% |
| Marshall, 20186 | USA | GT1 patients who initiated treatment at outpatient clinic care of an academic centre | | | | | 7% (during) 15% (after) | | 74% |
| Haridy, 20187 | Australia | Observational, prospective study of all treated patients in association with tertiary centres (including prisons and community health centres via remote consultation) | | | | 32% (Fibroscan) (community-based vs hospital 43% vs 30%) | | 14.7% | 80% |
| Sølund, 20188 | Denmark | Analysis of the Danish Database for Hepatitis B and C, including HCV patients eligible for treatment | | | | | 51% (of these, 30% were LTFU) | 1.5% (during) 3.2% (after) | 88% |
| Darvishian, 20209 | Canada | Multicentre cohort study of GT1 and 3 patients, treated by specialists or GPs | | | | | | 8% |

(Continues)
### TABLE 1 (Continued)

| References* | Country | Summary                                                                 | CHCoC step 2: HCV RNA not assessed in anti-HCV positive patients | CHCoC step 3: Absence at follow-up appointment after diagnosis/ referral | CHCoC step 4: Liver disease not assessed in diagnosed/attendees | CHCoC step 5: Treatment not initiated in attendees | CHCoC step 6: LTFU during or after treatment | Intention to treat sustained virological responseb |
|-------------|---------|------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------|-------------------------------------|--------------------------------------|---------------------------------------|
| Scaglione, 202016 | Italy  | Retrospective analysis of all treated HCV patients in a teaching hospital | 10% | 87% |
| Adamson, 202018 | USA    | Retrospective cohort study comparing treatment by HCV specialists in a primary care practice to treatment by HCV specialists in hospitals | 93% (of combined cohort) | 25% vs 52% | 58% vs 53% | 25% vs 22% |
| Dever, 201719 | USA    | HCV patients from the Veteran Affairs HCV registry with increased risk of advanced fibrosis that never attended an appointment or were LTFU were retrieved | 45% | | | |
| Trooskin, 201520 | USA    | POC testing (anti-HCV and RNA) in community-based settings, positive patients counselled and referred by patient navigator | 13% | 9% | 5% (liver ultrasound, HepaScore or FibroSure) | 43% |
| Coyle, 201921 | USA    | Implementation of routine HCV testing and linkage to care in five FQHCs, including medical assistant-initiated testing, automated health record prompts, reflex testing and care coordinators | 4% | 16% | 20% (liver fibrosis panel, liver biopsy, liver ultrasound or Fibroscan) | 78% | 53% |
| Bajis, 201922 | Australia | Liver health promotion campaign and noninvasive fibrosis assessment followed by RNA screening and linkage to care among homeless in a community centre | 1% | 38% (100% of these were confirmed LTFU) | 0% (Fibroscan) | 21% | 65% |
| Waked, 202023 | Egypt  | Reported progress of the Egypt HCV elimination programme | 33% | | 8% | 82% |
| Khalid, 202024 | Pakistan | Decentralised screening and treatment including POC testing for people ≥1 risk factor in primary health clinic and treatment free of charge | 82% | 1% (APRI) | 84% |
| Hsieh, 201925 | USA    | Known chronic HCV patients who visited the ED were offered linkage to care | 66% | 5% (FibroSure or Fibroscan) | 58% (27% of these were confirmed LTFU) | 94% |
| References | Country       | Summary                                                                                      | CHCoC step 2: HCV RNA not assessed in anti-HCV positive patients | CHCoC step 3: absence at follow-up appointment after diagnosis/ referral | CHCoC step 4: liver disease not assessed in diagnosed/attendees | CHCoC step 5: treatment not initiated in attendees | CHCoC step 6: LTFU during or after treatment | Intention to treat sustained virological response |
|------------|---------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Zuckerman, 2018²⁶ USA | Decentralised treatment by pharmacist-led multidisciplinary team  | 27%                                                                                       | 12% (ultrasound, liver biopsy, FIB-4 or FibroSure)                | 17% (4% of these were confirmed LTFU)                               | 5% (during) 4% (after)                                     | 88%                                             |                                                 |
| Evans, 2018²⁷ United Kingdom | Opt-out HBV and HCV screening and linkage to care for people ≥16 years at the ED, including reflex testing | 22% (100% of these were confirmed LTFU)                                                  | 40% (Fibroscan)                                                  | 50% (44% of these were confirmed LTFU)                               |                                                 | 80%                                             |                                                 |
| Benitez, 2020²⁸ USA | One-time testing according to CDC guidelines and treatment in FQHCs and satellite centres serving a predominantly homeless population, including reflex testing | 15%                                                                                       | 84%                                                           | 3.4% (during) 13% (after)                                        | 83%                                             |                                                 |                                                 |
| Capileno, 2017³³ Pakistan | Decentralised screening and treatment including POC testing for people ≥1 risk factor in primary health clinic and treatment free of charge | 13% (APRI)                                                              | 81%                                                           | 4.7% (during) 3% (after)                                        | 83%                                             |                                                 |                                                 |
| Cooper, 2017³⁴ Canada | Retrospective analysis of patients treated at outpatient clinic compared to patients mainly treated through telemedicine | 61% vs 84% (liver biopsy) 38% vs 41% (Fibroscan)                                      | 72% vs 83%                                                     | 72% vs 83%                                                     |                                                 |                                                 |                                                 |
| Shiha, 2018³⁵ Egypt | Free screening and treatment in rural village                                                   | 0%                                                                                       | 0% (Fibroscan)                                                  | 4%                                                                  | 98%                                             |                                                 |                                                 |
| Ford, 2017³⁶ USA | Decentralised screening and linkage to care in FQHCs and addiction care services, treatment both on- and off-site | 52%                                                                                       | 45%                                                           | 91%                                                                  |                                                 |                                                 |                                                 |
| Bartholomew, 2017³⁷ USA | Decentralised treatment in primary care by physician assistants and primary care physicians | 30%                                                                                       | 3.8% (during) 10% (after)                                        | 77%                                                                  |                                                 |                                                 |                                                 |
| Wade, 2018³⁸ Australia | Remote consultation by specialists for GPs, treatment by GPs or after referral to specialist | 29%                                                                                       |                                                 | 91%                                                                  |                                                 |                                                 |                                                 |
| References | Country | Summary | Percentage of loss to follow-up in each CHCoC step, including our definition | Intention to treat sustained virological response |
|------------|---------|---------|--------------------------------------------------------------------------------|-----------------------------------------------|
| Mendizabal, 2019 | Argentina | Tele-mentoring of primary care physicians and specialists by a multidisciplinary team of specialists at an academic centre (ECHO), compared to treatment in tertiary centre | CHCoC step 2: HCV RNA not assessed in anti-HCV positive patients 13% (in entire cohort) | 68% vs 72% |
| Norton, 2017 | USA | Patients treated by specialist and HCV care coordinator in a FQHC | CHCoC step 3: absence at follow-up appointment after diagnosis/ referral | 0% (during) 2.2% (after) |
| Kattakuzhy, 2017 | USA | Nonrandomized trial comparing decentralised treatment by nurse practitioners, GPs or specialists in community health centres 2% vs 2.5% vs 3.5% (during) 4% vs 5% vs 4.8% (after) | CHCoC step 4: liver disease not assessed in diagnosed/attendees | 96% |
| Carvalho-Louro, 2020 | Brazil | Free POC testing for people >40 years old visiting laboratories 3% vs 2.5% vs 3.5% (during) 4% vs 5% vs 4.8% (after) | CHCoC step 5: treatment not initiated in attendees | 92% |
| Averhoff, 2020 | Georgia | Reported progress of the Georgia HCV elimination programme | CHCoC step 6: LTFU during or after treatment | 92% |
| Hutton, 2019 | Australia | Screening and linkage to care of patients presented at ED with ≥1 risk factor, including POC testing 67% (85% of these were confirmed LTFU) | | 66% |
| Chiong, 2019 | Australia | Screening and linkage to care of inpatients in a tertiary hospital 23% (Fibroscan) 15% (50% of these were confirmed LTFU) | | 80% |
| Koren, 2019 | USA | Retrospective analysis of a pharmacist-driven multidisciplinary treatment model 1.8% (during) 5.5% (after) | | 86% |
| Nouch, 2018 | Canada | Decentralised multidisciplinary care in community health centres 3.6% (during) 9% (after) | | 86% |
| White, 2019 | Australia | Decentralised treatment by primary care physicians or in secondary care 4.3% (during) | | 89% |
| McMahon, 2019 | USA | Analysis of the cascade of care for Alaskan Natives tested anti-HCV positive via hepatitis programme 3% 37% (83% of these were confirmed LTFU) | | 23% |

(Continues)
| Referencesa | Country | Summary | CHCoC step 2: HCV RNA not assessed in anti-HCV positive patients | CHCoC step 3: absence at follow-up appointment after diagnosis/ referral | CHCoC step 4: liver disease not assessed in diagnosed/ attendees | CHCoC step 5: treatment not initiated in attendees | CHCoC step 6: LTFU during or after treatment | Intention to treat sustained virological responseb |
|---|---|---|---|---|---|---|---|---|
| Sherbuk, 201960 | USA | HCV patients treated in tertiary centre with dedicated nurse coordinator | 24% (47% of these were confirmed LTFU) | 20% | 19% (after) | 74% |
| Francheville, 201861 | Canada | Province-wide model of care with centralized referral, triage and intake by a nurse coordinator, treatment by specialist | 24% (0% of these were confirmed LTFU) | 88% |
| Mohsen, 201962 | Australia | Tele-mentoring of primary care physicians and specialists by a multidisciplinary team of specialists at an academic centre (ECHO), compared to treatment in tertiary centre | 22% (36% of these were confirmed LTFU) vs 19% | 0% vs 11% (during) 12% vs 3% (after) | 77% vs 83% |

**People who inject(ed) drugs**

| Referencesa | Country | Summary | CHCoC step 2: HCV RNA not assessed in anti-HCV positive patients | CHCoC step 3: absence at follow-up appointment after diagnosis/ referral | CHCoC step 4: liver disease not assessed in diagnosed/ attendees | CHCoC step 5: treatment not initiated in attendees | CHCoC step 6: LTFU during or after treatment | Intention to treat sustained virological responseb |
|---|---|---|---|---|---|---|---|---|
| Christensen, 20187 | Germany | Analysis of the German hepatitis C registry, comparing former/current drug users on OST with former/current drug users not on OST and people with no documented drug use | 2.7% vs 2.0% vs 0.7% (during) 7.6% vs 6.5% vs 2.5% (after) | 85% vs 86% vs 92% |
| Falade-Nwulia, 202099 | USA | Peer-promoted screening and linkage to care in a PWID population, including incentives for testing | 6% | 64% | 80% (66% including patients who were already linked to care) |
| Bajis, 202030 | Australia | Liver health promotion campaign and non-invasive fibrosis assessment followed by RNA screening and linkage to care in addiction care services | 51% | 0% (Fibroscan) | 47% (23% including patients who were already linked to care) |
| Alimohammadi, 201831 | Canada | Randomized controlled trial about decentralised treatment in community pop-up clinics for PWID through directly observed treatment, compared to group therapy and standard care, including POC testing and incentives | 50% | 39% | 6% (after) | 85% |
### References

**TABLE 1** Percentage of loss to follow-up in each CHCoC step, including our definition

| References       | Country                | Summary                                                                 | CHCoC step 2: HCV RNA not assessed in anti-HCV positive patients | CHCoC step 3: absence at follow-up appointment after diagnosis/ referral | CHCoC step 4: liver disease not assessed in diagnosed/attendees | CHCoC step 5: treatment not initiated in attendees | CHCoC step 6: LTFU during or after treatment | Intention to treat sustained virological response |
|------------------|------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Harrison, 2019   | United Kingdom         | Multicentre study on increasing screening and linkage to care in addiction care services | 35% (26% of these were confirmed LTFU)                            |                                                                    | 66% (6% of these were confirmed LTFU)                           | 82%                                             |                                                 |                                                 |
| Wade, 2020      | Australia, New Zealand | Randomized controlled trial on treatment of PWID in primary care facilities that provide OST, compared to treatment in hospital | 21% vs 38% (Fibroscan)                                           |                                                                    | 10% (40% of these were confirmed LTFU) vs 38% (45% of these were confirmed LTFU) | 4.7% vs 5.6% (during) vs 28% vs 6% (after) |                                                 |                                                 |
| O’Sullivan, 2020 | United Kingdom         | Decentralised screening and treatment in a nurse-led programme in addiction care services, including reflex testing | 0%                                                               | 13% (Fibroscan)                                                    | 52% (0% of these were confirmed LTFU)                            | 4.3% (after)                                     | 90%                                             |                                                 |
| Morris, 2017     | Australia              | Decentralised care including care coordinators for patients in addiction medicine |                                                                    |                                                                    | 2% (during)                                                     | 20% (after)                                     | 80%                                             |                                                 |
| Read, 2017       | Australia              | Decentralised treatment in primary care facility targeted to PWID       |                                                                    |                                                                    | 2.8% (during)                                                   | 12.5% (after)                                    | 82%                                             |                                                 |
| Koustenis, 2020  | Greece                 | Retrospective analysis of single centre PWID cohort treated in tertiary centre |                                                                    |                                                                    | 2.3% (during)                                                   | 10.3% (after)                                    | 80%                                             |                                                 |
| HIV/HCV-coinfected population |             |                                                                          |                                                                    |                                                                    | 5%                                                             | 18%                                             | 8.8% (after)                                     | 87%                                             |
| Falade-Nwulia, 2019 | USA                  | Retrospective analysis of all HIV/HCV-coinfected patients in an academic hospital |                                                                    |                                                                    |                                                                |                                                 |                                                 |                                                 |
| Saris, 2017      | Netherlands            | Retrospective analysis of all HIV/HCV-coinfected patients from two hospitals (one academic), planned for DAA treatment | 19% (Fibroscan)                                                   |                                                                    | 9% (none LTFU)                                                  |                                                 | 80%                                             |                                                 |
| Kronfl, 2018     | Canada                 | Retrospective analysis of multicentre HIV/HCV-coinfected cohort (hospitals, community-based clinics and street outreach programmes) |                                                                    |                                                                    | 64% (28% of these were confirmed LTFU)                          |                                                 |                                                 |                                                 |
| Adekunle, 2020   | USA                    | Retrospective analysis of HIV/HCV-coinfected hospital cohort            |                                                                    |                                                                    | 10% (8% of these were confirmed LTFU)                           | 0%                                              | 96%                                             |                                                 |
| (Continues)      |                        |                                                                         |                                                                    |                                                                    |                                                                |                                                 |                                                 |                                                 |
### References

| References          | Country       | Summary                                                                 |
|---------------------|---------------|-------------------------------------------------------------------------|
| Cachay, 2019        | USA, Spain, Italy | Retrospective analysis of all HIV/HCV-coinfected patients treated in five hospitals in three countries |
| Starbird, 2020      | USA           | Randomized controlled trial where HIV/HCV-coinfected patients who were not in HCV care would receive usual care or nurse case management focusing on linkage to care |
| Ward, 2019          | USA           | Randomized controlled trial of screening and linkage to care of HIV/HCV-coinfected patients, comparing usual care (nurse-led multidisciplinary team including incentives for study-specific visits) with usual care including peer support and usual care including incentives. Treatment was free of charge |
| Rizk, 2019          | USA           | Retrospective analysis of a single centre HIV/HCV-coinfected cohort treated by a dedicated multidisciplinary team |

### Table 1 (Continued)

| References          | Country       | Summary                                                                 | CHCoC step 2: HCV RNA not assessed in anti-HCV positive patients | CHCoC step 3: absence at follow-up appointment after diagnosis/ referral | CHCoC step 4: liver disease not assessed in diagnosed/attendees | CHCoC step 5: treatment not initiated in attendees | CHCoC step 6: LTFU during or after treatment | Intention to treat sustained virological response |
|---------------------|---------------|-------------------------------------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Cachay, 2019        | USA, Spain, Italy | Retrospective analysis of all HIV/HCV-coinfected patients treated in five hospitals in three countries | - 1%                                                             | - 93%                                                              | - 0% vs 75% (11% of these were confirmed LTFU)                                             |                                                                                                  |                                                                                                  |                                                                                                  |
| Starbird, 2020      | USA           | Randomized controlled trial where HIV/HCV-coinfected patients who were not in HCV care would receive usual care or nurse case management focusing on linkage to care | - 75% vs 53%                                                      | - 0% vs 75% (11% of these were confirmed LTFU)                                             |                                                                                                  |                                                                                                  |                                                                                                  |
| Ward, 2019          | USA           | Randomized controlled trial of screening and linkage to care of HIV/HCV-coinfected patients, comparing usual care (nurse-led multidisciplinary team including incentives for study-specific visits) with usual care including peer support and usual care including incentives. Treatment was free of charge | - 24% (33% vs 17% vs 24%)                                         | - 2.7% (during; 4.2% vs 2.2% vs 2.4%)                                                        | - 0% (after)                                                                                     | - 91% (92% vs 91% vs 90%)                                                                       |                                                                                                  |
| Rizk, 2019          | USA           | Retrospective analysis of a single centre HIV/HCV-coinfected cohort treated by a dedicated multidisciplinary team | - 9%                                                               | - 17%                                                              |                                                                                                  |                                                                                                  |                                                                                                  |

**CDC, Centers for Disease Control and Prevention; CHCoc, Consensus HCV Cascade of Care; DAA, direct acting antiviral; ED, emergency department; FQHC, federally qualified health centre; GP, general practitioner; GT, genotype; HCV, hepatitis C virus; LTFU, loss to follow-up; OST, opioid substitution therapy; POC, point of care; PWID, people who inject drugs; USA, United States of America.**

*In Supplementary file 1.*

*Defined as SVR among those who initiated therapy.*

*From this step on, patients without a viral load assessment were included.*

*HepaScore uses the patient’s age, sex and bilirubin, γ-glutamyl transferase, α2-macroglobulin and hyaluronic acid levels to determine fibrosis stage.*

*FibroSure uses the patient’s age, sex and ALT, bilirubin, γ-glutamyl transferase, α2 macroglobulin, haptoglobin and apolipoprotein A1 levels to determine fibrosis and necroinflammatory stage.*
LTFU DURING OR AFTER TREATMENT (CHCOC STEP 6)

As we know from registration trials, DAAs are highly effective. Real-world studies yield similar results. However, LTFU influences result in real-world studies significantly more. Recently, Darvishian et al showed that LTFU exceeded viral failure in their real-world study, impeding the cascade of care. Studies show that 0%-11% (median 3.4%) of patients become LTFU during therapy and that 0%-25% (median 4.9%) become LTFU after therapy completion, with missing SVR values. PWID show similar results with 0.7%-5.6% (median 2.5%) becoming LTFU during treatment and 2.5%-28% (median 7.1%) after. Many studies report intention-to-treat SVR percentages, defined as the proportion of patients who reached SVR out of the number of patients that initiated DAA therapy (see Figure 2). In studies including mixed populations, ITT SVR varies from 22% to 98% (median 83%). Studies focusing on PWID populations, ITT SVR ranges from 80% to 92% (median 85%). Lastly, in studies focusing on HIV/HCV-coinfected populations, ITT SVR ranges from 80% to 96% (median 91%).

LTFU AFTER SVR (CHCOC STEP 7)

Guidelines suggest that people with advanced fibrosis (METAVIR score F3) or cirrhosis (F4) who reached SVR should be subjected to surveillance for hepatocellular carcinoma (HCC) every six months by means of ultrasound. Furthermore, cirrhotic patients with varices present at pre-treatment endoscopy should be surveyed for oesophageal varices. Unfortunately, data on how many cured patients actually receive such surveillance are lacking. Most studies stop reporting on the care cascade at the moment SVR is reached. A recent review showed that less than 30% of cirrhotic patients are included in surveillance programmes, independent from aetiology. More studies on the surveillance adherence among cured HCV patients with an indication for surveillance are needed.

FACTORS ASSOCIATED WITH LTFU

Younger age (<45 and younger), treatment in hospital, a history of homelessness, mental illness, and insurance type were some of the most common factors associated with LTFU. Factors associated with retention in care were older age (~60 and older) and HIV coinfection. However, one study with HIV coinfected patients showed that detectable HIV viral load was actually associated with LTFU, possibly reflecting suboptimal retention in HIV care. Studies on the HCV care cascade in people living with HIV confirm relatively good retention in care, especially after starting treatment. The last factors that were often associated with LTFU are linked to injecting drug use, past, recent, or ongoing drug use was mentioned in several studies as being associated with LTFU. Receiving opioid substitution therapy in one centre and DAA treatment in another was also associated with LTFU.

MICRO-ELIMINATION OF LTFU PATIENTS THROUGH RETRIEVAL

LTFU occurs in all steps of the care cascade and may severely impact HCV care and opportunities for cure. It is reasonable to assume that data from the interferon era on LTFU are worse, due to the fact that fewer patients had an indication for treatment, more patients refused treatment, fewer patients finished the ill-tolerated treatment and only a limited number of patients achieved cure, compared to the DAA era. This hypothesis was confirmed in a recent study by Aleman et al. The authors included HCV patients from their national register diagnosed between 2001 and 2011 and alive in 2013, and found that an impressive 61% was LTFU. A study from Belgium using a similar approach showed that PWID and patients who never received HCV treatment had a higher risk of becoming LTFU (OR 2.2 for both). This provides us with an opportunity as the LTFU HCV population may be an excellent candidate for micro-elimination, the process of eliminating HCV in subpopulations. Micro-elimination is the favoured approach in many countries, especially in those with a relatively low national prevalence, but higher prevalence in specific subpopulations. Lazarus et al have recently described which subpopulations should be considered for micro-elimination, such as aboriginal and indigenous communities, HIV/HCV-coinfected people, migrants from high-prevalence countries, people who inject drugs, people with inherited blood disorders and prisoners. We propose that LTFU patients should be added to this list. As indicated, LTFU is a substantial problem across the entire care cascade. Because this HCV population has already been identified, it is obvious that retrieval of these patients can be considered 'low-hanging fruit'.
patients based on laboratory data, which we combine with information from their medical records. Patients who were still HCV-positive when they left care are classified as eligible for retrieval if they are alive and currently residing in the Netherlands. They are subsequently invited by letter to an outpatient clinic of their choice after their current address is verified through municipality records or general practitioners. Data will be collected on patient and disease characteristics of patients who sign informed consent.

What we have learned since the start of CELINE in 2018 is that retrieval is feasible when conducted by a dedicated team. The project gives great insight into our care cascade and gives vital information for our hepatitis elimination plan. The nationwide approach ensures that retrieval is done to the same standards in each participating centre. Identification of LTFU patients and ensuring they adhere to their clinic appointments are the most time-consuming. This is why we advise that a dedicated team, rather than individual clinicians, should execute these tasks.

13 | INCLUDE RETRIEVAL IN STANDARD CARE

Ideally, micro-elimination through retrieval should become standard of care. This concept is not (yet) mentioned in any guidelines or elimination plans, but deserves attention since it can contribute to HCV elimination. Retrieval could be done yearly, to reduce workload, and requires close collaboration between microbiologists/virologists, infectious disease specialists, hepatologists, hepatitis nurses and other parties such as addiction care medicine, prisons, public health institutes and/or general practitioners. Each centre could form a multidisciplinary team led by a dedicated retrieval coordinator, for example a hepatitis nurse. This coordinator could check the care cascade of all people who had a positive HCV test result in the previous year. The team could subsequently develop a multidisciplinary approach to retrieve LTFU patients. Patient-centred care is key in retrieving LTFU patients.

14 | ENSURING RETAINMENT IN CARE

Efforts should be made to retain LTFU and non-LTFU patients in care. The cascade of care should be simplified as much as possible, as is stated in the call to action from the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), the Asian Pacific Association for the Study of the Liver (APASL) and the Latin American Association for the Study of the Liver (ALEH), in partnership with the Clinton Health Access Initiative (CHAI).28 Pre-treatment diagnostic assessment should be performed in one appointment. Treatment should be offered to all RNA-positive patients. Patients should be
treated using pangenotypic regimens, making genotyping beforehand obsolete. Monitoring during treatment should be kept to a minimum. Care should be decentralized and/or integrated within other disease programmes as much as possible. Task-sharing between HCV specialists and other healthcare workers should be encouraged. Patients should be educated about the risk of re-infection. Lastly, some patients should be retained in post-SVR care, according to guidelines. This includes patients with a continuing risk of developing HCC, such as patients with advanced fibrosis (METAVIR score F3) or cirrhosis (F4) or patients with other risk factors such as excessive alcohol drinking, obesity and/or type 2 diabetes, but also patients with persisting abnormal liver tests that could indicate other causes of liver disease. These efforts can contribute to retainment in care and can therefore contribute to HCV elimination.

15 | CONCLUSION

LTFU is a problem in each step in the HCV care cascade, even in the current era where highly effective treatments are available and where it has been possible to simplify the cascade of care. HCV can be micro-eliminated in the LTFU population through retrieval. We present an example of nationwide retrieval in the Netherlands, which shows retrieval is feasible and can contribute to HCV elimination. We propose that micro-elimination through retrieval becomes standard of care on the road to viral hepatitis elimination. Furthermore, efforts to retain patients in care should be implemented in daily clinical practice.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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