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Hepatitis C cascade of care in the direct-acting antivirals era: a meta-analysis

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Abstract

Introduction: The hepatitis C virus (HCV) epidemic remains a public health problem worldwide. A systematic review and meta-analysis were conducted to provide evidence of outcomes attained across the HCV care cascade in the era of direct-acting antivirals (DAAs).

Methods: Studies from North America, Europe and Australia (January 2014 through March 2021) reporting on HCV care cascade outcomes (screening to cure) were included. When calculating the proportions of individuals completing each step, the numerator for steps 1-8 was the number of individuals completing each step; the denominator was the number of individuals completing the previous step for steps 1-3 and step 3 for steps 4-8. In 2022, random effects meta-analyses were conducted to estimate pooled proportions with 95% CIs.

Results: 65 studies comprising 7,402,185 individuals were identified. Among individuals with positive HCV RNA test results, 62% (95%CI 55%ï70%) attended their first care appointment, 41% (95%CI 37%ï45%) initiated treatment, 38% (95%CI 29%ï48%) completed treatment, and 29% (95%CI 25%ï33%) achieved cure. HCV screening rates were 43% (95%CI 22%ï66%) in prisons or jails, and 20% (95%CI 11%ï31%) in emergency departments (EDs). Linkage to care rates were 62% (95%CI 46%ï75%) for homeless individuals and 26% (95%CI 22%ï31%) for individuals diagnosed in EDs. Cure rates were 51% (95%CI 30%ï73%) in individuals with substance use disorder (SUD) and 17% (95%CI 17%ï17%) in homeless individuals. Cure rates were lowest in the U.S.

Discussion: Despite the availability of effective all-oral DAA therapies, persistent gaps remain across the HCV care cascade, especially among traditionally marginalized populations. Public health interventions targeting identified priority areas (e.g., EDs) may improve screening and health care retention of vulnerable populations with HCV infection (e.g., SUD populations).

Keywords: linkage to care; emergency departments; incarcerated individuals; substance use disorder; individuals experiencing homelessness

Introduction

The hepatitis C virus (HCV) epidemic has developed into a global public health problem.[1, 2] In the U.S. alone, between 2.4 and 3.9 million people are currently infected with HCV, with increasing incidence (about 40 per 100 person-years) among young people who inject drugs (PWID) and with approximately 50% of individuals unaware of their infection status.[3, 4] HCV incidence is also higher among PWID in other developed countries: in Australia, the incidence ranges from 7.6 to 12.8 per 100 person-years whereas the incidence in England is 8.7 per 100 person-years.[5, 6] In 2013, the advent of oral direct-acting antiviral (DAA) agents revolutionized the treatment of HCV infection. These new agents target different structures involved in the HCV replication process (e.g., they inhibit units of the replicase complex or the RNA chain polymerase),[7] they have 95% or higher therapeutic efficacy and limited adverse events, which has turned HCV infection into a curable disease.[2, 8] Thus, the World Health Organizationôs (WHO) goal of decreasing HCV infection incidence by 90% by 2030[9] appears feasible. However, individuals with HCV face multi-level barriers (e.g., comorbidities, job insecurity, lack of insurance)[3, 4, 10] and thus, the availability of an effective treatment alone is insufficient for reaching such an ambitious goal if affected populations lack proper access to care and support from healthcare systems.[11] Despite multiple efforts worldwide to improve screening and linkage to care for at-risk populations, persistent gaps have been identified in the HCV care cascade ï

which typically includes HCV antibody screening, HCV RNA confirmation testing, treatment initiation and completion, and sustained virologic response (SVR). Barriers are more challenging to overcome in large populations that includes traditionally marginalized groups, such as PWID and incarcerated or homeless individuals.[12]

Although evidence from different studies exists on the need to strengthen access to care for individuals with HCV infection, to the investigatorsô knowledge, no systematic review has compared HCV care cascade outcomes for various strategies and different venues implemented around the world to address this need. Therefore, a systematic review and meta-analysis were conducted to synthesize and evaluate the reported proportions of outcomes attained at each step of the HCV care cascade after the availability of DAAs.

Methods

The investigators searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, and PsycINFO from January 2014 through March 2021. The search strategy included terms for hepatitis C infection and each HCV care cascade step. The eight steps of this studyôs HCV care cascade included: (1) HCV screening, (2) positive HCV antibody test results, (3) positive HCV RNA test results, (4) successful patient contact, (5) linkage to care at first appointment, (6) treatment initiation, (7) treatment completion, and (8) confirmed SVR. Appendix Table 1 provides the full search strategy using MeSH terms and keywords**.** Observational studies, interventional studies, and clinical trials assessing outcomes at any point in the HCV care continuum, from screening to cure, were included. Additional manual searches were performed by reviewing the reference lists of the included studies. This systematic review

was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The studyôs protocol is registered in PROSPERO (CRD42021243759).

Studies were included if they (1) targeted adults with HCV screening or diagnosis, (2) reported at least two of the eight steps in the HCV care cascade, (3) were conducted in the U.S., Europe, Australia, New Zealand, or Canada, (4) were published after January 2014 (all-oral DAA therapy era), (5) were conducted as clinical trials, interventional studies (i.e., studies where an intervention was implemented but which did not have a comparator group), and retrospective or prospective observational studies, and (6) were reported in English. Studies were excluded if they (1) focused on specific populations from other countries (e.g., immigrants), (2) focused on specific races or ethnicities (e.g., American Indian, Alaska Native), (3) included <100 individuals, (4) included interferon-based therapy, (5) did not report the study period, and (6) were systematic reviews, case studies, conference abstracts, or studies with surveys (e.g., convenience sample, probability sample). Two investigators (PHC, NO, MR, IU, HS, AJ or XJ) independently screened titles, abstracts, and full-text articles and independently extracted data using a pre-specified standardized form. Differences were reconciled by a third investigator. Information on authors, publication journal, publication year, study design, population, study setting, study location, sample size, intervention description (when applicable), results, and conclusions, was extracted.

First, the number of individuals completing each step in the HCV care cascade step was obtained. Then, the investigators calculated the number of individuals screened among those eligible for HCV screening (step 1), with positive antibody test results among those screened (step 2), and with positive HCV RNA test results (HCV infection) among those with positive HCV antibody test results (step 3). Next, among individuals with positive HCV RNA test results, the investigators obtained the number of individuals who were successfully contacted by healthcare providers (step 4), attended their first clinic appointment (step 5), initiated (step 6) and completed DAA treatment (step 7), and achieved SVR at 12 weeks after therapy completion (step 8). The proportion of individuals completing steps 1ï3 was calculated by dividing the number of individuals completing each step (numerator) by the number of individuals completing the previous step (denominator). Similarly, the proportion of HCV-infected individuals completing steps 4ï8 was calculated by dividing the number of individuals completing each step (numerator) by the number of individuals with a positive HCV RNA test result (denominator), defined as receiving an HCV diagnosis.

The ñmetapropò command in Stata was used to calculate pooled prevalence estimates with exact binomial and score test-based 95% confidence intervals (CIs) for steps 1ï8 of the HCV care cascade using a random-effects model; this method appropriately combines rates close to margins using Freeman-Tukey Double Arcsine Transformation to stabilize variances.[14] Then, heterogeneity across studies using Cochranôs Q test and I^2 statistics was assessed. [15]

To account for potential sources of heterogeneity, the meta-analyses were stratified by (1) healthcare setting (i.e., emergency department [ED], ambulatory care, sexually transmitted

disease [STD]/substance use disorder [SUD]/syringe exchange program, jail or prison), (2) population (i.e., individuals with HIV, SUD, or experiencing homelessness, populations with ages ranging from 59 to 77 years old as of 2023 [born 1946-1964 or baby boomers]), and (3) country or territory (i.e., U.S., Europe, Australia, Canada). The meta-analyses were also stratified by country or territory due to differences in access to care and access to DAA therapy among countries or territories included in this study (e.g., universal access to DAAs has been available since 2015 in Spain, 2016 in Australia, 2017 in France and Italy, and 2018 in Canada; access to DAAs has been scaling-up in UK since 2017 and access remains restricted in U.S., largely depending on the type of health insurance).[5, 16-21] Funnel plots were used to assess for publication bias. All meta-analyses were performed in 2022, using Stata 16 statistical software (StataCorp LP).

Results

After applying exclusion criteria, 65 full-text articles comprising 7,402,185 total participants were included in the analysis (Figure 1). 49 studies (75%) were conducted in the U.S., 11 studies (17%) in Europe (3 studies in Italy and United Kingdom each, 2 studies in Ireland, and 1 study in Finland, France and Spain), 3 studies (5%) in Australia, and 2 studies (3%) in Canada. Additionally, 43 studies (66%) were interventional studies, 20 studies (31%) were retrospective or prospective observational studies, and 2 studies (3%) were clinical trials (Appendix Table 2). Most studies assessed outcomes in ambulatory care settings (42%). Other settings included SUD, STD, and syringe exchange programs (12%), EDs (12%), prisons or jails (8%), and other settings (e.g., in-patient, healthcare systems, [23%]). Two studies (3%) assessed outcomes in more than one setting.

Table 1 summarizes the pooled proportion of individuals completing each step of the HCV care cascade. Overall, 49% (95%CI 37%ï61%, I^2=100%, p<0.01) of individuals were screened for HCV (step 1), and 15% (95%CI 12%ï18%, I^2=100%, p<0.01) of individuals had positive HCV antibody tests (step 2); of those, 53% (95%CI 48%ï59%, I^2=99%, p<0.01) had positive HCV RNA test results (step 3). Among individuals with positive RNA test results (HCV diagnosis), 82% (95%CI 76%ï88%, I^2=97%, p<0.01) were successfully contacted (step 4), 62% (95%CI 55%ï70%, I^2=99%, p<0.01) attended their first appointment (step 5), 41% (95%CI 37%ï45%, I^2=99%, p<0.01) initiated HCV treatment (step 6), 38% (95%CI 29%ï48%, I^2=99%, p<0.01) completed treatment (step 7), and 29% (95%CI 25%ï33%, I^2=99%, p<0.01) achieved SVR (step 8).

Figures 2A and 2B show the proportions obtained at each step of the HCV care cascade by healthcare setting. For step 1 (Appendix Figure 1A), STD, SUD, and syringe programs had highest proportions of HCV screening (69% [95%CI 21%ï99%]), whereas prisons or jails and EDs had among the lowest proportions of HCV screening (43% [95%CI 22%ï66%] and 20% [95%CI 11%ï31%], respectively). The proportions of individuals with positive HCV antibody test results (step 2) ranged from 10% (95%CI 8%ï12%) to 34% (95%CI 21%ï50%), with individuals diagnosed in STD, SUD, and syringe programs achieving the highest proportions (Appendix Figure 1B). The proportions of individuals with positive HCV RNA test results (step 3) were similar by healthcare setting, ranging from 52% (95%CI 26%ï77%) to 57% (95%CI 43%ï71%) as shown in Appendix Figure 1C. Successful contact rates of individuals

identified with chronic HCV infection (step 4) ranged from 59% (95%CI 48%-69%) for those diagnosed in EDs to 94% (95%CI 75%ï100%) for those diagnosed in STD, SUD, and syringe programs (Appendix Figure 1D) Similarly, Appendix Figure 1E shows that higher proportions of linkage to care (step 5) were observed for individuals who were diagnosed in STD, SUD, and syringe programs (73%, 95%CI 54%ï87%) compared with individuals screened and diagnosed in ED settings (26%, 95%CI 22%ï31%).

The proportions of individuals initiating treatment (step 6) ranged from 22% (95%CI 6%ï45%) among individuals diagnosed in ED settings to 53% (95%CI 39%ï67%) among individuals diagnosed in STD, SUD, and syringe programs (Appendix Figure 1F). Whereas the proportions of individuals completing treatment (step 7) were highest for incarcerated individuals (49%, 95%CI 41%ï58%) and for individuals diagnosed in STD, SUD, and syringe programs (54%, 95%CI 36%ï71%), this proportion was lowest for individuals diagnosed in EDs (6%, 95%CI 4%ï8%) (Appendix Figure 1G). Similarly, the proportions of individuals achieving SVR (step 8) were highest for incarcerated individuals (35%, 95%CI 3%ï78%) and individuals diagnosed in STD, SUD, and syringe programs (47%, 95%CI 35%ï59%), whereas this proportion was lowest for individuals screened and diagnosed in EDs (9%, 95%CI 3%ï18%) (Appendix Figure 1H).

Figure 3A shows the proportion obtained at steps 1ï3 of the HCV care cascade by key subgroup population. Among eligible individuals, the proportion of individuals screened for HCV (step 1) was highest for those with HIV (88%, 95%CI 87%ï90%) followed by those experiencing homelessness (78%, 95%CI 78%ï78%) and those with SUD (69%, 95%CI 21%ï99%) (Appendix Figure 2A). The proportion of individuals with positive HCV antibody test results

(step 2) ranged from 11% (95%CI 15%ï46%) for populations with ages ranging from 59 to 77 years old as of 2023 (born 1946-1964 or baby boomers) to 28% (95%CI 15%ï44%) for those with SUD (Appendix Figure 2B). Among individuals with positive HCV antibody test results, the proportion of individuals with positive HCV RNA tests (step 3) varied from 30% (95%CI 3%ï18%) for those with SUD to 75% (95%CI 49%ï94%) for individuals with HIV (Appendix Figure 2C).

Figure 3B shows proportions of individuals completing steps 4ï8 of the HCV care cascade. Whereas individuals with SUD achieved highest ï or among the highest ï proportions at each step of the HCV care cascade from successful patient contact to confirmed SVR, individuals experiencing homelessness achieved lowest ï or among the lowest ï proportions at each of these steps (Appendix Figures 2D-2H). Specifically, among individuals with SUD, 73% (95%CI 45%ï 94%) were linked to a first appointment for HCV infection (step 5), 70% (95%CI 57%ï82%) completed HCV treatment (step 7) and 51% (95%CI 30%ï73%) achieved SVR (step 8). Conversely, among individuals experiencing homelessness, 62% (95%CI 46%ï75%) were linked to their first HCV infection appointment, 25% (95%CI 25%ï26%) initiated treatment (step 6) and 17% (95%CI 17%ï17%) achieved SVR.

Overall, there was evidence of publication bias for outcomes obtained at steps 1, 2 and 7 of the care cascade (Eggerôs test p-values = 0.004, 0.022 and 0.05, respectively), but not for steps 3 to 6 and step 8 (Eggerôs test p-values = 0.648, 0.767, 0.700 and 0.919, respectively).
Appendix Figures 3A and 3B compare results across some developed countries. The proportion of individuals screened for HCV was higher in Europe (67%, 95%CI 43%ï87%) compared with

the U.S. (44%, 95%CI 30%ï58%) and Australia or Canada (43%, 95%CI 23%ï63%). The proportion of individuals with positive HCV antibody test results in Europe (23%, 95%CI 13%ï 36%) was nearly double the U.S. proportion (13%, 95%CI 9%ï16%). The proportions of individuals with positive HCV RNA test results (56%, 95%CI 50%ï61%) and successfully contacted (84%, 95%CI 77%ï91%) were highest in the U.S. Although proportions of individuals linked to their first appointment for HCV infection treatment were similar between U.S. (62%, 95%CI 53%ï70%) and Europe (58%, 95%CI 43%ï73%), treatment initiation (39%, 95%CI 34%ï44%) and completion (32%, 95%CI 23%ï76%) were lower in the U.S. The proportion of individuals attaining SVR was higher in Europe (47%, 95%CI 20%ï76%) than in the U.S. (26%, 95%CI 22%ï31%) and Australia or Canada (29%, 95%CI 16%ï44%).

Discussion

This systematic review and meta-analysis demonstrate persistent gaps in achieved outcomes across the HCV care cascade in the era of all-oral DAA agents[8] despite prevalence rates of chronic HCV infection diagnosis, treatment initiation, and achieved SVR being double (or triple) those attained during the interferon-based therapy era.[22] The greater treatment effects, low adverse event occurrence, and short treatment duration for new DAA agents may have increased the number of individuals offered treatment, with subsequent improvement in proportions of HCV cure.[4, 10, 23] Although overall proportions of individuals treated for HCV have increased in the DAA era,[22] this meta-analysis showed that outcomes at each step of the HCV care cascade remain low and are still far from achieving the WHO goal of 80%ï90% cure by 2030.[9] These

results highlight multiple opportunities to improve engagement across the HCV care cascade, particularly for HCV diagnosis, DAA treatment initiation and completion, and SVR attainment.

The proportions of individuals screened for HCV infection and linked to care varied by setting and population. Whereas the proportion of positive HCV antibody test results among individuals visiting ED settings (10%) was comparable to most other settings in this study (except for STD, SUD, syringe programs [34%]), screening proportions in ED settings were lowest among eligible individuals. Although existing evidence has shown that EDs may be ideal venues to identify individuals with undiagnosed HCV infection,[4, 8] this study found that a large number of eligible individuals remained untested for HCV infection leaving a substantial proportion of individuals with HCV undetected. Such gaps may result from several barriers in implementing universal screening (e.g., populations with ages ranging from 59 to 77 years old as of 2023 [born 1946-1964 or baby boomers]) or targeted screening (e.g., PWID) in ED settings, including limited patient-clinician relationship,[24] patient stigma, clinician work burden, and financial and staffing burden to healthcare systems.[10, 25] Moreover, in the U.S., the Centers for Medicare and Medicaid Services currently exclude EDs from HCV screening reimbursement,[4, 23] which may discourage wide offering of HCV testing in those settings.

Poor outcomes for ED settings were not limited to step 1 (HCV screening) of the HCV care cascade. Indeed, compared with other settings, individuals from ED settings had considerably lower outcome proportions from step 4 (successful patient contact) to step 8 (confirmed SVR). Patient retention barriers in the HCV care cascade have been previously described.[4, 26, 27] Given the social vulnerability and complexity of many individuals attending EDs (e.g., PWID,