Journal Pre-proof

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

Pilar Hernandez-Con MD , Debbie L. Wilson PhD , Huilin Tang MS , Ikenna Unigwe MS , Munaza Riaz MS , Natalie Ourhaan PharmD , Xinyi Jiang PhD , Hyun Jin Song PhD , Amanda Joseph , Linda Henry PhD , Robert Cook MD , Dushyantha Jayaweera MD , Haesuk Park PhD

PII: S0749-3797(23)00278-7
DOI: https://doi.org/10.1016/j.amepre.2023.06.016
Reference: AMEPRE 7185

To appear in: *American Journal of Preventive Medicine*

Please cite this article as: Pilar Hernandez-Con MD , Debbie L. Wilson PhD , Huilin Tang MS , Ikenna Unigwe MS , Munaza Riaz MS , Natalie Ourhaan PharmD , Xinyi Jiang PhD , Hyun Jin Song PhD , Amanda Joseph , Linda Henry PhD , Robert Cook MD , Dushyantha Jayaweera MD , Haesuk Park PhD , Hepatitis C cascade of care in the direct-acting antivirals era: a meta-analysis, *American Journal of Preventive Medicine* (2023), doi: https://doi.org/10.1016/j.amepre.2023.06.016

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Published by Elsevier Inc. on behalf of American Journal of Preventive Medicine.

Journal Pre-proof

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

Pilar Hernandez-Con, MD[1], Debbie L. Wilson PhD[1], Huilin Tang, MS[1], Ikenna Unigwe, MS[1], Munaza Riaz, MS[1,2], Natalie Ourhaan, PharmD[1], Xinyi Jiang, PhD[1], Hyun Jin Song, PhD[1], Amanda Joseph[1], Linda Henry PhD[1], Robert Cook, MD[4], Dushyantha Jayaweera, MD[5], Haesuk Park, PhD[1,3]

[1]Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, Florida, USA

[2]Institute of Pharmacy, Lahore College for Women University, Lahore, Pakistan

[3]Center for Drug Evaluation and Safety (CoDES), University of Florida, Gainesville, Florida, USA

[4]Department of Medicine, University of Florida, Gainesville, Florida, USA

[5]Department of Medicine, Miller School of Medicine, University of Miami, Miami, Florida, USA

Journal Pre-proof

Corresponding Author Information

Haesuk Park, PhD**,** Department of Pharmaceutical Outcomes and Policy, University of Florida College of Pharmacy, 1225 Center Drive HPNP Building Room 3325, Gainesville, Florida 32610, USA. E-mail: hpark@cop.ufl.edu; fax: +1-352-273-6261

Journal Pre-proof

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%–70%) attended their first care appointment, 41% (95%CI 37%–45%) initiated treatment, 38% (95%CI 29%–48%) completed treatment, and 29% (95%CI 25%–33%) achieved cure. HCV screening rates were 43% (95%CI 22%–66%) in prisons or jails, and 20% (95%CI 11%–31%) in emergency departments (EDs). Linkage to care rates were 62% (95%CI 46%–75%) for homeless individuals and 26% (95%CI 22%–31%) for individuals diagnosed in EDs. Cure rates were 51% (95%CI 30%–73%) in individuals with substance use disorder (SUD) and 17% (95%CI 17%–17%) 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).

Journal Pre-proof

Journal Pre-proof

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 Organization's (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 –

Journal Pre-proof

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 investigators' 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 study's 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

Journal Pre-proof

was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The study's 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.

Journal Pre-proof

Journal Pre-proof

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 1–3 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 4–8 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 "metaprop" command in Stata was used to calculate pooled prevalence estimates with exact binomial and score test-based 95% confidence intervals (CIs) for steps 1–8 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 Cochran's 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

Journal Pre-proof

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.

Journal Pre-proof

Journal Pre-proof

Table 1 summarizes the pooled proportion of individuals completing each step of the HCV care cascade. Overall, 49% (95%CI 37%–61%, I^2=100%, p<0.01) of individuals were screened for HCV (step 1), and 15% (95%CI 12%–18%, I^2=100%, p<0.01) of individuals had positive HCV antibody tests (step 2); of those, 53% (95%CI 48%–59%, 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%–88%, I^2=97%, p<0.01) were successfully contacted (step 4), 62% (95%CI 55%–70%, I^2=99%, p<0.01) attended their first appointment (step 5), 41% (95%CI 37%–45%, I^2=99%, p<0.01) initiated HCV treatment (step 6), 38% (95%CI 29%–48%, I^2=99%, p<0.01) completed treatment (step 7), and 29% (95%CI 25%–33%, 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%–99%]), whereas prisons or jails and EDs had among the lowest proportions of HCV screening (43% [95%CI 22%–66%] and 20% [95%CI 11%–31%], respectively). The proportions of individuals with positive HCV antibody test results (step 2) ranged from 10% (95%CI 8%–12%) to 34% (95%CI 21%–50%), 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%–77%) to 57% (95%CI 43%–71%) as shown in Appendix Figure 1C. Successful contact rates of individuals

Journal Pre-proof

Journal Pre-proof

identified with chronic HCV infection (step 4) ranged from 59% (95%CI 48%-69%) for those diagnosed in EDs to 94% (95%CI 75%–100%) 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%–87%) compared with individuals screened and diagnosed in ED settings (26%, 95%CI 22%–31%).

The proportions of individuals initiating treatment (step 6) ranged from 22% (95%CI 6%–45%) among individuals diagnosed in ED settings to 53% (95%CI 39%–67%) 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%–58%) and for individuals diagnosed in STD, SUD, and syringe programs (54%, 95%CI 36%–71%), this proportion was lowest for individuals diagnosed in EDs (6%, 95%CI 4%–8%) (Appendix Figure 1G). Similarly, the proportions of individuals achieving SVR (step 8) were highest for incarcerated individuals (35%, 95%CI 3%–78%) and individuals diagnosed in STD, SUD, and syringe programs (47%, 95%CI 35%–59%), whereas this proportion was lowest for individuals screened and diagnosed in EDs (9%, 95%CI 3%–18%) (Appendix Figure 1H).

Figure 3A shows the proportion obtained at steps 1–3 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%–90%) followed by those experiencing homelessness (78%, 95%CI 78%–78%) and those with SUD (69%, 95%CI 21%–99%) (Appendix Figure 2A). The proportion of individuals with positive HCV antibody test results

Journal Pre-proof

(step 2) ranged from 11% (95%CI 15%–46%) 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%–44%) 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%–18%) for those with SUD to 75% (95%CI 49%–94%) for individuals with HIV (Appendix Figure 2C).

Figure 3B shows proportions of individuals completing steps 4–8 of the HCV care cascade. Whereas individuals with SUD achieved highest – or among the highest – proportions at each step of the HCV care cascade from successful patient contact to confirmed SVR, individuals experiencing homelessness achieved lowest – or among the lowest – proportions at each of these steps (Appendix Figures 2D-2H). Specifically, among individuals with SUD, 73% (95%CI 45%–94%) were linked to a first appointment for HCV infection (step 5), 70% (95%CI 57%–82%) completed HCV treatment (step 7) and 51% (95%CI 30%–73%) achieved SVR (step 8). Conversely, among individuals experiencing homelessness, 62% (95%CI 46%–75%) were linked to their first HCV infection appointment, 25% (95%CI 25%–26%) initiated treatment (step 6) and 17% (95%CI 17%–17%) achieved SVR.

Overall, there was evidence of publication bias for outcomes obtained at steps 1, 2 and 7 of the care cascade (Egger's test p-values = 0.004, 0.022 and 0.05, respectively), but not for steps 3 to 6 and step 8 (Egger's 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%–87%) compared with

Journal Pre-proof

the U.S. (44%, 95%CI 30%–58%) and Australia or Canada (43%, 95%CI 23%–63%). The proportion of individuals with positive HCV antibody test results in Europe (23%, 95%CI 13%–36%) was nearly double the U.S. proportion (13%, 95%CI 9%–16%). The proportions of individuals with positive HCV RNA test results (56%, 95%CI 50%–61%) and successfully contacted (84%, 95%CI 77%–91%) 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%–70%) and Europe (58%, 95%CI 43%–73%), treatment initiation (39%, 95%CI 34%–44%) and completion (32%, 95%CI 23%–76%) were lower in the U.S. The proportion of individuals attaining SVR was higher in Europe (47%, 95%CI 20%–76%) than in the U.S. (26%, 95%CI 22%–31%) and Australia or Canada (29%, 95%CI 16%–44%).

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%–90% cure by 2030.[9] These

Journal Pre-proof

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,

Journal Pre-proof

individuals experiencing homelessness or unemployment) and their restricted primary care services access,[3, 26] the transition through each HCV care cascade step may be more challenging for them. Although lack of health insurance has been reported as the main predictor of failure to link individuals to care,[4] competing priorities (e.g., securing food, associated comorbidities) and structural barriers (e.g., poor integration of ED services in healthcare systems, strict appointment schedules)[10, 26, 27] are additional difficulties that need to be addressed to keep these individuals in care.

Compared with other settings, incarcerated individuals had among the lowest proportion of HCV screening (43%), despite having the highest proportion of positive HCV RNA test results (57%). Although all five studies that assessed screening in jails or prisons included in this meta-analysis implemented an intervention to improve screening in various countries (e.g., opt-out screening, peer workers accompaniment for screening, dried blood spot test), this study's results revealed that HCV screening remained low among incarcerated individuals. Common barriers for step 1 of the HCV care cascade are the lack of standardized screening programs worldwide[28] which is likely the result of insufficient engagement and support from various stakeholders and government institutions (e.g., public health, healthcare systems)[29] and the complexity of these individuals' social environments before, during, and after incarceration, including frequent transfers between jails or prisons, or overall short stays, unstable housing when released, and lack of or restrictions to health insurance.[29, 30]

Whereas the proportions obtained for linkage to first appointment and treatment initiation were lower in incarcerated individuals, proportions of treatment completion and SVR were among the

Journal Pre-proof

Journal Pre-proof

highest. Although these results may be an overestimation of true outcomes due to the implementation of specific interventions that may be absent in standard practice, compared with other settings, prisons may indeed offer more stable and controlled conditions to complete the HCV continuum of care.[28, 31] This may be more applicable to individuals serving long sentences unless successful transitioning to the community is supported and achieved by a coordinated team.[29, 31] Finally, this study's results support previous findings showing that, despite some progress, the major bottleneck in the HCV care cascade for incarcerated individuals remains the screening phase (step 1).[32] Thus, efforts should be directed toward increasing HCV screening in incarcerated individuals. Using a combination of strategies, instead of a single one, would provide better outcomes at this step by addressing time of screening, fear of stigma, and lack of trust in prison or healthcare staff.[28, 29]

This meta-analysis showed that proportions of treatment initiation and completion and confirmed SVR were among the highest for individuals with SUD (PWID included). This study's findings confirmed existing evidence showing that individuals with SUD attain a similar proportion of HCV cure as the general population,[33] underscoring that persisting concerns regarding the medication adherence capacity of this population may be unfounded. Although findings from published literature suggest that these individuals face multilevel barriers,[34] including personal- and social-related barriers (e.g., competing concerns such as financial limitations, transportation difficulties, comorbidities, and social discrimination),[27, 35] clinician barriers (e.g., lack of experience interacting with individuals with SUD contributing to stigmatization and reinfection concerns)[33] and system-related barriers (e.g., DAA prescription restrictions based on clinician specialty, current SUD status, lack of insurance), preventing them from seeking and remaining in

Journal Pre-proof

care,[24] this study shows that, once screened, these individuals were successfully contacted and linked to a first appointment for HCV care. All except one of the studies looking at outcomes in individuals with SUD implemented an intervention; thus, this study's results suggest that existing barriers can be overcome by implementing appropriate health policies to identify and retain these individuals in care.

Although the proportion of HCV screening was among the highest for individuals experiencing homelessness (78%), based on two studies, these individuals were less likely to be successfully contacted (62%), linked to a first appointment (62%), receive DAA treatment (25%), and achieve SVR (17%). Individuals experiencing homelessness may face multilevel barriers to complete the HCV care cascade, from lack of knowledge of HCV acquisition, disease progression, and treatment availability[36] to experiencing concurrent alcohol or drug use,[37] which may interfere with adherence to appointments and referrals to specialists. Priorities such as housing or employment may outweigh seeking HCV-related treatment.[34] Moreover, lack of insurance coverage or clinician stigma may reduce participation in the HCV care cascade for these individuals, who often inject drugs.[37]

Differences were also found in outcomes across the HCV care cascade among developed countries. Specifically, proportions of individuals initially screened for HCV infection and proportions of treatment initiation, treatment completion, and SVR attainment were higher in Europe than in the U.S. These results may reflect overall difficulties experienced by many people in the U.S. in accessing care due to a healthcare system that is centered in private insurance with little government regulation and is thus fragmented, expensive, and complex to navigate.[38, 39]

Journal Pre-proof

Such limitations have a higher impact on individuals with chronic illnesses and in marginalized populations,[39] which describes many individuals affected by HCV infection. Some initiatives like the HCV surveillance program in the state of Louisiana – which has provided unrestricted access to generic DAAs to Medicaid enrollees and incarcerated individuals since 2019 – are a start to overcome the aforementioned pervasive structural barriers.[40]

Limitations

This systematic review and meta-analysis have limitations. First, outcomes of this study's HCV care cascade included eight steps evaluated at one time point, and each study included in this meta-analysis could have reported on some but not all eight steps. Second, the results of this meta-analysis showed significant heterogeneity due to the various care settings, countries, and study populations included. Although a random-effects model was used to account for study variability, other factors (e.g., different intervention programs) may have affected the estimates across the HCV care cascade. Third, the analysis revealed the potential for publication bias for steps 1, 2 and 7 of the HCV care cascade thus, the results obtained for outcomes representing steps 1, 2 and 7 should be interpreted with caution. Fourth, meta-analyses of some subgroups were limited by the relatively small number of studies identified, particularly for subgroups of incarcerated individuals and individuals with HIV or experiencing homelessness; thus, those small numbers may underestimate or overestimate the proportions obtained at each step of the HCV care cascade. Fifth, most studies assessing incarcerated individuals used the term *prison* interchangeably with *jail*; thus, this study's results do not differentiate outcomes between jails and prisons. Sixth, the investigators were unable to assess publication bias in this study because most included studies did not have a control group to compare to an intervention group. Finally,

Journal Pre-proof

Journal Pre-proof

most included studies were interventional; thus, the findings of this study may overestimate outcomes and may not be generalizable to real-world clinical settings in which no intervention is implemented.

Despite these limitations, this systematic review and meta-analysis assessed outcomes for each step of the HCV care cascade in the DAA therapy era. The meta-analyses of various subgroups in terms of setting, population, study design, and country/territory provided comprehensive and detailed information. This systematic review and meta-analysis identified gaps at each step of the HCV care cascade and strategies for future studies. The HCV care cascade may be useful in monitoring impact of new public health initiatives and treatment care models worldwide.

Conclusions

This systematic review and meta-analysis demonstrated persistent gaps across the HCV care cascade, confirming that the availability of effective all-oral DAA therapies does not guarantee medication access by populations most in need. This study's findings also suggest that continued efforts are needed to improve the care cascade for individuals with HCV infection. Increasing the number of people completing each HCV care cascade step, especially among individuals diagnosed with HCV in ED settings, individuals experiencing homelessness, incarcerated individuals and individuals with SUD, may be a strategy to achieve the WHO's goal of curing HCV infection and reducing the incidence of HCV infection.

Journal Pre-proof

Journal Pre-proof

Acknowledgments

Research reported in this publication was supported by grant K01DA045618 from the National Institute on Drug Abuse of the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The authors declare that there are no conflicts of interest relevant to this work. PHC, HT, IU, MR, XJ, HJS, AJ, LH, RC and DJ have no financial disclosures to report. HP received grant funding from Bristol-Myers Squibb/Pfizer Alliance American Thrombosis Investigator Initiated Research Program (ARISTA-USA). DLW received grant funding from Merck, Sharp & Dohme. NO is an employee of Johnson & Johnson. This work was conducted when she was affiliated with the University of Florida.

Journal Pre-proof

Journal Pre-proof

References

1. Morales-Arraez D, Hernández-Guerra M. Electronic Alerts as a Simple Method for Amplifying the Yield of Hepatitis C Virus Infection Screening and Diagnosis. Am J Gastroenterol. 2020;115(1):9-12. doi: http://doi.org/10.14309/ajg.0000000000000487.

2. Konerman MA, Thomson M, Gray K, Moore M, Choxi H, Seif E, et al. Impact of an electronic health record alert in primary care on increasing hepatitis c screening and curative treatment for baby boomers. Hepatology. 2017;66(6):1805-1813. doi: http://doi.org/10.1002/hep.29362.

3. Blackburn NA, Patel RC, Zibbell JE. Improving Screening Methods for Hepatitis C Among People Who Inject Drugs: Findings from the HepTLC Initiative, 2012-2014. Public Health Rep. 2016;131 Suppl 2(Suppl 2):91-7. doi: http://doi.org/10.1177/00333549161310s214.

4. Franco RA, Overton ET, Tamhane AR, Forsythe JM, Rodgers JB, Schexnayder JK, et al. Characterizing Failure to Establish Hepatitis C Care of Baby Boomers Diagnosed in the Emergency Department. Open Forum Infect Dis. 2016;3(4):ofw211. doi: http://doi.org/10.1093/ofid/ofw211.

5. Wilkinson AL, van Santen DK, Traeger MW, Sacks-Davis R, Asselin J, Scott N, et al. Hepatitis C incidence among patients attending primary care health services that specialise in the care of people who inject drugs, Victoria, Australia, 2009 to 2020. Int J Drug Policy. 2022;103:103655. doi: http://doi.org/10.1016/j.drugpo.2022.103655.

6. Artenie A, Stone J, Fraser H, Stewart D, Arum C, Lim AG, et al. Incidence of HIV and hepatitis C virus among people who inject drugs, and associations with age and sex or gender: a global systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2023. doi: http://doi.org/10.1016/s2468-1253(23)00018-3.

Journal Pre-proof

Journal Pre-proof

7. Kish T, Aziz A, Sorio M. Hepatitis C in a New Era: A Review of Current Therapies. P t. 2017;42(5):316-329.

8. Radley A, Robinson E, Aspinall EJ, Angus K, Tan L, Dillon JF. A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments. BMC Health Serv Res. 2019;19(1):765. doi: http://doi.org/10.1186/s12913-019-4635-7.

9. World Health Organization. Global Hepatitis Report. Geneva: WHO. doi: https://www.who.int/publications/i/item/9789241565455. Published 2017. Accessed June 30, 2022.

10. Ancona RM, Habib D, Faryar KA, Ruffner AH, Hart KW, Lyons MS. Clarifying the volume of estimated need for public health and prevention services within an emergency department population. J Am Coll Emerg Physicians Open. 2020;1(5):845-851. doi: http://doi.org/10.1002/emp2.12168.

11. Bajis S, Dore GJ, Hajarizadeh B, Cunningham EB, Maher L, Grebely J. Interventions to enhance testing, linkage to care and treatment uptake for hepatitis C virus infection among people who inject drugs: A systematic review. Int J Drug Policy. 2017;47:34-46. doi: http://doi.org/10.1016/j.drugpo.2017.07.002.

12. Facente SN, Patel S, Hecht J, Wilson E, McFarland W, Page K, et al. Hepatitis C Care Cascades for 3 Populations at High Risk: Low-income Trans Women, Young People Who Inject Drugs, and Men Who Have Sex With Men and Inject Drugs. Clin Infect Dis. 2021;73(6):e1290-e1295. doi: http://doi.org/10.1093/cid/ciab261.

Journal Pre-proof

Journal Pre-proof

13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):89. doi: http://doi.org/10.1186/s13643-021-01626-4.

14. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014;72(1):39. doi: http://doi.org/10.1186/2049-3258-72-39.

15. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006;11(2):193-206. doi: http://doi.org/10.1037/1082-989x.11.2.193.

16. Politi J, Regidor E, Donat M, Pulido J, Guerras JM, Barrio G, et al. Free Access to Direct-Acting Antivirals in Spain: More Favorable Impact on Hepatitis C Mortality Among Highly Educated People. Clin Infect Dis. 2023;76(8):1423-1430. doi: http://doi.org/10.1093/cid/ciac928.

17. Pol S, Lair-Mehiri L, Vallet-Pichard A. Is elimination of HCV realistic by 2030: France. Liver Int. 2021;41 Suppl 1:45-49. doi: http://doi.org/10.1111/liv.14862.

18. Russo P, Pani L, Staniscia T, Romano F, Marzioni M. Impact of reimbursement limits on patient access to direct-acting antivirals in Italy: analysis of data from national registries. Eur Rev Med Pharmacol Sci. 2020;24(10):5758-5768. doi: http://doi.org/10.26355/eurrev_202005_21368.

19. Jiang N, Bruneau J, Makarenko I, Minoyan N, Zang G, Høj SB, et al. HCV treatment initiation in the era of universal direct acting antiviral coverage - Improvements in access and persistent barriers. Int J Drug Policy. 2023;113:103954. doi: http://doi.org/10.1016/j.drugpo.2023.103954.

Journal Pre-proof

Journal Pre-proof

20. Bardsley M, Heinsbroek E, Harris R, Croxford S, Edmundson C, Hope V, et al. The impact of direct-acting antivirals on hepatitis C viraemia among people who inject drugs in England; real-world data 2011-2018. J Viral Hepat. 2021;28(10):1452-1463. doi: http://doi.org/10.1111/jvh.13575.

21. Yeung A, Palmateer NE, Dillon JF, McDonald SA, Smith S, Barclay S, et al. Population-level estimates of hepatitis C reinfection post scale-up of direct-acting antivirals among people who inject drugs. J Hepatol. 2022;76(3):549-557. doi: http://doi.org/10.1016/j.jhep.2021.09.038.

22. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V, 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. PLoS One. 2014;9(7):e101554. doi: http://doi.org/10.1371/journal.pone.0101554.

23. Hsieh YH, Patel AV, Loevinsohn GS, Thomas DL, Rothman RE. Emergency departments at the crossroads of intersecting epidemics (HIV, HCV, injection drug use and opioid overdose)-Estimating HCV incidence in an urban emergency department population. J Viral Hepat. 2018;25(11):1397-1400. doi: http://doi.org/10.1111/jvh.12948.

24. Marshall AD, Grebely J, Dore GJ, Treloar C. Barriers and facilitators to engaging in hepatitis C management and DAA therapy among general practitioners and drug and alcohol specialists-The practitioner experience. Drug Alcohol Depend. 2020;206:107705. doi: http://doi.org/10.1016/j.drugalcdep.2019.107705.

25. Paterson B, Hirsch G, Andres K. Structural factors that promote stigmatization of drug users with hepatitis C in hospital emergency departments. Int J Drug Policy. 2013;24(5):471-8. doi: http://doi.org/10.1016/j.drugpo.2013.01.008.

26. Minassian A, Vilke GM, Wilson MP. Frequent emergency department visits are more prevalent in psychiatric, alcohol abuse, and dual diagnosis conditions than in chronic viral

Journal Pre-proof

Journal Pre-proof

illnesses such as hepatitis and human immunodeficiency virus. J Emerg Med. 2013;45(4):520-5. doi: http://doi.org/10.1016/j.jemermed.2013.05.007.

27. Paisi M, Crombag N, Burns L, Bogaerts A, Withers L, Bates L, et al. Barriers and facilitators to hepatitis C screening and treatment for people with lived experience of homelessness: A mixed-methods systematic review. Health Expect. 2022;25(1):48-60. doi: http://doi.org/10.1111/hex.13400.

28. Kronfli N, Linthwaite B, Kouyoumdjian F, Klein MB, Lebouché B, Sebastiani G, et al. Interventions to increase testing, linkage to care and treatment of hepatitis C virus (HCV) infection among people in prisons: A systematic review. Int J Drug Policy. 2018;57:95-103. doi: http://doi.org/10.1016/j.drugpo.2018.04.003.

29. Wurcel AG, Reyes J, Zubiago J, Koutoujian PJ, Burke D, Knox TA, et al. "I'm not gonna be able to do anything about it, then what's the point?": A broad group of stakeholders identify barriers and facilitators to HCV testing in a Massachusetts jail. PLoS One. 2021;16(5):e0250901. doi: http://doi.org/10.1371/journal.pone.0250901.

30. Crowley D, Murtagh R, Cullen W, Lambert JS, McHugh T, Van Hout MC. Hepatitis C virus infection in Irish drug users and prisoners - a scoping review. BMC Infect Dis. 2019;19(1):702. doi: http://doi.org/10.1186/s12879-019-4218-6.

31. European Centre for Diseases Prevention and Control and the European Monitoring Centre for Drug and Drug Addiction. Systematic review on active case finding of communicable diseases in prison settings. Stockholm: ECDC. doi: https://www.ecdc.europa.eu/en/publications-data/systematic-review-active-case-finding-communicable-diseases-prison-settings. Published November 2017. Accessed June 30, 2022.

Journal Pre-proof

Journal Pre-proof

32. Rumble C, Pevalin DJ, O'Moore É. Routine testing for blood-borne viruses in prisons: a systematic review. Eur J Public Health. 2015;25(6):1078-88. doi: http://doi.org/10.1093/eurpub/ckv133.

33. Trooskin SB, Dore G, Kostman J. We Must Do Better: Addressing HCV Treatment Barriers in Persons Who Inject Drugs in the United States. J Infect Dis. 2020;222(Suppl 9):S773-s781. doi: http://doi.org/10.1093/infdis/jiaa574.

34. Gelberg L, Gallagher TC, Andersen RM, Koegel P. Competing priorities as a barrier to medical care among homeless adults in Los Angeles. Am J Public Health. 1997;87(2):217-20. doi: http://doi.org/10.2105/ajph.87.2.217.

35. Edlin BR, Kresina TF, Raymond DB, Carden MR, Gourevitch MN, Rich JD, et al. Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. Clin Infect Dis. 2005;40 Suppl 5(Suppl 5):S276-85. doi: http://doi.org/10.1086/427441.

36. Norton BL, Voils CI, Timberlake SH, Hecker EJ, Goswami ND, Huffman KM, et al. Community-based HCV screening: knowledge and attitudes in a high risk urban population. BMC Infect Dis. 2014;14:74. doi: http://doi.org/https://doi.org/10.1186/1471-2334-14-74.

37. Strehlow AJ, Robertson MJ, Zerger S, Rongey C, Arangua L, Farrell E, et al. Hepatitis C among clients of health care for the homeless primary care clinics. J Health Care Poor Underserved. 2012;23(2):811-33. doi: http://doi.org/10.1353/hpu.2012.0047.

38. Rethinking Health Care Delivery: What European And United States Health Care Systems can Learn From One Another. Washington, DC: Health Affairs Forefront. doi: https://www.healthaffairs.org/do/10.1377/forefront.20171214.835155. Published 2017. Accessed June 29, 2022.

Journal Pre-proof

Journal Pre-proof

39. Schoen C, Osborn R, Squires D, Doty MM. Access, affordability, and insurance complexity are often worse in the United States compared to ten other countries. Health Aff (Millwood). 2013;32(12):2205-15. doi: http://doi.org/10.1377/hlthaff.2013.0879.

40. STD/HIV/Hepatitis Program. Louisiana Hepatitis C Elimination Plan: 2019-2024: Louisiana Department of Health. doi: https://www.louisianahealthhub.org/wp-content/uploads/2021/03/Eliminate_Hepatitis_C_State_Plan.pdf. Published December 2019. Accessed April 28, 2023.

Journal Pre-proof

Journal Pre-proof

Tables and figure legends

Table 1: Pooled proportions of individuals completing each of the eight steps in the HCV care cascade

Step in the HCV care cascade	Number of studies (N=65)	Number of individuals	Random effects, estimate (95% CI)	I^2
Step 1: screening rate (among persons who were eligible for hepatitis C screening)	32	6,396,187	0. 49 (0.37, 0.61)	[a]100%
Step 2: prevalence of positive antibody test (among persons who were screened for HCV)	48	508,412	0.15 (0.12, 0.18)	[a]100%
Step 3: prevalence of positive HCV RNA test (among persons with positive HCV antibody test)	47	42,163	0.53 (0.48, 0.59)	[a]99%
Step 4: successful contact rate (among persons with positive HCV RNA test)	26	16,069	0.82 (0.76, 0.88)	[a]99%
Step 5: linkage to care at first appointment (among all persons with positive HCV RNA test)	47	31,842	0.62 (0.55, 0.70)	[a]99%
Step 6: treatment initiation (among all persons with positive HCV RNA test)	42	205,163	0.41 (0.37, 0.45)	[a]99%
Step 7: treatment completion (among all persons with positive HCV RNA test)	22	12,762	0.38 (0.29, 0.48)	[a]99%

[a] **Q test** indicates p<0.01

Journal Pre-proof

Journal Pre-proof

Step 8: confirmed sustained virologic response (among all persons with positive HCV RNA test)	34	204,015	0.29 (0.25, 0.33)	[a]99%

Note: Pooled proportions were separately calculated for each step. Thus, studies included to calculate pooled proportions of one step were not necessarily included when calculating the pooled proportions of subsequent steps.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; RNA, ribonucleic acid.

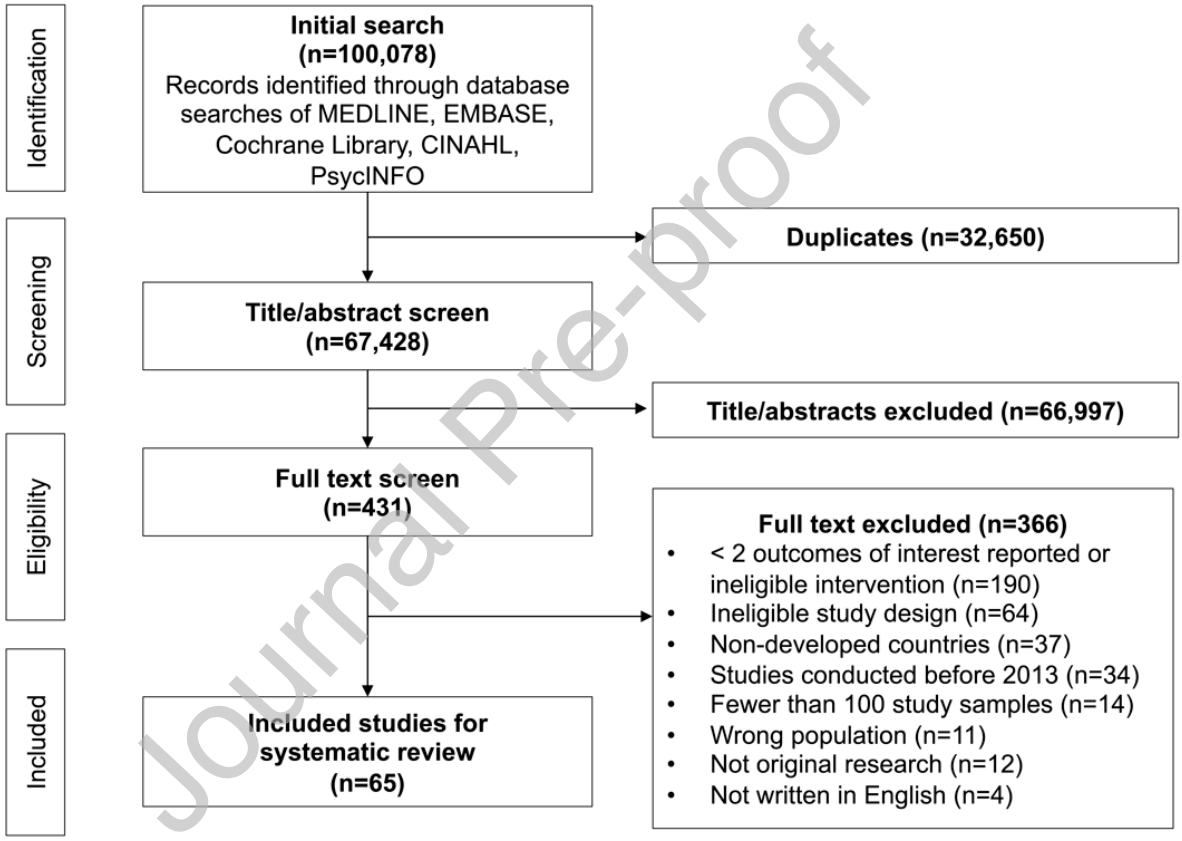
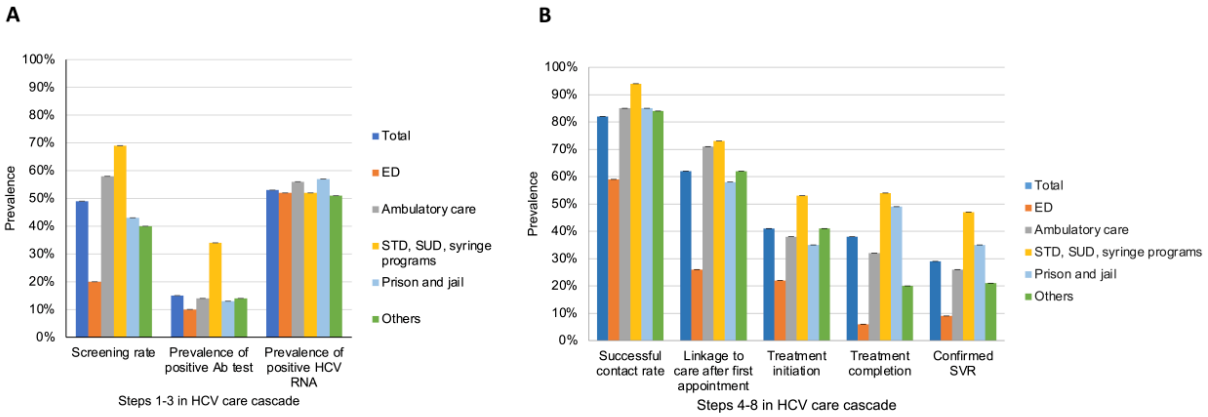


Figure 1: Flow diagram of study selection

Journal Pre-proof



	Step 1	Step 2	Step 3
	# of studies (participants)	# of studies (participants)	# of studies (participants)
Total	32 (6,396,187)	48 (508,412)	47 (42,163)
ED	6 (218,615)	9 (111,845)	8 (9,234)
Ambulatory care	14 (6,003,331)	19 (151,223)	19 (14,075)
STD, SUD, syringe programs	5 (22,763)	5 (5,732)	5 (1,582)
Prison and jail	4 (22,600)	4 (6,347)	4 (793)
Others	3 (128,878)	13 (233,265)	13 (16,479)

	Step 4	Step 5	Step 6	Step 7	Step 8
	# of studies (participants)	# of studies (participants)	# of studies (participants)	# of studies (participants)	# of studies (participants)
Total	26 (16,069)	47 (31,842)	42 (205,163)	22 (12,762)	34 (204,015)
ED	5 (1,923)	7 (3,628)	3 (1,364)	1 (990)	3 (1,337)
Ambulatory care	7 (1,568)	22 (7,328)	20 (184,294)	13 (5,968)	18 (184,153)
STD, SUD, syringe programs	5 (1,345)	3 (953)	8 (1,718)	6 (1,124)	7 (1,684)
Prison and jail	1 (413)	3 (234)	4 (314)	2 (130)	3 (146)
Others	10 (10,820)	15 (19,699)	10 (17,473)	3 (4,550)	6 (16,695)

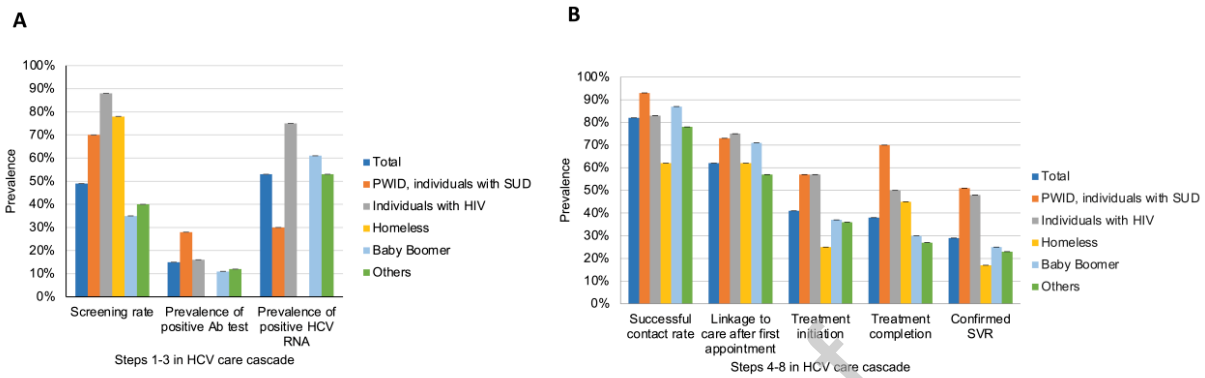
Figure 2: HCV treatment cascade steps by setting

(A) Steps 1–3. The proportion of individuals who were screened was calculated among individuals who were eligible for HCV screening (step 1). The proportion of individuals with positive antibody (Ab) test results was calculated among screened individuals (step 2), and the proportion of individuals with positive HCV RNA test results was calculated among individuals with positive Ab test results (step 3). (B) Steps 4–8. Using the pooled estimates of the eight steps and the number of participants from steps 1–3, the proportion of HCV-infected individuals completing each step of the HCV care cascade was calculated by dividing the number of individuals who completed each step (steps 4–8) by the number of individuals with positive HCV RNA test results.

Note: Calner et al. (2019) included 3 settings (ED, ambulatory care and others); Ford et al. (2017) included 2 settings (ambulatory care and STD, SUD and syringe service programs). The sum of the numbers for each individual setting may differ from the total for some of the steps of the HCV care cascade.

Journal Pre-proof

Abbreviations: ED, emergency department; STD, sexually transmitted disease; SUD, substance use disorder; SVR, sustained virologic response.



	Step 1	Step 2	Step 3
	# of studies (participants)	# of studies (participants)	# of studies (participants)
Total	32 (6,396,187)	48 (508,412)	47 (42,163)
PWID, indiviuals with SUD	5 (116,271)	8 (34,713)	6 (1,322)
Individuals with HIV	2 (2,550)	2 (366)	3 (584)
Homeless	2 (242,942)	0 (0)	0 (0)
Baby boomers	8 (330,934)	14 (12,026)	14 (11,759)
Others	16 (5,703,490)	24 (27,857)	24 (28,498)

	Step 4	Step 5	Step 6	Step 7	Step 8
	# of studies (participants)	# of studies (participants)	# of studies (participants)	# of studies (participants)	# of studies (participants)
Total	26 (16,069)	47 (31,842)	42 (205,163)	22 (12,762)	34 (204,015)
PWID, individuals with SUD	5 (758)	3 (3,905)	6 (4,494)	3 (625)	4 (4,338)
Individuals with HIV	2 (367)	2 (367)	4 (583)	4 (583)	4 (583)
Homeless	1 (47)	1 (47)	2 (29,110)	1 (47)	2 (29,110)
Baby boomers	3 (1,147)	11 (4,539)	6 (7,033)	4 (3,321)	5 (6,994)
Others	15 (13,750)	30 (22,984)	25 (163,943)	10 (8,186)	20 (162,990)

Figure 3: HCV treatment cascade steps by population

(A) Steps 1–3. The proportion of individuals who were screened was calculated among individuals who were eligible for HCV screening (step 1)., The proportion of individuals with positive antibody (Ab) test results was calculated among screened individuals (step 2), and the proportion of individuals with positive HCV RNA test results was calculated among individuals with positive Ab test results (step 3). (B) Steps 4–8. Using the pooled estimates of the eight steps and the numbers of participants from steps 1–3, the proportion of HCV-infected individuals completing each HCV cascade step was calculated by dividing the number of individuals who completed each step (steps 4–8) by the number of individuals with positive HCV RNA test results.

Journal Pre-proof

Journal Pre-proof

Note: Noska et al. (2017) included 2 subpopulations of U.S. veterans: homeless and not homeless. The sum of the numbers for each individual subpopulation may differ from the total for some of the steps of the HCV care cascade.

Abbreviations: PWID, people who inject drugs; SUD, substance use disorder; SVR, sustained virologic response.

Journal Pre-proof

Appendix material

Appendix Table 1: Strategy for literature search

Appendix Table 2: Characteristics and results of included studies

Abbreviations: AB = antibody; BPA = Best practice alert; baby boomers = individuals born between 1946 and 1964; CDC = Centers for Disease Control and Prevention; CDS = Clinical decision support; CNS = Clinical nurse specialist; DAA = direct acting antivirals; ED = emergency department; EHR = electronic health records; FQHCs = Federally Qualified Health Centers; GPs = General practitioners; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HE = health educator; HH = Highland Hospital; HIV = human immunodeficiency virus; HRQL = health related quality of life; ID = infectious disease; LTCC = Linkage to care coordinator; MDT = Multidisciplinary team (comprising viral hepatology consultants, pharmacists and nurses); N/A = Not applicable; PCP = Primary care provider; PN = Patient navigator; PWID = people who inject drugs; RCT = Randomized controlled trial; SUD = substance use disorder; SVR = sustained virologic response; UAB = University of Alabama at Birmingham; UCLA =

Journal Pre-proof

University of California, Los Angeles; UK = United Kingdom; U.S.= United States of America; U.S. VHA = United States Veterans Health Administration; VA = Veteran Affairs; VAHCS = Veteran Affairs Health Care System.

[a] Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Bloodborne Viruses and Sexually Transmitted Infections (ACCESS) sentinel surveillance system

Definitions of outcomes:

Proportion of individuals screened for HCV = # of individuals with HCV testing / # of eligible individuals for HCV screening

Proportion of individuals with positive HCV antibody tests = # of individuals with positive antibody test / # of individuals screened

Proportion of individuals with positive HCV RNA tests = # of individuals with positive HCV RNA results / # individuals with positive HCV antibody tests

Proportion of individuals successfully contacted = # individuals contacted / # individuals with positive HCV RNA tests

Proportion of individuals linked to first appointment = # of individuals attending first appointment at HCV clinic / # of individuals with positive HCV RNA tests

Proportion of individuals with treatment initiation = # of individuals who initiated DAA treatment / # of individuals with positive HCV RNA tests

Proportion of individuals with treatment completion = # of individuals who completed DAA treatment / # of individuals with positive HCV RNA tests

Journal Pre-proof

Journal Pre-proof

Proportion of individuals achieving SVR = # of individuals with confirmed SVR / of individuals with positive HCV RNA tests

Appendix Figure 1, A-H. Outcomes rates at each step of the HCV cascade of care (Steps 1-8), stratified by healthcare setting

Appendix Figure 2, A-H. Outcomes rates at each step of the HCV cascade of care (Steps 1-8), stratified by key populations

Appendix Figure 3: HCV treatment cascade by country (A) Steps 1–3 and (B) Steps 4–8

(A) Steps 1–3. The proportion of individuals who were screened was calculated among individuals who were eligible for HCV screening (step 1). The proportion of individuals with positive antibody (Ab) test results was calculated among screened individuals (step 2), and the proportion of individuals with positive HCV RNA test results was calculated among individuals with positive Ab test results (step 3). (B) Steps 4–8. Using the pooled estimates of the eight steps and the numbers of participants from steps 1–3, the proportion of HCV-infected individuals completing each HCV cascade step was calculated by dividing the number of individuals who completed each step (steps 4–8) by the number of individuals with positive HCV RNA test results.

Abbreviations: EU, Europe; U.S., United States; SVR, sustained virologic response.

Journal Pre-proof

Journal Pre-proof

CRediT author statement

Pilar Hernandez-Con: Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project Administration; **Debbie L. Wilson:** Investigation, Data Curation, Writing – Review & Editing, Visualization; **Huilin Tang:** Software, Formal analysis, Writing – Review & Editing; **Ikenna Unigwe:** Investigation, Writing – Original Draft; **Munaza Riaz:** Investigation, Writing – Original Draft, Writing – Review & Editing; **Nathalie Ourhaan:** Investigation, Writing – Original Draft; **Xinyi Jiang:** Investigation; **Hyun Jin Song:** Investigation, Writing – Original Draft; **Amanda Joseph:** Investigation; **Linda Hendry:** Writing – Review & Editing; **Robert Cook:** Writing – Review & Editing; **Dushyantha Jayaweera:** Writing – Review & Editing; **Haesuk Park:** Conceptualization, Methodology, Writing – Review & Editing, Visualization, Supervision, Funding Acquisition.

Journal Pre-proof