Regional differences in treatment rates for patients with chronic hepatitis C infection: Systematic review and meta-analysis

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Abstract

Background & aims
Treatment rates with interferon-based therapies for chronic hepatitis C have been low. Our aim was to perform a systematic review of available data to estimate the rates and barriers for antiviral therapy for chronic hepatitis C.

Methods
We conducted a systematic review and meta-analysis searching MEDLINE, SCOPUS through March 2016 and abstracts from recent major liver meetings for primary literature with available hepatitis C treatment rates. Random-effects models were used to estimate effect sizes and meta-regression to test for potential sources of heterogeneity.

Results
We included 39 studies with 476,443 chronic hepatitis C patients. The overall treatment rate was 25.5% (CI: 21.1–30.5%) and by region 34% for Europe, 28.3% for Asia/Pacific, and 18.7% for North America (p = 0.008). On multivariable meta-regression, practice setting (tertiary vs. population-based, p = 0.04), region (Europe vs. North America p = 0.004), and data source (clinical chart review vs. administrative database, p = 0.025) remained significant predictors of heterogeneity. The overall treatment eligibility rate was 52.5%, and 60% of these received therapy. Of the patients who refused treatment, 16.2% cited side effects, 13.8% cited cost as reasons for treatment refusal, and 30% lacked access to specialist care.

Conclusions
Only one-quarter of chronic hepatitis C patients received antiviral therapy in the pre-direct acting antiviral era. Treatment rates should improve in the new interferon-free era but, cost,
co-morbidities, and lack of specialist care will likely remain and need to be addressed. Linkage to care should even be of higher priority now that well-tolerated cure is available.

**Introduction**

Together with chronic hepatitis B, chronic hepatitis C (CHC) is a leading cause of death and disability worldwide.[1] The enormous health cost attributable to viral hepatitis and the availability of effective treatments suggests an important opportunity to improve public health, especially in the case of CHC now that a simple and well-tolerated therapeutic cure is available. As part of a global strategy for eliminating viral hepatitis as a major public health concern by 2030, the World Health Organization (WHO) has set a goal of treating 80% of eligible CHC with antiviral therapy.[2] Unfortunately, treatment rates are far below this number. Several U.S. based studies report treatment rates with pegylated-interferon (PEG-IFN) and ribavirin (RBV) that range from nine to 36%.[3–7] In their report the WHO also estimates that under 1% of treatment eligible CHC patients worldwide have received antiviral therapy.[2]

These low treatment rates are likely due to both PEG-IFN/RBV related toxicities and contraindications as well as systems-level barriers such as medication cost, insurance reimbursement, and appropriate specialist follow up. Newer direct acting antiviral agents (DAAs) will likely lower barriers related to treatment eligibility and patient/provider willingness to undergo treatment, but systems-level barriers will likely persist.[8, 9] In addition, it is unclear how treatment rates and barriers vary worldwide where patient populations and healthcare practices differ. As CHC becomes a more easily cured disease, it becomes increasingly important to understand where best to direct our resources to improve access to care.

Our aim was to perform a systematic review of available data to estimate treatment rates for CHC worldwide.

**Materials and methods**

**Data sources and searches**

We performed a systematic review and meta-analysis searching MEDLINE and SCOPUS databases for studies with available treatment rates for CHC patients from January 1991 through March 2016. Articles were queried from MEDLINE using the following search terms: ((hepatitis C[Title] OR HCV[Title]) AND (treatment[Title] OR antiviral[Title])) AND english[Language] AND (rate[Text Word] OR referral[Text Word] OR duration[Text Word] OR linkage [Text Word] OR specialist[Text Word] OR intake[Text Word] OR multivariate[Text Word]). Articles were queried from SCOPUS with the following search terms: (‘hepatitis C’ OR ‘HCV’) AND (‘treatment’). Non-English articles were excluded in both queries.

We also conducted a manual search of abstracts using the term ‘hepatitis C’ from annual international scientific meetings held in the 2 years preceding the literature search date and by the American Association for the Study of Liver Diseases (AASLD), Digestive Disease Week, the Asian Pacific Study of the Liver, and the European Association for the Study of the Liver (EASL). All data were collected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10]
Inclusion and exclusion criteria

We included original studies with ≥ 25 CHC patients with available antiviral treatment rates. Treatment was defined by receipt of interferon, PEG-IFN, RBV, or DAA-based therapies. Exclusion criteria included studies of populations from randomized control trials and studies of specialized populations including renal hemodialysis centers, human immunodeficiency virus (HIV) clinics, or drug rehabilitation programs. We also excluded studies of cohorts with high rates (≥ 10%) of HIV and/or hepatitis B co-infection. In the case of studies with overlapping patient populations, we excluded abstracts at major liver meetings if there was a corresponding published manuscript. If multiple manuscripts were published from a similar patient database then we included the study with the largest number of patients.

Study selection and study extraction

Four authors (PV, MJ, PN, ML) independently assessed study titles and abstracts for eligibility (Fig 1). Studies that were considered eligible were then selected for full-text review. The authors then extracted individual study characteristics, patient treatment and eligibility rates, and patient medical and demographic data using a standardized case report form. Any discrepancies were resolved by discussion with the authors including the senior author (MN).

Study definitions

Population-based studies were defined as those that queried patients from national or region-wide databases/registries and did not recruit from a distinct number of clinics or hospitals. Advanced fibrosis was defined by the presence of cirrhosis or by a score of F3 or F4 on the Metavir scale.[11] Studies were further characterized by type of CHC treatment data collection: patient questionnaires, individual clinical chart review, and electronic query of administrative databases (i.e. pharmaceutical prescription or national insurance databases).

Study quality assessment

Study quality was assessed using a scoring system adapted after a modified Newcastle-Ottawa Quality Assessment scale.[12] Two authors (MLY, JFH) scored each study by three criteria: selection (maximum of five points assessing representativeness of the study population, sample size, and ascertainment of HCV exposure), comparability (maximum of one point), and outcome (maximum of three points assessing for reliability of HCV treatment and the statistical test used). As defined by prior studies, a score of seven or more was considered a “good” quality study.[13]

Statistical analysis

We analyzed pooled treatment rates with corresponding 95% confidence intervals (CIs) using random-effects models and odds ratios (OR) for sub-analyses comparing groups within studies. We assessed for study heterogeneity with χ²-based Cochrane Q-statistic with p ≤ 0.1 and I² ≥ 50% as measures for substantial study heterogeneity in our models. Multiple separate meta-analyses were performed on study-level characteristics including study region, quality assessment scores, type of therapy studied, patient recruitment period, and data collection methodology. Multivariable random-effects meta-regression on study-level characteristics were also performed to explain any observed heterogeneity in CHC treatment rates. All statistical tests were performed using Comprehensive Meta-Analysis, version 3 (Biostat, Englewood, New Jersey, USA).
Results

Our literature search identified 1,958 articles from MEDLINE, 1,359 articles from SCOPUS and 1,293 abstracts (Fig 1). After reviewing titles and abstracts, the full texts of 73 studies (64 manuscripts and nine abstracts) were closely evaluated for eligibility.
As shown in Table 1, a total of 39 studies with 476,443 CHC patients (37 articles and 2 abstracts) met eligibility criteria and were included in our primary meta-analyses.[3, 4, 6, 7, 14–48] Most studies were from North America (19/39, 49%) or Europe (11/39, 28%). Eight (21%) were from the Asia or Pacific regions. By setting, approximately half of the studies were from tertiary/referral centers (19/40, 47.5%) and close to half were from population-based settings (17/40, 42.5%). Most studies (28/39, 71.7%) collected treatment information through clinical chart review. Seven studies (18%) collected treatment prescription via electronic data extraction of large administrative databases and 4 studies (10.3%) through patient questionnaires.

Based on the modified Newcastle-Ottawa quality score for cross-sectional studies, the mean score of our 39 studies was seven (S1 Table). Over half of the studies (22/39, 56%) were considered good quality, as defined by a quality score of seven or higher.[13]

Pooled CHC treatment rates and by patient-level characteristics across studies

The overall pooled treatment rate was 25.5% (CI: 21.1–30.5%) and there was significant heterogeneity ($I^2 = 99.8, p < 0.001$) (Fig 2). On a sub-analysis of eight studies with available data, HCV genotype 1 were less likely to be treated than non-HCV genotype 1 patients (OR = 0.7, CI: 0.63–0.78, $p < 0.001$) (S2 Table). There was no significant difference in treatment rates for patients with advanced fibrosis vs. without fibrosis (OR = 1.27, $p = 0.39$) or males vs. females (OR = 0.88, $p = 0.14$).

Treatment rates by region

By region, studies from Europe had the highest treatment rate (34%, 95% CI: 25.2–43.9%) compared to the Asia/Pacific region (28.3%, 95% CI: 11.8–53.8%) and North America (18.7%, 95% CI: 14.7–23.5%; $p = 0.008$) (Fig 3). In this meta-analysis Vigani et al. was excluded as it was the only study from South America.[43] When comparing separate regions, only the difference between Europe versus North America was statistically significant ($p = 0.002$). There were similar pooled treatment rates for studies from single-payer reimbursement systems (24%) as compared to multi-payer ones (19%, $p = 0.53$, data described in text only).

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Treatment rates by practice setting

Treatment rates were significantly higher in the 19 tertiary referral-based studies compared to those from 17 population-based studies (31.7% of referral vs. 17.7% of population-based studies, $p = 0.003$).

Treatment rates by data collection methods

Treatment rates were highest when studies collected treatment data by medical chart review (29.8%) and patient questionnaire (30.3%) as done in many studies from referral centers, as compared to electronic query and extraction of population-based administrative databases (11.1%, $p < 0.001$).

Treatment rates by therapy type

Studies that examined only CHC patients treated with triple therapies including boceprevir or telaprevir did not report higher treatment rates than those that reported treatment rates with dual therapies (32% for triple therapy vs. 25.2% for dual therapy studies, $p = 0.61$).
### Table 1. Characteristics of included studies.

| First Author, Year | Country      | Study setting         | Inclusion years | Number of patients | Therapy examined        | HCV treatment data collection |
|-------------------|--------------|-----------------------|-----------------|--------------------|------------------------|-------------------------------|
| Grebely, 2011     | Australia    | Population based*     | 2008            | 634                | PEG-IFN† + RBV†         | Patient questionnaire         |
| Stooee, 2005      | Australia    | Population based      | 2000–2002       | 659                | IFN§ or PEG-IFN + RBV   | Patient questionnaire         |
| Delwaide, 2005    | Belgium      | Tertiary referral     | 1996–2003       | 299                | IFN or PEG-IFN + RBV    | Chart review                  |
| Vigani, 2008      | Brazil       | Tertiary referral     | 2003–2006       | 275                | PEG-IFN + RBV           | Chart review                  |
| Moirand, 2007     | Canada       | Tertiary referral     | 2001–2002       | 635                | IFN or PEG-IFN + RBV    | Chart review                  |
| Yau, 2015         | Canada       | Tertiary referral     | 2008–2013       | 164                | PEG-IFN + RBV +/- BOC   | Chart review                  |
| Yan, 2010         | China        | Tertiary referral     | 2000–2009       | 303                | IFN or PEG-IFN + RBV    | Chart review                  |
| Feillant, 2016    | France       | Tertiary referral     | 2013            | 255                | PEG-IFN + RBV           | Chart review                  |
| Kutala, 2015      | France       | Tertiary referral     | 2000–2010       | 685                | IFN or PEG-IFN + RBV    | Chart review                  |
| Kittner, 2014     | Germany      | Tertiary referral     | 2011–2012       | 307                | PEG-IFN + RBV + BOC or TVL | Chart review                  |
| Gupta, 2015       | India        | Tertiary referral     | 2008–2014       | 530                | PEG-IFN + RBV           | Chart review                  |
| Stroffolini, 2010 | Italy        | Tertiary referral     | 2009            | 534                | PEG-IFN + RBV           | Chart review                  |
| Vukotic, 2015     | Italy        | Population based      | 2009–2010       | 1118               | PEG-IFN + RBV           | Chart review                  |
| Mizui, 2007       | Japan        | Population based      | 1991–2001       | 1019               | IFN or PEG-IFN + RBV    | Chart review                  |
| Lee, 2016         | Korea        | Tertiary referral     | 2007–2012       | 759                | PEG-IFN + RBV           | Chart review                  |
| Toresen, 2014     | Norway       | Tertiary referral     | 2007–2010       | 233                | PEG-IFN + RBV           | Chart review                  |
| Crespo, 2015      | Spain        | Mixed primary care, tertiary referral | 2012 | 769 | PEG-IFN + RBV | Chart review |
| Hsu, 2015         | Taiwan       | Population based      | 1997–2011       | 194506             | IFN or PEG-IFN + RBV    | Electronic query              |
| Yu (community), 2015 | Taiwan   | Community based       | 2012–2013       | 586                | PEG-IFN + RBV           | Patient questionnaire         |
| Yu (specialist), 2015 | Taiwan | Tertiary referral     | 2012–2013       | 3045               | PEG-IFN + RBV           | Patient questionnaire         |
| Howes, 2016       | United Kingdoms | Population based | 2010–2013       | 197                | PEG-IFN + RBV           | Chart review                  |
| Mcdonald, 2014    | United Kingdoms | Population based | 1996–2009       | 5736               | IFN or PEG-IFN + RBV    | Chart review                  |
| Tait, 2010        | United Kingdoms | Population based | 1994–2008       | 1012               | IFN or PEG-IFN + RBV    | Chart review                  |
| Chen, 2013        | United States | Tertiary referral     | 2011–2012       | 487                | PEG-IFN + RBV + BOC or TVL | Chart review |
| Chirikov, 2015    | United States | Population based      | 2006–2008       | 1936               | IFN or PEG-IFN + RBV    | Electronic query              |
| Clark, 2012       | United States | Tertiary referral     | Not available   | 212                | PEG-IFN + RBV           | Chart review                  |
| Cozen, 2013       | United States | Tertiary referral     | 1992–2007       | 358                | IFN or PEG-IFN + RBV    | Chart review                  |
| Gundlapalli, 2015 | United States | Population based      | 2004–2009       | 101,444            | PEG-IFN + RBV           | Electronic query              |
| Livingston, 2012  | United States | Tertiary referral     | 2003–2007       | 240                | PEG-IFN + RBV           | Chart review                  |
| Markowitz, 2005   | United States | Population based      | 1996–2015       | 5135               | IFN or PEG-IFN + RBV    | Electronic query              |
| Moorman, 2013     | United States | Population based      | 2006–2008       | 8810               | PEG-IFN + RBV           | Chart review                  |
| Morrill, 2005     | United States | Community based       | 2001–2004       | 208                | IFN or PEG-IFN + RBV    | Chart review                  |
| Narasimhan, 2006  | United States | Tertiary referral     | 1998–2002       | 433                | IFN or PEG-IFN + RBV    | Chart review                  |
| Nguyen, 2014      | United States | Tertiary referral     | 1999–2014       | 9330               | Dual, triple, and DAA** based therapies | Chart review |
| Nyberg, 2014      | United States | Population based      | 2002–2012       | 51984              | PEG-IFN + RBV           | Electronic query              |
| Schaeffer, 2015   | United States | Tertiary referral     | 2006–2011       | 129                | PEG-IFN + RBV           | Chart review                  |
| Shatin, 2004      | United States | Population based      | 1997–1999       | 3259               | IFN + RBV               | Electronic query              |
Table 2 shows the meta-regression of five study-level factors (practice setting, region, quality assessment score, therapy type, and type of data collection for CHC treatment) testing for sources of heterogeneity of HCV treatment rates.

On meta-regression model practice setting (tertiary vs. population-based, \( p = 0.04 \)), region (Europe vs. North America \( p = 0.004 \)), and treatment data collection type (chart review vs. electronic query, \( p = 0.025 \)) remained significant predictors of heterogeneity.

Treatment eligibility rates

Analysis of twenty-one studies with available data showed a pooled eligibility rate of 52.5\% (CI: 45.9–59\%), and 60\% (CI: 49.2–69.9\%) of eligible patients were treated. There was no statistically significant difference in eligibility rates by region (64.5\% for Asia/Pacific region, 54.6\% for Europe, and 47\% for North America, \( p = 0.48 \)) (Fig 4). On sub-analysis of treatment rates among eligible patients by region, studies from Europe had higher treatment rates (76.8\%), while studies from the Asia/Pacific (53.2\%), and North America had lower rates (42.2\%, \( p \) for overall model = 0.01) (S1 Fig).

Reasons for treatment ineligibility and treatment refusal

Loss to follow up or lack of referral to HCV specialists was the most common reason for no treatment (14.6\%, CI: 5.5–33.6\%) (Table 3). Other reasons include normal liver tests or lack of significant fibrosis (8.6\%, CI: 4.1–17.2\%), medical contraindications (11.4\%, CI: 6–20.7\%), psychiatric contraindications (3.6\%, CI: 2.5–5.3\%), and active substance abuse (2.8\%, CI: 1.2–6.4\%). The most common reasons for treatment refusal by eligible patients was concern for treatment side effects (16.2\%, CI: 13.3–19.5\%), cost or insurance issues (13.8\%, CI: 6.4–27.2\%), and waiting for better treatment (12.2\%, CI: 8.2–17.6\%) (Table 4).

Discussion

In this systematic review, we found that only one-quarter (25.5\%) of CHC patients received antiviral therapy. Fifty-two percent of patients were eligible for treatment and only 60\% of these eligible patients received antiviral therapy. In addition, for the 47\% of patients who were not eligible for treatment, we found the most common reasons for treatment ineligibility were...
loss to follow up or lack of referral to HCV specialists. This overall low treatment rate is well below the WHO’s goal treatment rate of 80% and demonstrates the importance of proper referral and follow up for CHC patients to receive treatment. [4, 6, 25, 49, 50] While many of the reasons for treatment ineligibility were specific to PEG-IFN + RBV, this issue in linkage-to-care is multifactorial and related in part to the asymptomatic nature of CHC but also to a
We also found no statistical difference in treatment rates with PEG-IFN + RBV combined with first generation DAAbs boceprevir or telaprevir (32%) compared to those examining PEG-IFN + RBV alone (25%, \( p = 0.61 \)). Despite the improved sustained viral response rates, the similar treatment rates with triple therapy were likely reflective of the significant barriers inherent to PEG-IFN + RBV. The use of the well tolerated newer all-oral DAA therapies will likely diminish the barriers related to treatment eligibility and provider/patient acceptance, especially those related to medical and/or psychiatric contraindications.
Table 2. Meta-regression for predictors for antiviral therapy for chronic hepatitis C.

| Predictors for treatment                      | Univariate analysis | Multivariate analysis |
|----------------------------------------------|---------------------|-----------------------|
|                                              | Coefficient (95% CI)| P value               | Coefficient (95% CI) | P value |
| Tertiary center vs. population based         | 0.77 (0.33–1.21)    | < 0.001               | 0.41 (0.02–0.8)      | 0.04    |
| Region                                       |                     |                       |                       |         |
| North America                               | Referent            | -                     | -                     | -       |
| Asia/Pacific                                | 0.53 (-0.12–1.2)    | 0.11                  | 0.28 (-0.17–0.72)    | 0.22    |
| Europe                                      | 0.8 (0.18–1.43)     | 0.011                 | 0.61 (0.2–1)         | 0.004   |
| Quality assessment score of ≥7 vs. <7       | -0.22 (-0.7–0.24)   | 0.34                  |                       |         |
| Triple vs. dual interferon-based therapy     | 0.33 (-0.62–0.13)   | 0.69                  | -                     | -       |
| Ascertainment of chronic hepatitis C diagnosis |                     |                       |                       |         |
| Chart review                                 | Referent            | -                     | Referent              | -       |
| Electronic query                            | 0.03 (-0.4–0.46)    | <0.001                | -0.6 (-1.1–0.07)     | 0.025   |
| Patient questionnaire                        | 0.03 (-0.4–0.46)    | 0.9                   | 0.18 (-0.4–0.78)     | 0.57    |

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Fig 4. Pooled treatment eligibility rates for patients with chronic hepatitis C, by region.

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Another significant barrier to treatment for eligible patients in this study was cost and insurance related. An estimated 14% of treatment-eligible patients declined therapy because of cost or were denied insurance coverage. This is an important point as the evolution of the newer and more expensive interferon free DAA’s continues and more drugs enter the market. With the current costs of all-oral DAAs well exceeding that of PEG-IFN-based therapies, the non-treatment rate due to insurance approval and cost may actually rise compared to that from the PEG-IFN era even in high income countries.[52, 53]

Furthermore, our pooled treatment rates, while low, are still likely an underestimation of the overall CHC treatment rate considering that many CHC patients remain undiagnosed. As we now have highly effective DAAs, it becomes even more important to identify patients with CHC early in their disease course and also issues in our linkage to specialist care or primary providers comfortable in the management of these patients.

On our meta-analysis of treatment rates by region, Europe had the highest treatment rate (34%), followed by the Asia/Pacific region (28.3%), and finally North America (18.7%). Some of these differences may be attributable to study methodologies which were also important predictors of treatment rate heterogeneity. North America had the highest proportions of population-based studies and also studies that queried HCV treatment electronically both found to be predictors of treatment rate heterogeneity. Population-based studies may have lower treatment rates due to the inclusion of all-comers with CHC: patients evaluated in community clinics and emergency rooms who are not referred to specialists.

However, on our final meta-regression model adjusting for these study methodologies, we found that region (Europe vs. North America) remained a significant source of heterogeneity ($p = 0.004$). In addition, on a separate analysis, treatment eligibility rates were not significantly different among the 3 geographic regions (47% for North America vs. 65% for Asia/Pacific and 55% for Europe, overall $p = 0.48$). This suggests that some of the barriers are specific to North America and include insurance reimbursement criteria, and patient-physician preferences.

Small, but potentially significant differences between international guidelines for the use of PEG-IFN and RBV based therapies may also have affected treatment rates. While all three

### Table 3. Pooled treatment ineligibility rates for patients with chronic hepatitis C, by reasons for ineligibility.

| Treatment ineligibility criteria                              | Treatment ineligibility rate (95% CI) | No. of studies included |
|---------------------------------------------------------------|--------------------------------------|------------------------|
| Normal liver tests or lack of fibrosis                        | 8.6% (4.1–17.2%)                     | 9                      |
| Medical comorbidities (includes decompensated liver disease)  | 11.4% (6–20.7%)                      | 16                     |
| Psychiatric comorbidities                                     | 3.6% (2.5–5.3%)                      | 13                     |
| Substance abuse                                               | 2.8% (1.2–6.4%)                      | 9                      |
| Loss to follow up                                             | 14.6% (5.5–33.6%)                    | 13                     |

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### Table 4. Pooled patient refusal rates in treatment-eligible patients with chronic hepatitis C, by reasons for refusal.

| Reason for patient refusal          | Patient refusal rates (95% CI) | No. of studies included |
|------------------------------------|-------------------------------|------------------------|
| Side effects                        | 16.2% (13.3–19.5%)            | 5                      |
| Cost or insurance issues            | 13.8% (6.4–27.2%)             | 6                      |
| Waiting for better treatment        | 12.2% (8.2–17.6%)             | 5                      |

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major international guidelines (EASL, AASLD, and APASL) recommend against treating
decompensated cirrhotics with interferon-based therapies, the guidelines from AASLD further
specify acceptable laboratory parameters: total serum bilirubin < 1.5 g/dL, International Nor-
malized Ratio < 1.5, platelet count < 75,000, and serum albumin > 3.4). In the guidelines
published by EASL and APASL many of these laboratory criteria are absent or considered relative
contraindications to treatment. The AASLD guidelines also strongly recommend a
baseline liver biopsy to assess baseline liver inflammation and fibrosis prior to initiating treat-
ment. In contrast the guidelines from APASL and EASL, published in subsequent years,
cluded other non-invasive methods including transient elastography and blood marker pan-
els as potential substitutes for liver biopsy.

Based on this systematic review, there are no studies that directly examined treatment rates
and barriers to care with the newer DAA therapies and this is an area that will require further
research. One paper, presented by Moon et al., reported a significant increase in treatment pre-
scriptions in 2015 compared to the prior PEG-IFN years. The investigators attributed this
large increase to the introduction of 2nd generation DAA therapies into the CHC treatment
armament. This is likely a result of the lower treatment threshold of DAA-based therapies:
the revised recommendations for DAA therapy from EASL, AASLD, and APASL have recom-

Our study does have a few limitations. Several of the sub-analyses included fewer studies
so the results should be interpreted with caution. There was also high heterogeneity among
our studies, which is due to the variety of patient populations, regional practices, time
period of the study, and sample sizes. To address this, we analyzed by subgroups and also
attempted to control for confounders through the use of a multivariable meta-regression
model. Finally, our results may not be generalizable to certain regions such as Africa and
the Middle East due to the lack or relative underrepresentation of studies from these
regions. This is concerning because these regions have the largest HCV disease burden in
the world. A recent meta-analysis examining operational interventions to enhance
chronic viral hepatitis testing and linkage to care found that several simple, inexpensive
operational interventions can improve engagement and retention in the cascade of care of
patients with chronic viral hepatitis, but further operational research is needed in these
regions.

Our study is the first systematic review to examine HCV treatment rates for all geographic
regions with available data. We found that treatment rates were suboptimal with only 25.5%
overall, and only 60% of CHC patients worldwide, who met treatment criteria and did not
have any medical or psychiatric contraindication, received treatment before the availability of
IFN-free regimens. While these low treatment rates are partly attributable to PEG-IFN and
ribavirin, further research efforts are needed to identify and quantify other treatment barriers
that may persist in this IFN-free DAA era and especially those related to cost, insurance autho-
rization, and lack of linkage to care with providers familiar with the management of patients
with CHC.

Supporting information

S1 Table. Newcastle-Ottawa quality assessment scores for individual studies.

S2 Table. Predictors for treatment by patient-level factors across studies.
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Writing – review & editing: Philip Vutien, Michelle Jin, Michael H. Le, Pauline Nguyen, Sam Trinh, Jee-Fu Huang, Ming-Lung Yu, Wan-Long Chuang, Mindie H. Nguyen.

References

1. Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet. 2016;388(10049):1081–8. https://doi.org/10.1016/S0140-6736(16)30579-7 PMID: 27394647.

2. Organization WH. Combating hepatitis B and C to reach elimination by 2030.

3. Gundlapalli AV, Nelson RE, Haroldsen C, Carter ME, LaFleur J, Shoukry NH. Correlates of initiation of treatment for chronic hepatitis C infection in United States Veterans, 2004–2009. PLoS ONE. 2015;10(7). https://doi.org/10.1371/journal.pone.0132056 PMID: 26167690

4. Younossi ZM, Stepanova M, Afendy M, Lam BP, Mishra A. Knowledge about infection is the only predictor of treatment in patients with chronic hepatitis C. J Viral Hepat. 2013; 20(8):550–5. Epub 2013/07/03. https://doi.org/10.1111/jvh.12080 PMID: 23808993.

5. Butt AA, Justice AC, Skanderson M, Rigsby MO, Good CB, Kwoh CK. Rate and predictors of treatment prescription for hepatitis C. Gut. 2007; 56(3):385–9. Epub 2006/09/29. https://doi.org/10.1136/gut.2006.099150 PMID: 17005764.
6. Morrill JA, Shrestha M, Grant RW. Barriers to the treatment of hepatitis C. Patient, provider, and system factors. J Gen Intern Med. 2005; 20(8):754–8. Epub 2005/07/30. https://doi.org/10.1111/j.1525-1497.2005.0161.x PMID: 16050887.

7. Vutien P, Hoang J, Brooks L Jr., Nguyen NH, Nguyen MH. Racial Disparities in Treatment Rates for Chronic Hepatitis C: Analysis of a Population-Based Cohort of 73,665 Patients in the United States. Medicine (Baltimore). 2016; 95(22):e3719. https://doi.org/10.1097/MD.0000000000003719 PMID: 27258498.

8. Gane EJ, Stedman CA, Hyland RD, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013; 368(1):34–44. https://doi.org/10.1056/NEJMoa1208953 PMID: 23261974.

9. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanine T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014; 370(3):211–21. https://doi.org/10.1056/NEJMoa1306218 PMID: 24428467.

10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of clinical epidemiology. 2009; 62(10):1006–12. https://doi.org/10.1016/j.jclinepi.2009.06.005 PMID: 19631508.

11. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996; 24(2):289–93. https://doi.org/10.1002/hep.510240201 PMID: 8690394.

12. Wells GA, Shea B, O’Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2009. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

13. McPheeters ML, Kripalani S, Peterson NB, Idowu RT, Jerome RN, Potter SA, et al. Closing the quality gap: revisiting the state of the science (vol. 3: quality improvement interventions to address health disparities). Evidence report/technology assessment. 2012; (208.3):1–475. PMID: 24422952.

14. Chen EY, Sclair SN, Czul F, Apica B, Dubin P, Martin P, et al. A small percentage of patients with hepatitis C receive triple therapy with boceprevir or telaprevir. Clin Gastroenterol Hepatol. 2013; 11(8):1014–20 e1–2. https://doi.org/10.1016/j.cgh.2013.03.032 PMID: 23602817.

15. Chirikov VV, Shaya FT, Mullins CD, Dosreis S, Onukwugha E, Howell CD. Determinants of quality of care and treatment initiation in Medicare disabled patients with chronic hepatitis C. Expert Rev Gastroenterol Hepatol. 2015; 9(11):1447–62. https://doi.org/10.1586/17474124.2015.1095087 PMID: 26524244.

16. Clark BT, Garcia-Tsao G, Fraenkel L. Patterns and predictors of treatment initiation and completion in patients with chronic hepatitis C virus infection. Patient Preference Adherence. 2012; 6:285–95. https://doi.org/10.2147/PPA.S30111 PMID: 22536063.

17. Cozen ML, Ryan JC, Shen H, Lerrigo R, Yee RM, Sheen E, et al. Nonresponse to Interferon-α Based Treatment for Chronic Hepatitis C Infection Is Associated with Increased Hazard of Cirrhosis. PLoS ONE. 2013; 8(4). https://doi.org/10.1371/journal.pone.0061568 PMID: 23637856.

18. Crespo J, Cabezás J, Sacristán B, Olcoz JL, Perez R, De la Vega J, et al. Barriers to HCV treatment in the era of triple therapy: a prospective multi-centred study in clinical practice. Liver Int. 2015; 35(2):401–8. Epub 2014/03/22. https://doi.org/10.1111/liv.12536 PMID: 24650000.

19. Delwaide J, El Saouda R, Gerard C, Belaiche J. Hepatitis C infection: eligibility for antiviral therapies. Eur J Gastroenterol Hepatol. 2005; 17(11):1185–9. Epub 2005/10/11. PMID: 16215430.

20. Feillard M, Jezequel C, Lison H, Dulluc A, Tanne F, Le Gruyer A, et al. Chronic hepatitis C: treat or wait? A prospective study on reasons for treatment or nontreatment in the era of first-generation protease inhibitors. Eur J Gastroenterol Hepatol. 2016; 28(2):164–72. https://doi.org/10.1097/MEG.0000000000000506 PMID: 26560750.

21. Grebely J, Bryant J, Hull P, Hopwood M, Lavis Y, Dore GJ, et al. Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia. J Viral Hepat. 2011; 18(4):e104–16. Epub 2010/08/16. https://doi.org/10.1111/j.1365-2893.2010.01370.x PMID: 20840350.

22. Gupta V, Kumar A, Sharma P, Bansal N, Singla V, Arora A. Most Patients of Hepatitis C Virus Infection in India Present Late for Interferon-Based Antiviral Treatment: An Epidemiological Study of 777 Patients from a North Indian Tertiary Care Center. J Clin Exp Hepatol. 2015; 5(2):134–41. https://doi.org/10.1016/j.jceh.2015.05.001 PMID: 26155041.

23. Howes N, Lattimore S, Irving WL, Thomson BJ. Clinical Care Pathways for Patients With Hepatitis C: Reducing Critical Barriers to Effective Treatment. Open forum infectious diseases. 2016; 3(1):ofv218. https://doi.org/10.1093/ofid/ofv218 PMID: 26900576.
24. Hsu YC, Ho HJ, Huang YT, Wang HH, Wu MS, Lin JT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. Gut. 2015; 64(3):495–503. https://doi.org/10.1136/gutjnl-2014-308163 PMID: 25398770.

25. Kittner JM, Weiss NM, Wiltink J, Schattenberg JM, Grambihler A, Thieringer F, et al. Defer or treat? Reasons for treatment decisions in patients with chronic hepatitis C genotype 1 in the early era of directly acting antiviral agents. Dig Liver Dis. 2014; 46(1):67–71. Epub 2013/10/16. https://doi.org/10.1016/j.dld.2013.08.139 PMID: 24125691.

26. Kutala BK, Guedj J, Asselah T, Boyer N, Mouri F, Martinot-Peignoux M, et al. Impact of treatment against hepatitis C virus on overall survival of naive patients with advanced liver disease. Antimicrob Agents Chemother. 2015; 59(2):803–10. Epub 2014/11/19. https://doi.org/10.1128/AAC.04027-14 PMID: 25403673.

27. Lee SS, Jeong SH, Jang ES, Kim YS, Lee YJ, Jung EU, et al. Treatment rate and factors related to interferon-based treatment initiation for chronic hepatitis C in South Korea. J MED VIROL. 2016; 88(2):275–81. https://doi.org/10.1002/jmv.24335 PMID: 26211752.

28. Livingston SE, Townshend-Bulson LJ, Bruden DL, McMahon BJ, Homan CE, Gove JE, et al. Treatment eligibility in Alaska Native and American Indian persons with hepatitis C virus infection. Int J Circumpolar Health. 2012; 71(1). https://doi.org/10.3402/ijch.v71i0.18445 PMID: 22564468.

29. Markowitz JS, Gutterman EM, Hodes D, Klasakala W. Factors associated with the initiation of alpha-interferon treatment in Medicaid patients diagnosed with hepatitis C. J Viral Hepat. 2005; 12(2):176–85. Epub 2005/02/22. https://doi.org/10.1111/j.1365-2893.2005.00607.x PMID: 15720533.

30. McDonald SA, Hutchinson SJ, Innes HA, Allen S, Bramley P, Bhattacharyya D, et al. Attendance at specialist hepatitis clinics and initiation of antiviral treatment among persons chronically infected with hepatitis C: examining the early impact of Scotland’s Hepatitis C Action Plan. J Viral Hepat. 2014; 21(5):366–76. Epub 2014/04/11. https://doi.org/10.1111/jvhe.12163 PMID: 24716839.

31. Mizui M, Tanaka J, Katayama K, Nakanishi T, Obayashi M, Aimitsu S, et al. Liver disease in hepatitis C virus carriers identified at blood donation and their outcomes with or without interferon treatment: Study on 1019 carriers followed for 5–10 years. HEPATOL RES. 2007; 37(12):994–1001. https://doi.org/10.10111/j.17-02-034X.2007.00157.x PMID: 17627620.

32. Moirand R, Bilodeau M, Brissette S, Bruneau J. Determinants of antiviral treatment initiation in a hepatitis C-infected population benefiting from universal health care coverage. Can J Gastroenterol. 2007; 21(6):355–61. Epub 2007/06/16. PMID: 17571168.

33. Mooman AC, Gordon SC, Rupp LB, Spradling PR, Teshale EH, Lu M, et al. Baseline characteristics and mortality among people in care for chronic viral hepatitis: the chronic hepatitis cohort study. Clin Infect Dis. 2013; 56(1):40–50. https://doi.org/10.1093/cid/cis815 PMID: 22990852.

34. Narasimhan G, Sargios TN, Kalakuntla R, Homel P, Clain DJ, Theise ND, et al. Treatment rates in patients with chronic hepatitis C after liver biopsy. J Viral Hepat. 2006; 13(11):783–6. Epub 2006/10/21. https://doi.org/10.1111/j.1365-2893.2006.00763.x PMID: 17052279.

35. Nguyen PT, Nguyen NH, Hoang JK, Zhao C, Le AK, Chang CY, et al. Low HCV treatment for chronic hepatitis C (CHC) patients in pre-protease inhibitor (PI) and post-PI/pre-direct acting antiviral (DAA) eras compared to post-DAA era, especially in African Americans: analysis of a large real-world cohort of 7105 patients. Hepatology. 2015; 62(S1):1094A–A. Epub 2015/10/01

36. Nyberg LM, Chiang KM, Li Z, Nyberg AH, Younossi ZM, Cheetham TC. Comorbid conditions associated With decision-making regarding treating or not treating chronic hepatitis C in U.S. health maintenance organization. Gastroenterology. 2014; 146(5):S973–S4.

37. Schaeffer S, Khalili M. Reasons for HCV non-Treatment in underserved African Americans: Implications for treatment with new therapeutics. Ann Hepatol. 2015; 14(2):234–42. PMID: 25671833.

38. Shatin D, Schech SD, Patel K, McHutchison JG. Population-based hepatitis C surveillance and treatment in a national managed care organization. Am J Manag Care. 2004; 10(4):250–6. Epub 2004/05/06. PMID: 15124501.

39. Stoove MA, Gifford SM, Dore GJ. The impact of injecting drug use status on hepatitis C-related referral and treatment. Drug Alcohol Depend. 2005; 77(1):81–6. Epub 2004/12/21. https://doi.org/10.1016/j.drugalcdep.2004.07.002 PMID: 15607844.

40. Stroffolini T, Spadaro A, Guadagnino V, Cosentino S, Fatuzzo F, Gaidieri A, et al. Current practice of hepatitis C treatment in Southern Italy. Dig Liver Dis. 2010; 42(11):822–5. Epub 2010/05/04. https://doi.org/10.1016/j.dld.2010.03.020 PMID: 20435532.

41. Tait JM, McIntyre PG, McLeod S, Nathwani D, Dillon JF. The impact of a managed care network on attendance, follow-up and treatment at a hepatitis C specialist centre. J Viral Hepat. 2010; 17(10):698–704. Epub 2009/12/17. https://doi.org/10.1111/j.1365-2893.2009.01227.x PMID: 20002561.

42. Toresen KH, Salte IM, Skrede S, Nilsen RM, Leiva RA. Clinical outcomes in a cohort of anti-hepatitis C virus-positive patients with significant barriers to treatment referred to a Norwegian outpatient clinic.
Systematic review of hepatitis C treatment rates and barriers worldwide

Scand J Gastroenterol. 2014; 49(4):465–72. Epub 2014/01/30. https://doi.org/10.3109/00365521.2013.863965 PMID: 24472091.

43. Vigani AG, Pavan MH, Tozzo R, Gonçalves ESL, Feltrin A, Fais VC, et al. Comparative study of patients with chronic hepatitis C virus infection due to genotypes 1 and 3 referred for treatment in southeast Brazil. BMC Infect Dis. 2008; 8. https://doi.org/10.1186/1471-2334-8-164 PMID: 19055835.

44. Vukotic R, Gamal N, Andreone P. Prospective, observational real-life study on eligibility for and outcomes of antiviral treatment with peginterferon alpha plus ribavirin in chronic hepatitis C. Dig Liver Dis. 2015; 47(2):151–6. Epub 2014/12/09. https://doi.org/10.1016/j.dld.2014.11.002 PMID: 25483909.

45. Yan KK, Wong GL, Wong VW, Chan HL. Rate and factors affecting treatment uptake of patients with chronic hepatitis C in a tertiary referral hospital. Dig Dis Sci. 2010; 55(12):3541–7. Epub 2010/10/12. https://doi.org/10.1007/s10620-010-1412-1 PMID: 20927593.

46. You HL, Lee T, Ramji A, Ko HH. Rate, delay and predictors of hepatitis C treatment in British Columbia. Can J Gastroenterol Hepatol. 2015. Epub 2015/04/16. PMID: 25874651.

47. Yawn BP, Rocca LG, Wollan PC. 10-year trends in the diagnosis and treatment of hepatitis C and concomitant mental health disorders: 1995 to 2005. Prim Care Companion J Clin Psychiatry. 2008; 10(5):349–54. Epub 2009/01/23. PMID: 19158972.

48. Yau HL,Lee T, Ramji A, Ko HH. Rate, delay and predictors of hepatitis C treatment in British Columbia. Can J Gastroenterol Hepatol. 2015. Epub 2015/04/16. PMID: 25874651.

49. Kanwal F, Hoang T, Spiegel BM, Eisen S, Dominitz JA, Gifford A, et al. Predictors of treatment in patients with chronic hepatitis C infection—role of patient versus nonpatient factors. Hepatology. 2007; 46(6):1741–9. Epub 2007/11/30. https://doi.org/10.1002/hep.21927 PMID: 18046707.

50. Khokhar OS, Lewis JH. Reasons why patients infected with chronic hepatitis C virus choose to defer treatment: do they alter their decision with time? Dig Dis Sci. 2007; 52(5):1168–76. Epub 2007/03/16. https://doi.org/10.1007/s10620-006-9579-1 PMID: 17357838.

51. Kramer JR, Kanwal F, Richardson P, Giordano TP, Petersen LA, El-Serag HB. Importance of patient, provider, and facility predictors of hepatitis C virus treatment in veterans: a national study. Am J Gastroenterol. 2011; 106(3):483–91. Epub 2010/11/11. https://doi.org/10.1038/ajg.2010.430 PMID: 21063393.

52. Lo Re V 3rd, Gowda C, Urick PN, Halladay JT, Binkley A, Carbonari DM, et al. Disparities in Absolute Denial of Modern Hepatitis C Therapy by Type of Insurance. Clin Gastroenterol Hepatol. 2016; 14(7):1035–43. https://doi.org/10.1016/j.cgh.2016.03.040 PMID: 27062903.

53. Rein DB, Wittenborn JS, Smith BD, Liffmann DK, Ward JW. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus. Clin Infect Dis. 2015; 61(2):157–68. https://doi.org/10.1093/cid/civ220 PMID: 25778747.

54. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009; 49(4):1335–74. https://doi.org/10.1002/hep.22759 PMID: 19330875.

55. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2011; 55(2):245–64. https://doi.org/10.1016/j.jhep.2011.02.023 PMID: 21371579.

56. Omata M, Kanda T, Yu ML, Yokosuka O, Lim SG, Jafri W, et al. APASL consensus statements and management algorithms for hepatitis C virus infection. Hepatol Int. 2012; 6(2):409–35. https://doi.org/10.1007/s12072-012-9342-y PMID: 26201405.

57. Moon AM, Green PK, Berry K, Ioannou GN. Transformation of hepatitis C antiviral treatment in a national healthcare system following the introduction of direct antiviral agents. Aliment Pharmacol Ther. 2017. https://doi.org/10.1111/apt.14021 PMID: 28271521.

58. European Association for the Study of the Liver. Electronic address eee. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2016. https://doi.org/10.1016/j.jhep.2016.09.001 PMID: 27667367.

59. Omata M, Kanda T, Wei L, Yu ML, Chuang WL, Ibrahim A, et al. APASL consensus statements and recommendation on treatment of hepatitis C. Hepatol Int. 2016; 10(5):702–26. https://doi.org/10.1007/s12072-016-9717-6 PMID: 27130427.

60. Panel AIHG. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015; 62(3):932–54. https://doi.org/10.1002/hep.27950 PMID: 26111063.
61. Thrift AP, El-Serag HB, Kanwal F. Global epidemiology and burden of HCV infection and HCV-related disease. Nat Rev Gastroenterol Hepatol. 2016. https://doi.org/10.1038/nrgastro.2016.176 PMID: 27924080.

62. Zhou K, Fitzpatrick T, Walsh N, Kim JY, Chou R, Lackey M, et al. Interventions to optimise the care continuum for chronic viral hepatitis: a systematic review and meta-analyses. Lancet Infect Dis. 2016. https://doi.org/10.1016/S1473-3099(16)30208-0 PMID: 27615026.