Interventions to optimize the chronic viral hepatitis care continuum: a systematic review and meta-analysis of interventions to improve hepatitis B and C testing, linkage to care, treatment uptake, adherence, and viral suppression or cure

Kali Zhou, MD[1*]; Thomas Fitzpatrick, BA[2*]; Nick Walsh, MD[3]; Ji Young Kim, BA[3]; Roger Chou, MD[4]; Mellanye Lackey, MSI[5]; Julia Scott, MD[3]; Ying-Ru Lo, MD[3]; and Joseph D. Tucker, MD[6,7+]

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[1] University of California, San Francisco, Department of Medicine, Division of Gastroenterology, San Francisco, California, USA

[2] University of Washington School of Medicine, Seattle, Washington, USA

[3] World Health Organization, Regional Office for the Western Pacific, Manila, Philippines

[4] Department of Medical Informatics & Clinical Epidemiology, Oregon Health & Science University, Portland, Oregon, USA

[5] Spencer S. Eccles Health Sciences Library, University of Utah, Salt Lake City, Utah, USA

[6] UNC-Project China, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[7] International Diagnostics Centre, London School of Hygiene and Tropical Medicine, London, UK

*These authors contributed equally to this work.

[+]Corresponding author: Dr. Joseph D. Tucker

Address: 2 Lujing Road, Guangdong STD Control Center, Guangzhou, 510075

Phone number: (86) 13560294997

Email: jdtucker@med.unc.edu

Abstract

Background

Recent advances in therapy for hepatitis B virus (HBV) and hepatitis C virus (HCV) have ushered in a new era in chronic hepatitis treatment. Maximizing efficacy of these medicines will require engaging and retaining individuals in care. We carried out a systematic review of operational interventions to enhance chronic viral hepatitis (HBV, HCV) testing, linkage to care, treatment uptake, adherence, and viral suppression or cure.

Methods

We searched seven databases for randomized controlled trials (RCTs) or controlled non-randomized studies (NRSs) examining operational interventions along the chronic viral hepatitis care continuum. Data from similar interventions were pooled and quality of evidence was assessed using the GRADE approach.

Findings

We included 56 studies that reported outcomes along the care continuum (41 for HCV and 18 for HBV). All studies except one were from high-income countries. Lay health worker HBV test promotion interventions increased HBV testing rates (RR = 2.68 [1.82 – 3.93]). Clinician reminders to prompt HCV testing during clinical visits increased HCV testing rates (RR = 3.70 [1.81 – 7.57]). Nurse-led educational interventions improved HCV treatment completion (RR = 1.14 [1.05 – 1.23]) and cure (OR = 1.93 [1.44 – 2.59]). Coordinated mental health, substance use, and hepatitis treatment services increased HCV treatment uptake (OR = 3.03 [1.24 – 7.37]), adherence (RR = 1.22 [1.05 – 1.41]), and cure (RR = 1.21 [1.07 – 1.38]) compared to usual care.

Interpretation

Several simple, inexpensive operational interventions can substantially improve engagement and retention along the chronic viral hepatitis care continuum. Further operational research to inform scale up of hepatitis services is needed in low- and middle-income countries.

Introduction

Viral hepatitis is the seventh leading cause of mortality worldwide with an estimated 1.45 million deaths each year.[1] Over 90% of these deaths are attributable to chronic infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV).[1] Effective antiviral treatment of chronic HBV and HCV infection can halt or even reverse progression of liver disease[2,3] and reduce hepatitis related mortality.[4] Current therapies for HBV and HCV are transforming clinical management of both diseases. The development of nucleos(t)ide analogues with low rates of resistance has provided improved treatment options for patients with HBV.[5] The landscape of HCV has been altered by the introduction of short regimen all-oral direct acting agents.[6] The full clinical impact of these therapies will be contingent on first engaging and then retaining individuals across a care continuum (Figure 1).

Operational interventions are public health interventions to expedite movement across a continuum of care. Identifying which interventions can maximize engagement and retention along the chronic viral hepatitis care continuum is essential for several reasons. First, global data suggest most people with HBV[7,8] or HCV[9-11] do not know their serostatus, especially those from vulnerable groups and those living in low- and middle-income countries. Second, currently available population-level data indicate there is low test uptake and substantial loss throughout both the HBV and HCV care continuums.[12,13] Third, the greatest burden of HBV and HCV is in low- and middle-income countries where health services are fragile and hepatology services are rudimentary.[14-16] Simple and inexpensive operational interventions can maximize the impact of limited health services in these low-resource settings and some have shown efficacy in HIV research.[17]

Although there are differences in the clinical management of HBV and HCV, we combined them for the purposes of this review because some interventions focus on both diseases and there are similar opportunities to improve service delivery. The WHO has proposed the goal of global elimination of viral hepatitis by 2030 with a 65% reduction in viral hepatitis related mortality.[18] These are ambitious targets. Operational interventions to optimize the delivery of hepatitis services are necessary in order to achieve this goal. The purpose of this review was to synthesize data on operational interventions for HBV and HCV testing, linkage to care, treatment uptake, adherence, and viral suppression or cure in adults.

Methods

Search strategy and selection criteria

This review was registered in PROSPERO (42014015094) and carried out according to PRISMA guidelines. Databases searched include PubMed/MEDLINE, EMBASE, WHO library, International Clinical Trials Registry, PsycInfo and CINAHL. Additionally, clinicaltrials.gov and conference archives for AIDS 2014 and IAS 2013 were searched to retrieve registered trials and accepted abstracts, respectively. The search was performed 09 March 2015 with a publication date limit of 31 December 2014. References of articles selected for inclusion were searched for additional citations. Search terms, with facets for HBV/HCV, interventions and adherence, are detailed in Supplementary Data 1. Only peer-reviewed randomized controlled trials (RCTs) or controlled non-randomized studies (NRSs) were included. We contacted authors directly regarding unclear study details.

Our search strategy can be found in Supplementary Data 2. Briefly, we included studies investigating operational interventions at any point in the chronic viral hepatitis care continuum for people living with diagnosed or undiagnosed chronic viral hepatitis (HBV or HCV). Only non-pharmaceutical intervention studies with primary or secondary outcomes of testing, linkage to care, treatment uptake, treatment adherence, treatment completion, treatment outcome, or disease endpoints were included. Study designs were required to have a comparator or control. In NRSs, control groups could be generated through historical comparisons before and after implementation of an intervention, convenience sampling, or other non-randomized design. Exclusion criteria included dissertations, non-English language publications, studies enrolling only pediatric populations, and publications failing to report the outcome data necessary for extraction. Operational interventions to prevent new infections, including vaccination programs, were excluded because they were not considered part of the chronic viral hepatitis care continuum.

Data extraction and risk of bias assessment

Titles, abstracts, and full texts were sequentially screened for inclusion by two independent reviewers. Disagreements were resolved by a third reviewer. Data were also extracted by two independent reviewers, with differences reconciled by a third reviewer. The following variables were extracted: authors, journal of publication, publication year, study design, population, inclusion and exclusion criteria, participant characteristics, sample size, study setting, intervention and control description, duration of intervention, results, and conclusions. To

maximize comparability between studies, data were extracted and analyzed according to intention-to-treat when possible, even if individual authors reported results or conclusions based on per-protocol analyses. Participants lost to follow-up were assumed to have not achieved the outcome under investigation in our intention-to-treat analyses. If a single study included two intervention arms that were grossly similar, data from both arms were pooled and compared against the control arm.

Following data extraction, risk of bias was assessed for both RCTs and NRSs using the Cochrane Collaboration's risk of bias tool.[19] If a single study reported outcomes at multiple stages of the care cascade, risk of bias was assessed for each stage independently. Outcomes were evaluated along six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Reporting bias was assessed by comparing published outcomes to outcomes outlined in original study protocols, if original protocols were registered on Clinicaltrials.gov.

Data analysis and quality assessment

All included publications were assessed for comparability on the basis of intervention type, control condition, and outcome. Studies determined to be similar for intervention, control, and outcome were included in meta-analyses to determine pooled effect size. Pooled relative risks or odds ratios with confidence intervals and forest plots were generated using a random-effects model in Review Manager 5.3. The degree of heterogeneity between studies in a comparison was assessed by calculating I^2.

Meta-analyses that included both RCTs and NRSs were stratified by study design, and separate pooled effect sizes are available in Supplementary Data 3. Effect sizes reported in the results section only combined RCT and NRS results if the inclusion of NRSs did not meaningfully alter the estimate of an intervention's effect.

Whenever possible pooled results were reported as relative risk. When studies only reported odds ratios with confidence intervals, data were pooled using the generic inverse variance method, and a pooled odds ratio was reported. If a portion of the studies included in a comparison reported outcomes that had been adjusted using matching or statistical modeling (e.g. regression modeling), a sub-analysis was generated using only adjusted results. Funnel

plots were only used to screen for reporting bias if ten or more studies were included in a meta-analysis.

The quality of evidence was assessed according to the methodology described by the GRADE working group,[20] and a GRADE table was generated for each meta-analysis and sub-analysis. Where specific interventions were directed at specific populations we did not downgrade for indirectness as these were populations of interest. For imprecision, the pooled sample size for each meta-analysis was compared against the optimal information size (OIS), which was calculated using an alpha of 0.05 and power of 80%.

Results

A total of 7,583 unduplicated citations were identified, and 56 studies were included (Figure 2). Figure 2 shows 56 studies included in our overall qualitative synthesis, but only 33 studies were included in our quantitative synthesis because their interventions and outcomes were directly comparable to at least one other included study, allowing for a total of 14 meta-analyses. A summary of findings from all 14 meta-analyses is presented in Table 1. Figure 3 shows forest plots for the three meta-analyses we thought were of greatest importance. Other forest plots are in Supplementary Data 3.

The 56 studies included 47 published full-text manuscripts, five abstracts, and four clinical trials. Among all studies, 15 reported an outcome along the HBV care continuum, 38 reported an outcome along the HCV care continuum, and three studies reported outcomes involving both HCV and HBV. Details of all included studies for HBV testing, HCV testing, and HCV cure stages are reported in Tables 2, 3, and 4, respectively. Details of other stages are in Supplementary Data 4 and 5.

All stages of the HCV care continuum were represented by included studies. The HBV care continuum was less well studied, with no studies reporting outcomes related to HBV treatment uptake, adherence, or viral suppression. Among studies investigating HCV treatment uptake, adherence, and cure, only two interventions provided participants with DAA-based treatment regimens at some point during the study period.[21,22] The remaining studies exclusively provided interferon-based treatment regimens.

Fifty-five out of 56 studies were conducted in high-income countries, and one study was from a middle-income country (Turkey). Twenty-five studies (44.6%, 25/56) were RCTs, including eight cluster RCTs. The other 31 studies (55.4%, 31/56) were NRSs. Sample sizes ranged from 21 to 36,987.

All of the included studies were designed to investigate the impact of an intervention on progression through the viral hepatitis care continuum, and the results presented here are not a secondary analysis. One study included a cost-effectiveness evaluation of the intervention.[23] Risk of bias tables for included studies are presented in Supplementary Data 6. Fourteen meta-analyses were performed where data were sufficiently comparable. GRADE results for all meta-analyses are presented in Table 1. No funnel plots were generated because none of the 14 meta-analyses included ten or more studies.

HBV testing[24-39]

Nine of the 16 studies of interventions to promote HBV testing were conducted in community settings. The remaining seven occurred in facilities where high-risk populations either lived or received healthcare (Table 2). All 16 interventional studies targeted populations at high-risk of HBV infection or HBV-related morbidity and mortality, mainly Asian migrants (Table 2).

Self-reported HBV testing rates were higher among groups that received a single lay health worker educational intervention to improve HBV knowledge and promote testing compared to groups that received no or unrelated educational interventions (RR = 2.68, CI95 1.82 – 3.93, I^2 = 56%, n = 2757, moderate quality of evidence) (Figure 3). Six RCTs were included in this meta-analysis. In each intervention bicultural and bilingual community members were educated on HBV infection and trained to provide basic culturally-tailored HBV information and encourage referral for testing. These test promotion activities either occurred in individuals' homes or at community-based organizations, such as churches, language study programs, or nail salons. All six studies targeted Asian migrant communities in the United States or Canada.

Three before-after NRSs compared new institutional testing protocols for high-risk populations and supplemental provider education to previous standards of care. The meta-analysis showed improved HBV testing rates (RR = 3.77, CI95 2.04 – 6.97, n = 37,547, very low quality of evidence), though heterogeneity was high (I^2 = 91%).

Two RCTs evaluated HBV education and pre-test counseling with on-site testing by healthcare professionals at health or social service sites utilized by high-risk groups. Meta-analysis found these interventions improved HBV testing rates (RR = 6.20, CI95 3.19 – 12.08, n = 2,789, low quality of evidence), however heterogeneity was moderately high (I^2 = 69%).

HBV linkage to care[40,41]

Only two studies reported an outcome related to HBV linkage to care. One evaluated the impact of an informational letter on local HBV services, while the second compared a new electronic patient referral system to the prior standard of care (Supplementary Data 4).

HCV testing[28,34,35,42-51]

In contrast to interventions to improve HBV testing, which were primarily delivered in community settings, all 13 interventions to improve HCV testing either targeted healthcare providers or took place at an established healthcare or social service facility. The majority of studies limited their interventions to a specific high-risk population, most frequently current and former drug users and patients with mental health comorbidities (Table 3).

Clinician reminders to prompt HCV testing during clinical visits increased HCV testing rates compared to no clinician reminders (RR = 3.70, CI95 1.81 – 7.57, n = 52,947, very low quality of evidence) (Figure 3). In one cluster RCT and two NRSs reminder stickers were placed in patient charts that either prompted providers to ask about HCV-associated risk behaviors or order testing for patients born within a high-prevalence birth cohort. Two studies used physical reminder stickers, while one study incorporated reminders into an electronic medical records system. Although all three studies involved patients seeing primary care providers in New York City clinics, heterogeneity was very high (I^2 = 99%).

HCV education and pre-test counseling with on-site testing by healthcare professions at facilities serving high-risk populations increased HCV testing compared to no education or counseling (RR = 2.77, CI95 1.11 – 6.93, n = 4,209, very low quality of evidence). Facilities were notably different among the studies, and included a shelter, methadone treatment site, hospital emergency department, outpatient mental health clinic, and inpatient psychiatric department. Heterogeneity was very high (I^2 = 97%).

HCV linkage to care[28,34,43,52-56]

There were eight studies reporting outcomes for interventions to link people with suspected or confirmed chronic HCV to care. Five of the eight interventions promoting linkage to care focused on people with current or past substance use (Supplementary Data 5).

Interventions that provided facilitated referral increased patient attendance to HCV specialist visits compared to no facilitated referral (RR = 1.57, CI95 1.03 – 2.41, n = 437, moderate quality of evidence). In three RCTs specially trained staff at a site of established care guided patients with a positive HCV serology result through the referral process and helped them schedule specialist visits. There was high heterogeneity between reported effect sizes (I^2 = 74%).

Psychological counseling and motivational therapy for mental health and/or substance use issues as well as referral to longer term mental health services increased the number of referred patients eligible for treatment compared to usual care (OR = 3.42, CI95 1.81 – 6.49, n = 120, very low quality of evidence) and heterogeneity was very low (I^2 = 0%).

HCV treatment uptake[43,52,54,57-61]

Eight studies reported HCV treatment uptake as an outcome. Interventions to improve HCV treatment uptake predominantly targeted patients with mental health and/or substance use comorbidities, with six of the eight studies at this stage exclusively studying this population (Supplementary Data 5).

Coordinated mental health, substance use, and hepatitis treatment services did not significantly increase HCV treatment uptake (RR = 1.36, CI95 0.94 – 1.97, n = 846, very low quality evidence). Results from three studies, one RCT and two NRSs, were pooled for this meta-analysis. In all three interventions a multi-disciplinary care team regularly met to discuss patient issues and coordinate treatment plans. All studies found rates of HCV treatment uptake to be higher in the intervention group compared to control, however heterogeneity was high (I^2 = 77%).

HCV treatment adherence[22,23,54,56,57,59,60,62-75]

With 21 studies reporting HCV treatment adherence (including treatment completion), this stage of the care continuum was best represented in the published literature. Unlike previous stages of the HCV care continuum, the majority of interventions reporting HCV treatment adherence outcomes did not target a particular high-risk group. Fifteen out of 21 studies included all adults

with chronic HCV infection who qualified for treatment. The other six studies only included adults living with HCV who also had mental health and/or substance use comorbidities (Supplementary Data 5).

Coordinated mental health, substance use, and hepatitis treatment services improved treatment completion compared to usual care (RR = 1.22, CI95 1.05 – 1.41, n = 399, very low quality of evidence). Two RCTs and two NRSs were included in this meta-analysis. All four interventions involved regular contact between mental health and specialist treatment providers throughout the course of HCV treatment, and mental health services were arranged for those with comorbidities. Two studies also provided additional case management for the intervention group. All four studies reported increased treatment completion in the intervention group, and heterogeneity was very low (I^2 = 0%).

Two meta-analyses evaluated the impact of nurse-led educational sessions about HCV treatment on treatment adherence and treatment completion, respectively. This intervention did not significantly improve treatment adherence (RR = 1.08, CI95 0.87 – 1.34, n = 891, very low quality of evidence) though it did improve treatment completion (RR = 1.14, CI95 1.05 – 1.23, n = 965, very low quality of evidence). Three NRSs reported treatment adherence as an outcome, with moderate heterogeneity (I^2 = 64%). Three NRSs and one RCT reported treatment completion as an outcome, with very low heterogeneity (I^2 = 0%). The frequency and intensity of educational sessions varied widely across studies.

HCV cure[23,54,56-66,68,69,72,74-77]

Twenty studies reported SVR as an outcome. Most studies at this stage included all adults with chronic HCV who qualified for treatment, but eight studies exclusively targeted adults who had mental health and/or substance use comorbidities (Table 4).

Coordinated mental health, substance use, and hepatitis treatment services improved SVR compared to usual care (RR = 1.21, CI95 1.07 – 1.38, n = 846, very low quality of evidence) (Figure 3). All five studies included in this meta-analysis, including two RCTs and three NRSs, reported increased SVR in the intervention group. Two of five studies also provided additional case management, while two others included enhanced therapeutic education for the intervention group. One study facilitated family member involvement in care decisions and community support. Heterogeneity in this meta-analysis was very low (I^2 = 2%).

Nurse-led educational sessions about HCV treatment improved SVR compared to no education (OR = 1.93, CI95 1.44 – 2.59, n = 1460, low quality of evidence). Of the six studies examining this intervention, four were included in this meta-analysis because they reported results that employed statistical methods to adjust for confounding potentially introduced by non-randomized study designs. All four studies reported increased SVR in groups that had received the educational intervention, and heterogeneity was very low (I^2 = 0%).

Directly observed therapy did not improve SVR compared to self-administered interferon therapy (OR = 1.49, CI95 0.72 – 3.08, n = 219, very low quality of evidence). Two of the three studies in this meta-analysis examined patients currently receiving methadone maintenance therapy, and heterogeneity between effect sizes was very low (I^2 = 0%).

Discussion

Our review demonstrates that operational interventions can optimize the chronic viral hepatitis care continuum. Included studies were diverse with a range of interventions targeting both patients and providers. Existing systematic reviews have focused solely on HCV[78-80] or restricted their study to one step of the care continuum[78,80,81] or one type of intervention.[82] Furthermore, several reviews allowed inclusion of single arm studies[79,81] or did not pool outcomes.[79-82] Our review extends the literature by excluding non-comparator studies and carrying out meta-analyses on key HBV and HCV operational interventions and outcomes. We also improve the rigor of our analysis by using GRADE methodology to assess quality of evidence (Table 1).

Our meta-analysis demonstrates task shifting educational programs to culturally appropriate lay health workers is effective in increasing HBV testing uptake. The six included studies were graded as moderate quality evidence. Although all lay health worker interventions were conducted among Asian immigrant populations in high-income countries, this particular type of intervention may apply to other settings.[83] Training provided for the lay health workers in the six studies was relatively simple and low cost. Qualitative research supports these types of interventions as feasible and acceptable to both those individuals tested and the lay health workers employed.[84] Task shifting is a well-documented approach and recommended for strengthening service delivery capacity in a variety of clinical settings, particularly in the context of the efficient use of limited health resources in low- and middle-income countries.[85-87]

Our analysis found clinician reminders were effective in increasing HCV testing during clinical consultations. Included studies used electronic medical record prompts[47] and physical 'risk testing' stickers placed on printed charts.[44,49] This simple intervention could be easily implemented at low cost in both inpatient and outpatient settings. Clinician reminders are consistent with the broader shift towards improving health care quality through provider-initiated testing[88] and systems-based approaches[89] to improving clinical outcomes. Implementation is relatively easy and similar systems have demonstrated the effectiveness of clinician reminders in resource limited settings[90]. While increasing antibody testing is important, a crucial next step that was not evaluated in the majority of included studies is confirmatory RNA testing. Reflexive RNA testing is a similarly simple electronic task that has been validated[53] but needs additional study.

We found integration of mental health and substance use management with HCV treatment services was effective in promoting HCV treatment completion and cure (SVR). HCV disproportionately affects individuals with mental health and substance use disorders[91]. Traditionally, services for HCV treatment, mental health, and addiction management have been provided by separate clinicians located in different health facilities, which impedes communication and follow-up for the management of each respective condition[92]. While the multidisciplinary care interventions in this review were diverse, and at times complex, a likely key contributor to improved outcomes was co-location of services. Support for co-location as the primary driver of effect comes from literature from other communicable diseases in which co-location of infectious disease and mental health services improved outcomes[93,94]. Furthermore, lack of transportation[95], inadequate access to healthcare[95], and delay in specialist input[96] have all been identified as barriers to delivery of HCV treatment.

Our review findings on operational interventions to promote testing can be generalized to a number of populations and settings. Among HCV studies, we found many interventions focused on serving PWID,[21,28,31,34,43,46,50,52,55,60] including in settings such as general practice clinics,[43] substance use disorder clinics,[28,46] emergency medical services,[50] hepatitis clinics,[31] methadone clinics,[43,55] and prisons.[46] Our data included one study among those actively using drugs[50] and one study among those previously denied HCV treatment,[52] suggesting a broad cross-section of PWID. Although similar structural issues challenge HCV service delivery in low and middle-income countries, we identified no PWID HCV operational intervention research from these

settings. We speculate that some of the interventions identified in high-income countries, such as clinician reminders for HCV testing, could be adapted and used in low and middle-income country settings. Among HBV studies, all interventions targeted populations at high-risk of HBV infection or HBV-related complications, including nine studies of Asian migrants. The generalizability of these high-income studies to low and middle-income settings should be done with caution.

Our review has several policy implications. First, we grouped the HBV and HCV care continuums together. While laboratory testing, antiviral therapy, and outcomes differ between these two viruses, the basic steps from testing to treatment are similar. Oral direct acting antivirals (DAAs) for treatment of HCV are ostensibly analogous to HBV antivirals, although treatment is of finite duration. While affected populations may vary between countries and contexts, similar programmatic structures may suit the management of both infections, including the operational interventions described here. Second, a number of the interventions analyzed in this review were of low cost and could be implemented in resource-limited settings. Finally, the interventions described are essentially systems based, dependent on the organization of programs rather than the quality of hospital care or types of medicines available. The technology to implement these interventions is already available in many settings. In addition, many of these interventions can be implemented at the local level and are not dependent on higher-level governmental authorization.

There are several limitations to our review. First, outcomes that were studied were intermediate outcomes related to diagnosis and treatment, not disease endpoints such as morbidity and mortality associated with HBV and HCV. However, it is well known that treatment reduces liver-related complications and hepatocellular carcinoma incidence[4,97]. Second, almost all studies in HCV were carried out with interferon-based therapies. Compared with pegylated interferon, current DAA-based regimens are simpler to administer, more effective, and better tolerated[6]. With these agents, treatment uptake and outcomes will likely improve [98]. The emphasis now shifts to testing and linkage to care interventions as treatment eligibility expands. The psychosocial issues that impact compliance in vulnerable HCV populations however remain the same. With development of resistance a major concern with DAAs, interventions that promote adherence remain relevant. Third, nearly all studies were implemented in high-income countries. Further research is needed in low and middle-income countries. Fourth, several meta-analyses only had a few contributing studies. As a result, there were insufficient data to

undertake subanalyses based on HIV-hepatitis co-infection, subpopulation, and other variables that may contribute to effectiveness. Fifth, we excluded non-English literature. This was due to a concern about lower quality of evidence in non-English journals, empirical evidence that restricting non-English language research does not lead to selection bias, and logistical issues.

Finally, there was a relative dearth of quality studies in our review. More than half the studies used a non-randomized design, and the majority did not adjust for potential confounders. Combining NRSs with RCTs increases the potential for selection bias and may contribute to high degree of heterogeneity observed in several meta-analyses. As several stages and intervention types were primarily investigated through NRSs, the inclusion of NRSs was necessary to accurately represent the full spectrum of operational interventions evaluated in the literature. Stratification of meta-analyses by study design did not find large differences between estimated effect sizes. Heterogeneity in pooled effect sizes was more likely due to differences in frequency and duration of intervention exposure, implementation, and populations under study, rather than study design. Most meta-analyses included a small number of studies (less than four), which also contributes to high heterogeneity and limits confidence in the effect size estimates. Assessments of some interventions were also disproportionately affected by results of a single study. It should also be noted that a number of innovative interventions such as point-of-care testing and electronic patient referral systems appeared promising and require further research.

We identified several priorities for future research. The lack of data from low- and middle-income settings was disappointing, given the vast bulk of people living with HBV and HCV across the world reside in these settings[14,15]. Most of our review findings were graded low or very low. High quality evidence provides a strong basis for forming guideline recommendations for program managers, clinicians, and others working in the field. RCTs in operational research can be costly, difficult to carry out, and potentially unethical in resource constrained settings. Methods to ameliorate these issues include pragmatic trials that mirror real world conditions to maximize generalizability and effectiveness-implementation hybrid trials that simultaneously evaluate impact and strategy of intervention delivery.[99] These types of implementation science trials could help move forward hepatitis service provision while definitive RCT trials are underway. Formal cost-effectiveness research may be useful to convince policy makers about the importance of developing HBV and HCV operational interventions. Further research is also

needed in a number of key steps across the care continuum, in particular HBV treatment uptake, adherence, and viral suppression.

Our systematic review demonstrates a range of relatively simple, inexpensive operational interventions can substantially improve engagement and retention along the chronic viral hepatitis care continuum. We identified the importance of integrated approaches to hepatitis care and treatment for specific vulnerable populations. High uptake along the continuum will become increasingly important as access to effective HBV and all-oral HCV medicines expands. The interventions identified in this review may be useful to augment hepatitis programs worldwide. As global momentum grows for addressing hepatitis at the population level, further operational research is necessary to optimize chronic hepatitis services.

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Author Contributions

Literature search: KZ, TF, NW, JK, ML, JS, YL, JT; Study design: KZ, NW, YL, JT; Data collection: KZ, TF, NW; Data analysis: KZ, TF, NW, RC; Data interpretation: KZ, TF, NW, YL, JT; Figures: KZ, TF, NW, RC, YL, JT; Writing: KZ, TF, NW, RC, YL, JT

Declaration of interests

The author(s) declare that they have no conflicts of interests.

Research in context

Evidence before this study

Chronic hepatitis B and C are major public health threats; however current therapies for HBV and HCV are transforming clinical management of both diseases. Optimal care and treatment are dependent on effective program implementation. Operational interventions may expedite movement across the continuum (cascade) of care. Existing systematic reviews have focused solely on HCV, restricted investigation to one step of the care continuum, a single type of intervention or did not pool outcomes from individual studies. Our search focused on studies investigating operational interventions at any point in the chronic viral hepatitis care continuum for people living with diagnosed or undiagnosed chronic viral hepatitis. We searched Pubmed, EMBASE, WHO library, International Clinical Trials Registry Platform, Psychinfo, and Cinahl for full-text or abstract entries, accepted scientific conference abstracts, clinical trials registered on Clinicaltrials.gov and references of included articles. The combination of search terms included “Hepatitis B”, ”Hepatitis C”, “chronic viral hepatitis”, “Intervention” and various types of operational interventions including behavior and structural as well as terms focused on steps in the continuum including “Screen”, “ test”, “ Linkage”, “Referral” as well as adherence, SVR or viral suppression. We included literature published up to 31 December 2014.

Added value of this study

Our review extends the literature by excluding non-comparator studies and carrying out meta-analyses on key HBV and HCV operational interventions and outcomes. We also improve the rigor of our analysis by using GRADE methodology to assess quality of evidence. Our systematic review demonstrated a range of relatively simple, inexpensive operational interventions can substantially improve engagement and retention along the chronic viral hepatitis care continuum, thereby optimizing the implementation of screening, care and treatment programmes.

Implications of all the available evidence

Operational interventions should be included in chronic viral hepatitis screening, diagnosis and treatment programmes to optimize hepatitis care outcomes. Our findings suggest that a range of operational interventions have been developed which could enhance HBV and HCV service delivery.

Figures and Tables

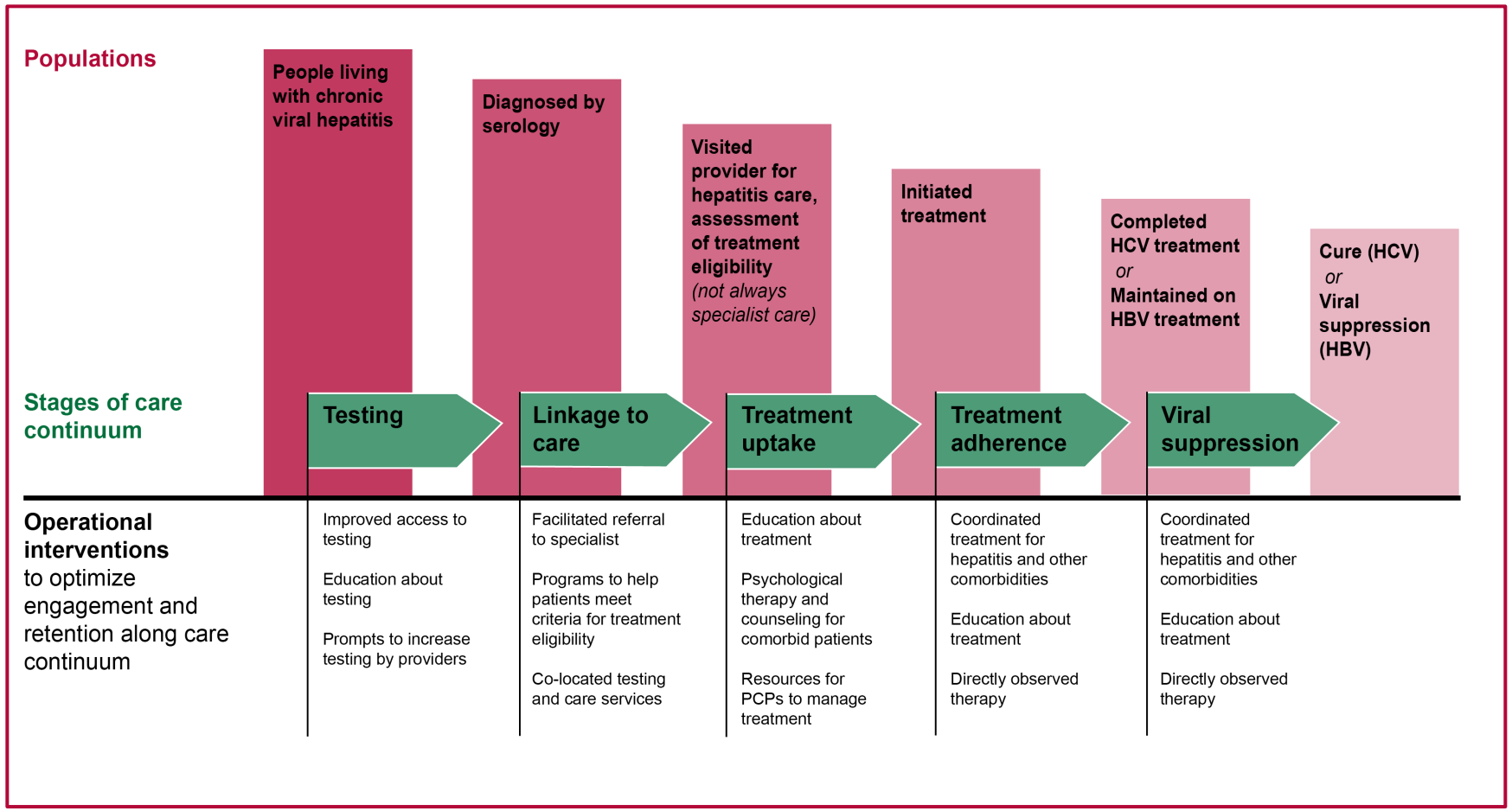

Figure 1: Overview of the chronic viral hepatitis care continuum, including testing, linkage to care, treatment uptake, treatment adherence, and viral suppression or cure.

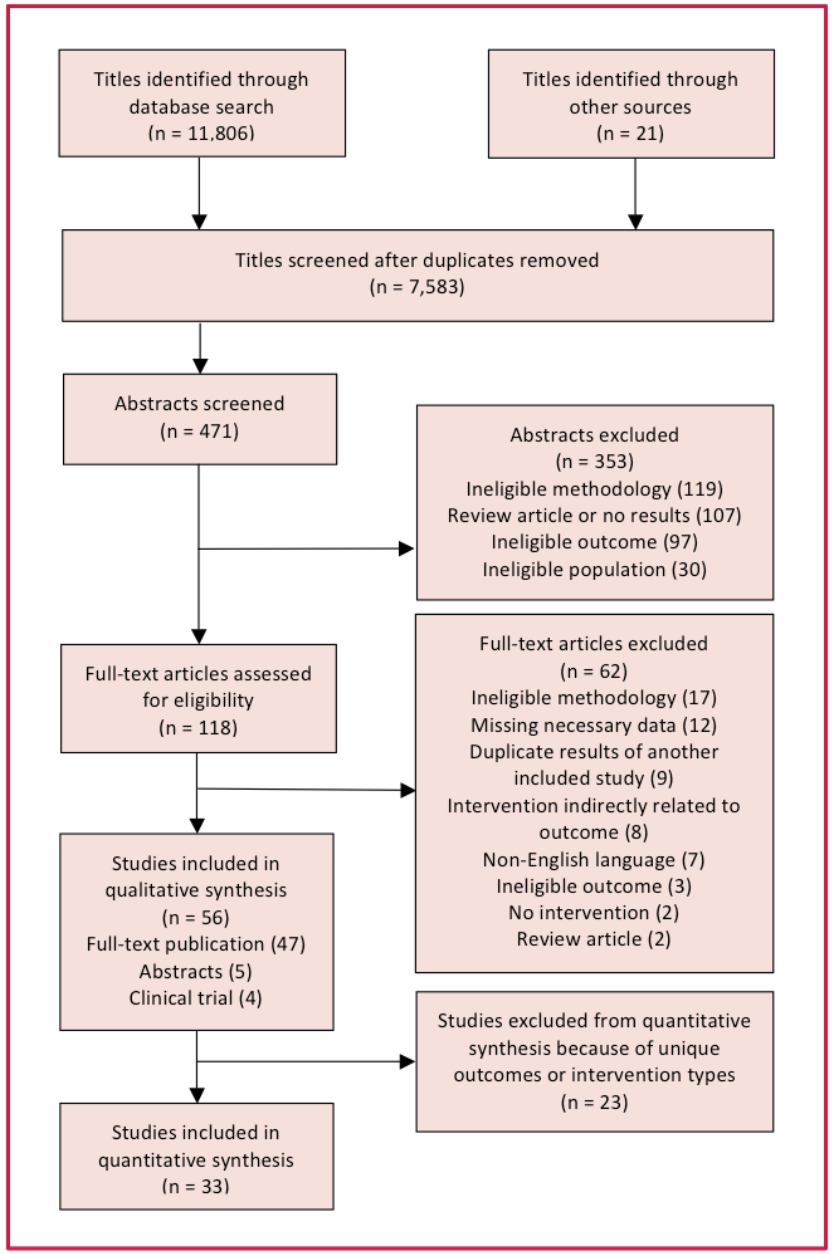
Titles identified through database search (n = 11,806)
Titles identified through other sources (n = 21)
Titles screened after duplicates removed (n = 7,583)
Abstracts screened (n = 471)
Abstracts excluded (n = 353)
Ineligible methodology (119)
Review article or no results (107)
Ineligible outcome (97)
Ineligible population (30)
Full-text articles assessed for eligibility (n = 118)
Full-text articles excluded (n = 62)
Ineligible methodology (17)
Missing necessary data (12)
Duplicate results of another included study (9)
Intervention indirectly related to outcome (8)
Non-English language (7)
Ineligible outcome (3)
No intervention (2)
Review article (2)
Studies included in qualitative synthesis (n = 56)
Full-text publication (47)
Abstracts (5)
Clinical trial (4)
Studies excluded from quantitative synthesis because of unique outcomes or intervention types (n = 23)
Studies included in quantitative synthesis (n = 33)

Figure 2: Summary of the Article Search, Screening, and Selection Process.

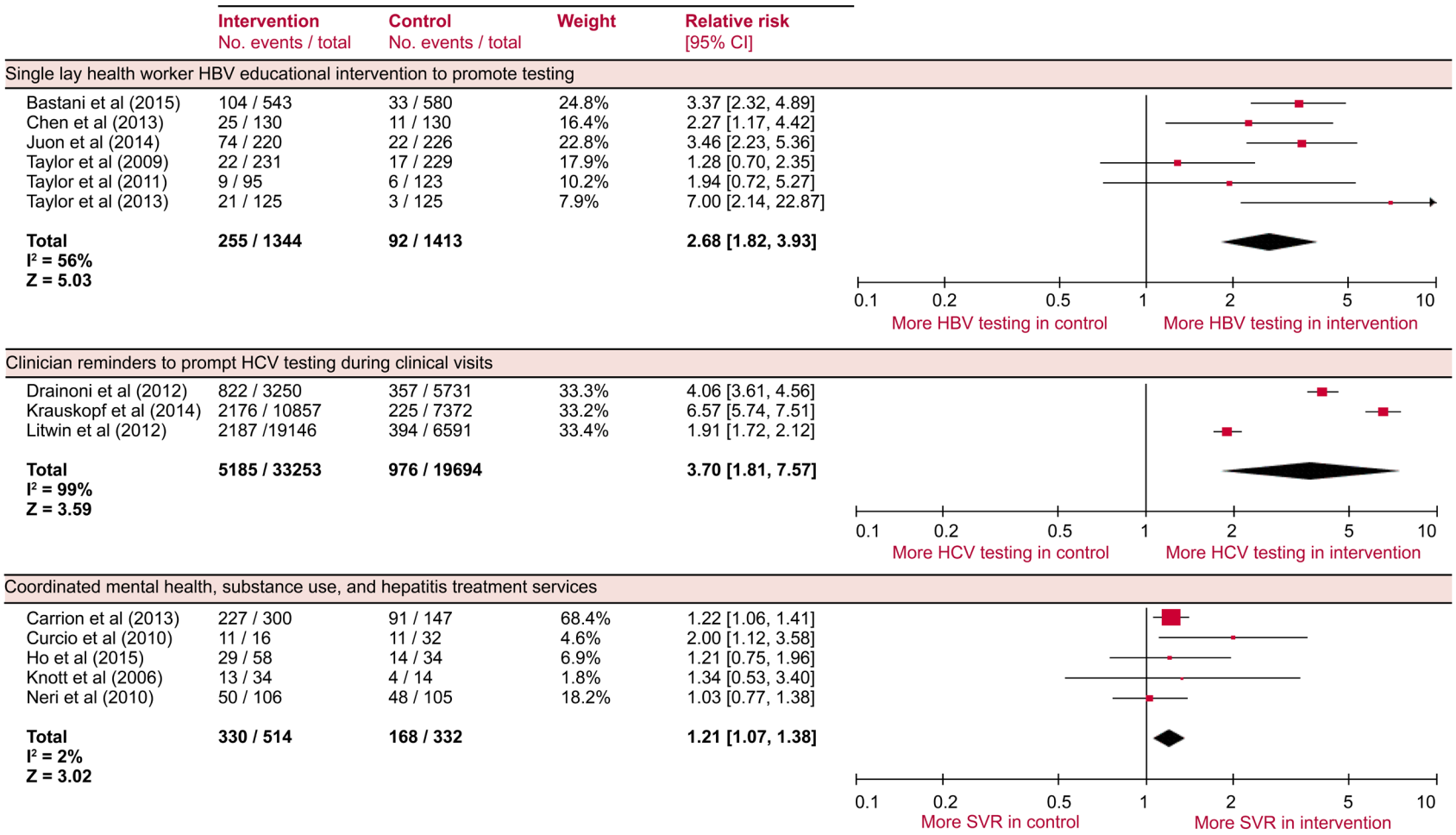

Figure 3: Meta-analysis of the impact of lay health worker educational interventions on HBV testing uptake, clinician reminders to test during clinical visits on HCV testing, and coordinated mental health, substance use, and hepatitis treatment services on SVR. Forest plots for all 14 meta-analysis included in this review can be found in Supplemental Data 3.

Meta-analysis					GRADE score§					
Intervention	**Outcome**	**No. studies (RCT/NRS)**	**Effect size§§**	**I^2**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Single lay health worker education	HBV testing	6 (6/0)	RR 2.68 [1.82 - 3.93]	56%	Serious	Not serious	Not serious	Not serious	None	Moderate
New institutional testing protocols	HBV testing	3 (0/3)	RR 3.77 [2.04 - 6.97]	91%	Serious	Serious	Not serious	Serious	None	Very low
Education by healthcare professionals, on-site testing	HBV testing	2 (2/0)	RR 6.20 [3.19 - 12.08]	69%	Not serious	Serious	Not serious	Serious	None	Low
Clinician reminders to prompt testing	HCV testing	3 (1/2)	RR 3.70 [1.81 - 7.57]	99%	Serious	Serious	Not serious	Serious	None	Very low
Education by healthcare professionals, on-site testing	HCV testing	5 (4/1)	RR 2.77 [1.11 - 6.93]	97%	Serious	Serious	Not serious	Serious	None	Very low
Facilitated referral	Attendance to HCV specialist visit	3 (3/0)	RR 1.57 [1.03 - 2.41]	74%	Not serious	Serious	Not serious	Not serious	None	Moderate
Psychological counseling and motivational therapy	Referral as eligible for treatment	2 (1/1)	OR 3.42 [1.81 - 6.49]	0%	Serious	Not serious	Not serious	Serious	None	Very low
Coordinated mental health, substance use, and hepatitis treatment services	HCV treatment uptake	3 (1/2)	RR 1.36 [0.94 - 1.97]	77%	Serious	Serious	Not serious	Serious	None	Very low
Coordinated mental health, substance use, and hepatitis treatment services	Treatment completion	4 (2/2)	RR 1.22 [1.05 - 1.41]	0%	Serious	Not serious	Not serious	Serious	None	Very low
Nurse-led educational sessions	Treatment adherence	3 (0/3)	RR 1.08 [0.87 - 1.34]	64%	Serious	Serious	Not serious	Serious	None	Very low
Nurse-led educational sessions	Treatment completion	4 (1/3)	RR 1.14 [1.05 - 1.23]	0%	Serious	Not serious	Not serious	Not serious	None	Very low
Coordinated mental health, substance use, and hepatitis treatment services	SVR	5 (2/3)	RR 1.21 [1.07 - 1.38]	2%	Serious	Not serious	Not serious	Not serious	None	Very low
Nurse-led educational sessions	SVR	4 (1/3)	OR 1.93 [1.44 - 2.59]	0%	Not serious	Not serious	Not serious	Not serious	None	Low
Directly observed therapy	SVR	3 (2/1)	OR 1.49 [0.72 - 3.08]	0%	Serious	Not serous	Not serious	Serious	None	Very low

§ GRADE tables, including justifications for downgrading quality of evidence, can be found in supplementary materials. §§ Pooled effect sizes were calculated using a random effects model.

Table 1: Summary of findings for quantitative analysis and GRADE quality of evidence assessment

HBV testing¶

Author	Study design	Location	Intervention type	Population	Setting	Outcomes	Sample size	No. domains at high risk of bias§
Asthana et al (2012)	NRS	Australia	Provider education about importance of testing	Patients receiving chemotherapy	Facility (hospital)	HBsAg test uptake	229	2
Bastani et al (2015)	RCT (cluster)	U.S.	Lay health worker educational intervention	Korean Americans	Community (churches)	Self reported first HBV test	1123	2
Chakrabarty et al (2013)	RCT	Not specified	Self-administered blood spot tests mailed to home	Contacts of chronic HBV patients	Community (mailing)	HBsAg test uptake	79	2
Chen et al (2013)	RCT	U.S.	Lay health worker educational intervention	Hmong Americans	Community (home visit)	Self reported first HBV test	260	2
Hagedorn et al (2007)	NRS	U.S.	New institutional testing protocols for high-risk populations, provider education	Patients attending substance use disorder clinic	Facility (clinic)	HBsAg test uptake	275	2
Hsu et al (2013)	RCT	U.S.	Clinician reminder to test prior to clinical visit	Chinese or Vietnamese Americans	Facility (clinic)	HBsAg test uptake, physician ordering of HBsAg test	175	0
Juon et al (2014)	RCT (cluster)	U.S.	Lay health worker educational intervention	Asian Americans	Community (language programs, churches)	Self reported first HBV test	446	2
Koruk et al (2011)	NRS	Turkey	New institutional testing protocols for high-risk populations, provider education	Pregnant women	Facility (hospital)	HBsAg test uptake	36987	2
Lee et al (2010)	NRS	Canada	New institutional testing protocols for high-risk populations, provider education	Patients receiving chemotherapy	Facility (hospital)	HBsAg test uptake	285	2
Ma et al (2012)	NRS	U.S.	Lay health worker educational intervention, price reductions for testing, facilitated linkage to testing	Korean Americans	Community (churches)	Self reported first HBV test	158	4
Rosenberg et al (2010)	RCT	U.S.	HBV education and pre-test counseling by healthcare professionals, on-site testing	Patients with mental health and substance use comorbidities	Facility (mental health program)	HBsAg test uptake	153	1
Sahajian et al (2010)	RCT (cluster)	France	HBV education and pre-test counseling by healthcare professionals, on-site testing	People living in long-term shelters	Facility (social service facilities)	HBsAg test uptake	2636	0
Taylor et al (2009)	RCT	Canada, U.S.	Lay health worker educational intervention	Chinese Americans, Chinese Canadians	Community (home visit)	Self reported first HBV test, verified HBV test	460	2
Taylor et al (2011)	RCT (cluster)	Canada	Lay health worker educational intervention	Asian migrants	Community (language programs)	Self reported first HBV test, verified HBV test	180	2
Taylor et al (2013)	RCT	U.S.	Lay health worker educational intervention	Cambodian Americans	Community (home visit)	Self reported first HBV test	250	2
Van Der Veen et al (2013)	RCT	Netherlands	Educational website	Turkish migrants	Community (online)	HBsAg test uptake	1400	0

¶ Some studies investigated multiple stages of the care continuum, and may have differed in intervention type, population, outcome, sample size, and risk of bias across stages. Only study characteristics relevant to this stage of the care continuum are presented here. § All included studies were assessed for high, unclear, or low risk of bias along six domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias). Complete risk of bias tables are available in supplementary materials.

Table 2: HBV testing, included studies. Tables of included studies for other stages of the HBV care continuum are available in supplementary materials.

HCV testing¶

Author	Study design	Location	Intervention type	Population	Setting	Outcomes	Sample size	No. domains at high risk of bias§
Craine et al (2014)	RCT (cluster)	U.K.	Institutional adoption of bloodspot testing	Prisoners	Facility (prison)	HCV antibody test uptake	Not given	3
Cullen et al (2006)	RCT (cluster)	Ireland	HCV education and pre-test counseling by healthcare professionals, on-site testing	Patients receiving methadone therapy	Facility (clinic)	HCV antibody test uptake	196	0
Drainoni et al (2012)	NRS	U.S.	Clinician reminder to test during clinical visit	Patients attending urban clinics	Facility (clinic)	HCV antibody test uptake	8981	3
Hagedorn et al (2007)	NRS	U.S.	New institutional testing protocols for high-risk populations, provider education	Patients attending substance use disorder clinic	Facility (clinic)	HCV antibody test uptake	275	2
Helsper et al (2010)	NRS	Netherlands	Regional education campaign for providers	GPs with primary care practices	Facility (clinic)	Orders for HCV antibody test by provider	Not given	3
Hickman et al (2008)	RCT (cluster)	U.K.	Institutional adoption of bloodspot testing	Prisoners, drug users	Facility (prison, drug clinic)	Change in HCV antibody test rate	12350	1
Krauskopf et al (2014)	RCT (cluster)	U.S.	Clinician reminder to test during clinical visit	Patients born 1945-1965 attending PCP clinic	Facility (clinic)	HCV antibody test uptake	18229	1
Lacey et al (2007)	NRS	Australia	HCV education and pre-test counseling by healthcare professionals, on-site testing	Psychiatric inpatients	Facility (hospital)	HCV antibody test uptake	832	2
Litwin et al (2012)	NRS	U.S.	Clinician reminder to test during clinical visit	Patients born 1945-1965 or reporting risk factors attending PCP clinic	Facility (clinic)	HCV antibody test uptake	25737	1
Merchant et al (2014)	RCT	U.S.	HCV education and pre-test counseling by healthcare professionals, motivational interviewing	Drug users attending ED	Facility (emergency department)	HCV antibody test uptake	395	0
Rosenberg et al (2010)	RCT	U.S.	HCV education and pre-test counseling by healthcare professionals, on-site testing	Patients with mental health or substance use comorbidities	Facility (clinic)	Self reported first HBV test	150	1
Sahajian et al (2004)	NRS	France	Regional education campaign for providers	GPs and specialist physicians	Facility (clinic)	Orders for HCV antibody test by provider	3052	3
Sahajian et al (2010)	RCT (cluster)	France	HCV education and pre-test counseling by healthcare professionals, on-site testing	People living in long-term shelters	Facility (social service facilities)	HCV antibody test uptake	2636	0

¶ Some studies investigated multiple stages of the care continuum, and may have differed in intervention type, population, outcome, sample size, and risk of bias across stages. Only study characteristics relevant to this stage of the care continuum are presented here. § All included studies were assessed for high, unclear, or low risk of bias along six domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias). Complete risk of bias tables are available in supplementary materials.

Table 3: HCV testing, included studies. Tables of included studies for HCV linkage to care, treatment uptake, and treatment adherence are available in supplementary materials.

HCV SVR[¶]

Author	Study design	Location	Intervention type	Population	Treatment regimen	Outcomes	Sample size	No. domains at high risk of bias[§]
Ahmed et al (2013)	NRS	U.K.	Coordinated mental health, substance use, and hepatitis treatment services, community and family support program	Patients enrolled in HCV treatment	Interferon/ribavirin, interferon monotherapy	SVR (6 months post treatment), EVR (early virological response), ETR (end treatment response)	70	3
Arora et al (2011)	NRS	U.S.	Training and support for primary care physicians to manage HCV treatment	Patients enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR	407	2
Bonkovsky et al (2008)	RCT	U.S.	Directly observed therapy	Patients receiving methadone therapy and enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR, ETR (end treatment response)	48	0
Bruce et al (2012)	RCT	U.S.	Directly observed therapy	Patients receiving methadone therapy and enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR	16	2
Cacoub et al (2008)	NRS	France	Nurse-led education about HCV therapy	Patients enrolled in HCV treatment (majority current or former drug use)	Pegylated interferon/ribavirin	SVR (12 weeks post treatment)	674	2
Carrion et al (2013)	NRS	Spain	Coordinated mental health, substance use, and hepatitis treatment services	Patients enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR	447	1
Chen et al (2014)	RCT	Taiwan	Telephone-based nursing support	Patients enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR	298	0
Cioe et al (2013)	NRS	U.S.	Directly observed therapy	Patients enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR	155	1
Curcio et al (2010)	NRS	Italy	Coordinated mental health, substance use, and hepatitis treatment services, case management	Patients enrolled in HCV treatment with substance use comorbidities	Pegylated interferon/ribavirin	SVR	48	2
Ho et al (2015)	RCT	U.S.	Coordinated mental health, substance use, and hepatitis treatment services, case management	Patients enrolled in HCV treatment with mental health or substance use comorbidities	Pegylated interferon/ribavirin, DAA at end of study period	SVR (12 or 24 weeks post treatment)	92	0
Knott et al (2006)	NRS	U.S.	Coordinated mental health, substance use, and hepatitis treatment services	Patients enrolled in HCV treatment with mental health or substance use comorbidities	Pegylated interferon/ribavirin	SVR (24 weeks post treatment)	48	2
Lan et al (2012)	NRS	France	HCV education, psychological therapy and counseling for patients with substance use comorbidities	HCV patients with alcohol-dependence	Pegylated interferon/ribavirin	SVR	146	2
Larrey et al (2011)	RCT	France	Nurse-led education about HCV therapy	Patients enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR (24 weeks post treatment)	244	0
Lubega et al (2013)	NRS	U.S.	Nurse-led education about HCV therapy	Patients enrolled in HCV treatment (majority current or past injection drug use)	Pegylated interferon/ribavirin	SVR (24 weeks post treatment)	118	1
Merck Sharp & Dohme Corp. (2007)	NRS	Poland	Nurse-led education about HCV therapy	Patients enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR (6 months post treatment)	99	3
Neri et al (2010)	RCT	Italy	Coordinated mental health, substance use, and hepatitis treatment services	Patients enrolled in HCV treatment (excluded mental health and substance use comorbidities)	Pegylated interferon/ribavirin	SVR (24 weeks post treatment)	211	0
Reimer et al (2013)	NRS	Germany	HCV education, psychological therapy and counseling for patients, without coordinated care	Patients enrolled in HCV treatment and receiving opioid substitution therapy	Pegylated interferon/ribavirin	SVR (24 weeks post treatment)	189	2
Renou et al (2009)	NRS		Nurse-led education about HCV therapy	Patients enrolled in HCV treatment	Pegylated interferon/ribavirin	SVR, ETR (end treatment response)	424	1
Rifai et al (2006)	NRS	U.S.	Inpatient substance use treatment prior to therapy, outpatient psychological counseling during therapy	Patients enrolled in HCV treatment with substance use comorbidities	Pegylated interferon/ribavirin, interferon/ribavirin	SVR (6 months post treatment)	48	2
Tait et al (2009)	NRS	Scotland	Nurse-led education about HCV therapy	Patients enrolled in HCV treatment (majority past or current substance use)	Interferon/ribavirin, Pegylated interferon/ribavirin	SVR	198	3

¶ Some studies investigated multiple stages of the care continuum, and may have differed in intervention type, population, outcome, sample size, and risk of bias across stages. Only study characteristics relevant to this stage of the care continuum are presented here. § All included studies were assessed for high, unclear, or low risk of bias along six domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias). Complete risk of bias tables are available in supplementary materials.

Table 4: HCV SVR, included studies. Tables of included studies for HCV linkage to care, treatment uptake, and treatment adherence are available in supplementary materials.

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