Systematic Evidence Review
Number 24

Screening for Hepatitis C Virus Infection

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the U.S. Preventive Services Task Force[*] (USPSTF) and input from Federal partners and primary care specialty societies, the Evidence-based Practice Center at the Oregon Health Sciences University systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/clinic/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the USPSTF in print and on the Web. These are available through the AHRQ Web site and through the National Guideline Clearinghouse (http://www.ngc.gov).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Suite 3000, Rockville, MD 20850.

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[*]The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, and chemoprevention--in the primary care setting. AHRQ convened the USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

Abstract

Purpose

This report focuses on whether it is useful to order a hepatitis C virus (HCV) antibody test in either the general population of asymptomatic adults or selected high-risk subpopulations who have no history of liver disease or known liver function test abnormalities.

Data Sources

A MEDLINE® search, supplemented by searches of the Cochrane Library, reference lists, and periodic hand searches of relevant major journals.

Study Selection

We selected systematic reviews and controlled studies of antiviral treatment that used HCV infection in treatment-naïve patients as an inclusion criterion and reported relevant intermediate (virologic response) or clinical (symptoms, quality of life, cirrhosis, hepatocellular cancer, mortality) outcomes. We reviewed controlled and observational studies that evaluated clinical outcomes related to hepatitis A infection, hepatitis B infection, alcohol use, or spread of disease in patients found to have HCV. We also reviewed observational studies of the natural history, prevalence, progression, and consequences of untreated subclinical or asymptomatic hepatitis C virus infection.

Data Extraction and Synthesis

Using preset criteria, we assessed the quality of each systematic review and abstracted information about included studies and results. We also assessed each trial and abstracted information about its setting, patients, interventions, and outcomes to verify the results of the systematic review as it pertains to our population.

Results

Screening can detect hepatitis C virus antibodies in about 2% of the general US adult population, of whom 55-84% will have evidence of chronic infection (viremia). In certain settings, particularly in those associated with a high prevalence of intravenous drug use, the yield is much higher (50-90% in intravenous drug users). There is no direct evidence on benefits of screening in the general adult population. Many patients in the general population identified by screening will have a low probability of progressing to cirrhosis or another serious complication. Antiviral treatment is generally considered effective in improving intermediate outcomes in patients referred for treatment of chronic hepatitis C, but no trials have been performed specifically in patients likely to be identified by screening, who are likely to have milder or earlier disease. Data are insufficient to determine whether long-term outcomes are improved in patients referred for antiviral treatment of chronic hepatitis. There are no data to estimate the benefit from other interventions in patients identified by screening such as counseling on preventing spread of disease, obtaining appropriate immunizations, or alcohol counseling. Data on the adverse effects of screening (labeling, anxiety) and broader use of treatment are sparse.

Conclusions

Screening can detect chronic HCV infection. Antiviral treatment can successfully eradicate viremia, but data on long-term clinical outcomes are lacking. Most antiviral trials evaluated patients with more severe liver disease. Although counseling and appropriate immunizations in patients identified by screening are likely to be beneficial, studies estimating the degree of benefit are not available. Harms from antiviral treatment and work-up (liver biopsy) appear minimal, but other harms (labeling, false-positives, anxiety) are more difficult to measure. There is insufficient evidence to accurately weigh the benefits and risks of screening for HCV in the general population of otherwise healthy, asymptomatic adults. The yield from targeted screening in high-risk patients, particularly intravenous drug users, would be substantially higher.

Contents

Screening for Hepatitis C

Chapter 1. Introduction

In this systematic review, we focus on whether it is useful to test for anti-hepatitis C virus (anti-HCV) antibody (Ab) in asymptomatic adults who have no history of liver disease or known liver function test abnormalities. The review is intended for use by the US Preventive Services Task Force (USPTF), which will make recommendations regarding screening in the general adult population or high-risk subpopulations.

Published Guidelines

The USPTF has not previously made recommendations regarding HCV screening. Published guidelines from other major panels are presented in Table 1.

Burden of Suffering

HCV is a single-stranded, positive-sense RNA virus of the family *Flaviviridae*. After its characterization in 1989, studies identified HCV as the major cause of post-transfusion and community-acquired non-A, non-B hepatitis (NANBH).[1-6] There are six HCV genotypes and more than 50 (as many as 90) subtypes.[7] These genotypes can differ by up to 50% of their nucleotide sequences, and the virus has a high propensity to mutate. These characteristics may help explain some of the difficulties in developing effective vaccines and treatments.

HCV is the most common chronic bloodborne pathogen in the United States.[8] In a large population-based study, 1.8% of a large household-based sample was positive for anti-HCV antibody (2.3% in adults 20 years or older), which would translate into an estimated 3.9 million infected persons in the U.S.[9] Of these, 74% had viremia, indicating chronic infection (an estimated 2.7 million). Because sampling was based on households,

some groups with a higher prevalence of infection (such as the homeless or incarcerated) were not included. Studies in other specific populations and settings have reported a higher prevalence of anti-HCV antibodies, with the highest rates consistently in intravenous drug users.[10-13]

The incidence of HCV infection has fallen since the 1990s. The yearly incidence of HCV infection was estimated to average 230,000 cases per year in the 1980s, but by 2001 had declined to 25,000 cases per year.[14] The reduction in incidence is a result of mostly unknown factors, though a decrease in incidence among injection drug users, which could be partially related to safer needle-using practices, may explain some of this change.[8]

A high proportion of infected adults are thought to be unaware of their status. No reliable data are available for the proportion of patients in the United States with HCV who know they are infected; estimates range from 5 to 50%.[15-17] In a French population-based study, 24% (17/72) were aware that they were seropositive for HCV infection.[18]

HCV infection is a leading cause of complications from chronic liver disease in the United States. Approximately 40% of cases of chronic liver disease are HCV-related, and HCV infection is associated with an estimated 8,000-10,000 deaths each year.[8] HCV-related end-stage liver disease is now the most common indication for liver transplantation among American adults, accounting for over 30% of cases, and there was a 5-fold increase in the number of patients with HCV who underwent liver transplantation between 1990 and 2000.[19, 20] Data from the Healthcare Cost and Utilization Project database indicated that in 1998, 140,000 discharges listed an HCV diagnosis, accounting for approximately 2% of all discharges in the database, and were

associated with an estimated total hospital charge in excess of $1 billion, a substantial increase from only a few years earlier.[20, 21] Although the incidence of HCV infection has declined, the morbidity, mortality, and costs associated with chronic HCV infection are expected to increase 2-4-fold in the next 2 decades because of the delay between acute infection and presentation with serious liver disease.[22-24]

Despite the above data, there is uncertainty about the degree of excess mortality associated with chronic HCV infection. In a widely-publicized prospective cohort study of people who received transfusions, in 568 patients with acute NANBH (about 80% presumed to have HCV infection) there was no difference in 20-year overall mortality compared to controls (54% in patients with NANBH versus 57% in controls), even though there was an increase in cause-specific mortality from liver disease (3.3% vs. 1.1-2.0%, p=0.03).[25, 26] Similar findings were reported when 222 patients from this study with confirmed HCV infection were followed for an additional 5 years (67% mortality [4.1% from liver disease] in patients with chronic HCV versus 65% [1.3% from liver disease] in controls).[27] Because patients were older (average age 49) when enrolled in this study and had a high mortality rate (which could have been related to the condition for which they received the transfusion), the results may have been affected by confounding from co-morbid conditions. In two other longitudinal cohort studies that evaluated patients who acquired illness as younger adults, there was a non-significant trend towards worse survival in patients with anti-HCV antibodies. In one study, 11-year mortality in patients with HCV infection was 12.7% (117/924) versus 9% (43/475) (p=0.08) in matched controls.[28] Risk factors for decreased survival in patients with HCV infection compared to patients without HCV infection were older age, male gender, and

alcohol consumption. In the other study, mortality was 41% (7/17) after at least 45 years in seropositive patients versus 26% (2,226/8,551) in controls (relative risk [RR] 1.48; 95% confidence interval [CI], 0.8-2.6).[29] On the other hand, most other longitudinal studies of patients who acquired infection as younger adults or children from transfusion of blood products have reported few deaths after around 20 years of infection; longer duration of follow-up in these populations may be necessary.[30-33]

Chronic HCV infection can also cause morbidity in the absence of cirrhosis or other serious complications. HCV infection without cirrhosis is associated with significantly worse quality of life measures and symptoms (primarily fatigue) compared to the general population, though confounding factors such as intravenous drug use and other co-morbid conditions have not been well-controlled in studies.[32, 34, 35] One study in women with a low prevalence of intravenous drug use, however, found high levels of psychological distress and impaired quality of life in women with anti-HCV antibodies that did not correlate to the presence or absence of chronic infection.[36] In some adults with chronic HCV infection who are unaware of their status, the term "asymptomatic" may not be appropriate, as preliminary data suggest that some quality of life measures are lower than in age-matched controls.[37]

Definitions

This section summarizes terminology describing the tests used to identify patients with HCV infection, the results of these tests (Table 2), and the response to treatment. The Centers for Disease Control and Prevention has recently published detailed guidelines for laboratory testing and how to report results of anti-HCV and supplemental testing.[38]

Enzyme-linked immunoassay (ELISA) or enzyme immunoassay (EIA): ELISA (also referred to as EIA) detects antibodies against recombinant HCV antigens. "First generation" ELISA tests used a single antigen; later-generation tests added additional antigens.[39-41] Both second and third-generation tests are in standard use. Because of concerns about false-positive tests, particularly in low-prevalence populations (such as blood donors or asymptomatic adults), the CDC has recommended confirming positive ELISA results with a supplemental test (recombinant immunoblot assay or polymerase chain reaction), unless the signal-to-cut-off ratio is above a pre-determined threshold that has been shown to confirm positive >95% of the time.[38]

ELISA are the least expensive diagnostic test for HCV infection, with an average charge of about $60.00.[42]

Recombinant immunoblot assay (RIBA): RIBA is a supplemental test that also detects antibodies against HCV antigens. In these assays, multiple HCV antigens are individually displayed on a nitrocellulose strip as bands. Positive RIBA results have at least two reactive bands; indeterminate results have one reactive band. Because positive RIBA results require reactivity to more than one HCV antigen, they are considered more specific (but not more sensitive) than ELISA for past HCV infection, and are used to confirm positive ELISA results in low-prevalence populations.[42] However, RIBA is not an independent gold standard for ELISA because the two tests use similar antigens to detect anti-HCV antibodies.

Currently available third-generation RIBA are thought to be more specific than earlier-generation tests because they produce fewer indeterminate results.[43] The interpretation of indeterminate RIBA results remains uncertain.[38, 44, 45] The relative

proportion of RIBA-positive, indeterminate, and negative tests in ELISA-positive patients varies according to the population studied.

RIBA is typically 2-3 times more expensive than ELISA and usual charges are about $140.00.[42]

Reverse transcription polymerase chain reaction (RT-PCR or PCR): PCR is a laboratory method used to detect circulating HCV RNA in blood. PCR can be quantitative or qualitative, and under optimal conditions qualitative PCR can detect 100 international units (IU)/mL or less of circulating virus.[42, 46] Because the absence of viremia in anti-HCV-antibody positive patients is associated with little or no risk for HCV infectivity[47] or complications related to chronic HCV infection, sustained PCR-detected viremia has become the gold standard for chronic HCV infection.[29, 33, 48-50] In patients who are PCR-positive, the degree of viremia correlates poorly with degree of liver damage,[50-54] though it may help predict the likelihood of response to treatment.[55]

Strict quality control is necessary for PCR testing to be reliable. False negative test results can occur because some patients with active infection have intermittent viremia, and a small portion of patients with chronic HCV infection can become non-viremic, particularly with the development of liver cancer.[56 57, 58] For this reason, repeat PCR resting is suggested in high-risk patients who are anti-HCV antibody-positive but negative on initial PCR. False-positive PCR tests may also occur due to contamination of samples (11% in one early quality control study) but appear to be much less frequent since standardization of assay techniques.[57]

PCR testing is associated with charges of about $130.00 for a qualitative test and $200.00 for a quantitative test.[42]

"False-positive" ELISA: Patients who are ELISA-positive but RIBA-negative or RIBA- and PCR-negative are usually considered "false-positives"; i.e., no evidence of past or current HCV infection. False positive ELISA results may occur in patients with autoimmune diseases and in neonates born to mothers with chronic HCV infection, who frequently pass on antibodies to their neonates but usually do not pass the virus.[42, 46]

"False-negative" ELISA: Patients who are ELISA-negative but PCR-positive are usually considered "false-negatives." False-negatives are probably most common very early after infection (6-8 weeks for third-generation-ELISA to become positive versus 2-3 weeks for PCR) or in patients who have an impaired immune system.[42]

"Cleared" or "resolved" HCV infection: Patients who are ELISA- and RIBA-positive but PCR-negative on repeated testing are generally considered to have "cleared" or "resolved" HCV infection. This is usually not considered a "false-positive" finding because the positive RIBA test provides "specific" evidence of past exposure to HCV.[59] Patients who are ELISA-positive, RIBA-indeterminate (or not performed), and PCR-negative may be either false-positives or have cleared their HCV infection. The proportion of positive tests that are false-positive is higher in low prevalence settings.[60, 61]

"Chronic" or "active" HCV infection: Patients who are persistently PCR-positive are said to have chronic HCV infection. Chronic infection may present with or without symptoms, abnormal transaminase levels, or abnormal biopsy findings. In this review, the term "asymptomatic chronic HCV infection" refers to patients who report no symptoms of HCV infection. Like symptomatic patients, asymptomatic patients may or may not have abnormal biopsies or transaminases.

Liver biopsy results: The Histologic Activity Index (HAI) is used to grade histologic findings. The Knodell score and the METAVIR scoring system are common methods used to report the HAI.[62, 63] The Knodell score is a semiquantitative scoring system in which fibrosis and portal, periportal, and lobular necrotic and inflammatory components are assessed separately and their coding values added. Total maximum scores vary depending on exactly how the scores are totaled.[64] The METAVIR system reports both the inflammatory and the fibrosis scores using separate standardized scores for activity and fibrosis.[63]

Early responders (ER): Patients with HCV infection who receive treatment and clear their viremia (become undetectable by PCR) or have a significant response (usually defined as a 2-log drop in HCV RNA level) in the first few months of treatment are referred to as early responders. People who are not early responders (usually measured at 12 weeks of therapy) have a low chance of successful treatment and may not benefit from further therapy.[46] Normalization of transaminases (biochemical response) was reported in earlier trials of HCV treatment, but has been replaced by assessments of virologic status, which are thought to be more accurate predictors of successful treatment.

End of treatment responders (ETR): Patients with HCV infection who receive treatment, clear their viremia, and maintain this response until the end of treatment are referred to as end of treatment responders. Presence of HCV RNA at the end of treatment is highly predictive of relapse when therapy is stopped.[46]

Sustained responders (SR) or sustained virologic responders (SVR): Patients with HCV infection who receive treatment, clear their viremia, and maintain this response 6 to

12 months after the completion of treatment are referred to as sustained responders or sustained virologic responders (SVR).

Non-responders (NR): Patients with HCV infection who do not clear their viremia during treatment.

Relapsers: Patients with HCV infection who initially respond virologically to treatment but later suffer a recurrence of viremia.

Natural History

In this section, we review modes of acquisition of HCV, clinical presentations of chronic HCV infection, and risk factors associated with more rapid or frequent progression to cirrhosis and other long-term complications. We also review the literature regarding the natural history of chronic HCV, and when available we highlight data that appear more applicable to patients likely to be identified by screening.

HCV is acquired primarily by large or repeated percutaneous exposures to blood. In approximately 1/3 of patients, acute HCV infection causes symptomatic illness (primarily jaundice, nausea, right upper quadrant pain, or fatigue) after a mean incubation period of 7 weeks.[65] In other patients, acute HCV infection is anicteric and not associated with symptoms or transaminase elevations. HCV viremia is detectable in the blood within 2 weeks of acute infection.[65] In large population-based cross-sectional studies and good-quality cohort studies, 16%-45% of patients cleared acute HCV infection, as defined by sustained absence of HCV RNA in serum and normalization of transaminase levels.[8, 9, 18, 32, 33, 66] Chronic HCV infection is thought to be present in the other 55-84% of patients.

The natural course of chronic HCV infection varies widely. A proportion of patients with chronic HCV infection have only mild liver disease even after decades of infection or never develop histologic evidence of liver disease.[67] In other patients, inflammation and fibrosis of the liver may progress to cirrhosis, which can lead to end stage liver disease (ESLD) or hepatocellular carcinoma (HCC).[8, 68, 69] Once cirrhosis develops, patients have a much higher risk of death, and some may benefit from liver transplantation.

The strongest predictors of a progressive course of chronic HCV infection appear to be older age at acquisition,[51, 70] co-morbid medical conditions (such as heavy alcohol use,[70-76] HIV,[77, 78] and other chronic liver disease[79, 80]), and duration of infection. The mode of acquisition, viral load, transaminase level, and viral genotype have not been established as consistent predictors of disease progression, though some cross-sectional and longitudinal studies[81-85] have found associations.

Race and gender may also have some effect on the natural history of chronic HCV infection, though data are preliminary. African Americans have generally been under-represented in studies on the natural history of HCV infection, despite a higher prevalence of infection. One recent cross-sectional study, however, found less advanced liver disease in African Americans with chronic HCV infection compared to non-African Americans, despite a longer estimated duration of infection.[86] A systematic review of 57 studies on the natural history of HCV infection found that male gender was associated with more rapid disease progression.[70]

Estimating the proportion of patients in the general population with HCV infection who will progress to cirrhosis has been difficult because the time of acquisition

is rarely recognized, particularly in asymptomatic patients, and a long duration (decades) is required to track patients to important endpoints.[87] Factors affecting the rate of cirrhosis in a particular population include the prevalence of co-morbid conditions, the age at acquisition, the proportion receiving treatment, and whether the population was referred or community-based.[70] Most data on the natural history of HCV infection has been in referral populations, but community-based cohort studies appear to be more representative of the general population.

A systematic review of studies of HCV natural history included 57 of 145 identified studies, and divided them into four broad categories: liver clinic series (number of studies=33), posttransfusion cohorts (n=5), blood donor series (n=10), and community-based cohorts (n=9).[70] Estimates of the prevalence of cirrhosis after 20 years of chronic HCV were 22% (95% CI, 18-26%) for liver clinic series, 24% (11%-37%) for posttransfusion cohorts, 4% (1%-7%) for blood donor series, and 7% (4%-10%) for community-based cohorts. After accounting for age of acquisition, gender effects, and alcohol intake, estimates of cirrhosis were still substantially higher in liver clinic series, and were thought to be an effect of selection bias. The authors concluded that in the general population of patients who acquire HCV infection in young adulthood, less than 10% are estimated to develop cirrhosis within 20 years.

The systematic review included both cross-sectional and cohort community-based studies, and included studies that may not have accurately estimated the duration of infection. We reviewed in detail six retrospective cohort studies that identified HCV patients near the time they were first infected after a known exposure, and determined their outcome 10-45 years later (Table 3).[28, 29, 32, 33, 66, 88] Three of these studies[28, 29, 33]

were not included in the systematic review. We excluded retrospective cohorts[27, 89] in which patients were initially identified based on presentation with acute symptoms, in order to focus on more representative populations with both symptomatic and asymptomatic acute infection. We also did not review in detail two retrospective cohort studies of children who acquired HCV, since the natural history may be different in this population (cirrhosis 0% and 0.3% after 17-20 years).[30, 31] Most of the included studies evaluated patients who acquired HCV infection via exposure to infected blood products;[28, 29, 32, 33, 66] one screened acknowledged injection drug users for chronic HCV infection.[88] In two studies,[33, 66] about 10% of viremic patients received treatment for HCV infection; no patients were reported to have received treatment in the other studies. Two studies[32, 33] evaluated Irish women infected by contaminated anti-D immune globulin in 1977 and 1978 but treated in different centers; histopathologic findings in these populations were reported in two other studies.[90, 91] All of these studies were characterized by patients who contracted HCV infection while young and relatively healthy.

Cirrhosis was found in 0%[33] to 10%[28] of patients after at least 10 years of HCV infection (Table 3). Approximately 90% of patients had mild or moderate hepatitis, with fewer than 5% having higher grade histologic lesions without cirrhosis.[32, 33, 66, 88, 90, 91] In the study of intravenous drug users (currently the most common mode of acquisition), 2.4% (40/1667) had evidence of ESLD after a median of 15 years of infection; 1% (2/210) without ESLD had cirrhosis on biopsy.[88] One longitudinal study[91] that performed sequential biopsies found little evidence for progression of disease 2 years after initial biopsy, and another[33] reported that 22% (10/44) of patients had improvement in

inflammation on sequential biopsies 4 years apart, suggesting that chronic HCV could remain undetected for at least several years.

The retrospective cohort studies described above included both symptomatic and asymptomatic patients with HCV. We identified no cohort studies specifically of asymptomatic patients, a subgroup of HCV patients likely to be identified only by screening. A recent community-based, cross-sectional Italian study found 116 anti-HCV positive (85 viremic) patients in a population of 4,820 screened; 5% (4/78) of viremic patients had cirrhosis (fibrosis score F4) on liver biopy and 38% (20/78) had more than minimal fibrosis (F2-F4).[92] Other representative cross-sectional (i.e., uncertain duration of infection) studies of asymptomatic patients in the US and Europe reported prevalences of cirrhosis ranging from 0-9%.[3, 49, 85, 93-97]

We did not identify studies evaluating whether patients with untreated asymptomatic chronic HCV infection progress to symptomatic illness over time. Symptoms that could be related to HCV infection (primarily fatigue and arthralgias) were reported in over 80% of viremic women in one community-based study,[32] but another study in a similar population found symptoms reported more frequently in non-viremic rather than viremic patients.[33] We also did not identify studies evaluating how long patients unaware of their HCV status would remain undetected without screening.

In summary, it appears that few (10% or less) patients who acquire chronic HCV as young adults will progress to cirrhosis after 10-20 years of follow-up. There are no cohort studies specifically of patients with asymptomatic HCV infection, but cross-sectional studies have also found low rates of cirrhosis. The majority of patients now acquire HCV infection via injection drug use, but most data on natural history are from

patients who became infected from contaminated blood products. The most important predictors of progressive HCV infection appear to be older age at acquisition; longer duration of infection; and presence of co-morbid conditions such as alcohol use, HIV, or other liver disease.

Analytic Framework and Key Questions

The analytic framework in Figure 1 indicates the strategy we used to evaluate screening for HCV infection in adults without known or suspected liver disease or liver function test abnormalities. We defined universal screening to mean that everyone is tested, regardless of symptoms or risk factors; selective screening means that only those who meet specific criteria are tested. The key questions, which guided our literature review, were determined in conjunction with liaisons from the USPSTF.

The analytic framework shows the target populations, interventions, and intermediate and health outcome measures we examined. We narrowed the scope of the literature review after a preliminary search. We excluded children from the review because of the low prevalence of anti-HCV antibodies (0.2-0.4% in 6-19 years old)[9] and the unclear safety and efficacy of treatment in this population.[98] We also excluded pregnant women because of unclear safety of treatment and insufficient evidence regarding ability to lower vertical transmission rates (estimated at around 5% in mothers without HIV).[99-102] We excluded other specific populations such as post-transplant patients, HIV patients, and hemodialysis patients. In these patients, screening test characteristics and natural history of HCV infection may differ from what is observed in the general population.[78, 103-106] In addition, these populations have generally been excluded from large trials of treatment and data regarding clinical outcomes are lacking.

Patients with occupational exposures were also excluded because of clear consensus regarding screening after percutaneous exposures.[8]

Our review evaluated the screening strategy in which a later-generation HCV ELISA is the initial test, with confirmatory RIBA. These are the screening tests that are currently in standard use for the diagnosis of current or resolved HCV infection.[38] PCR testing, transaminase testing, and liver biopsy was considered the standard work-up to determine presence of chronic HCV infection and eligibility for treatment in patients who tested positive for anti-HCV antibodies.

For treatment of chronic HCV infection, we focused on evidence regarding efficacy and safety of pegylated interferon with ribavirin, the treatment regimen found in good-quality clinical trials and systematic reviews to have the highest efficacy. Because of the short duration that this treatment regimen has been available for evaluation, we also reviewed evidence regarding the effect of other interferon-based treatment regimens on long-term clinical outcomes. Ribavirin alone, amantadine, and corticosteroids were not included as they have not been found to be efficacious.[8, 68, 69]

For outcomes, we were particularly interested in reviewing any literature regarding the benefit of early antiviral treatment of chronic HCV in asymptomatic patients. Clinical outcomes that we evaluated were mortality, end-stage liver disease, cirrhosis, and hepatocellular cancer. Quality of life outcomes were also evaluated. Intermediate outcomes were loss of detectable viremia, improvement in histologic findings, and normalization of transaminase levels. We also reviewed adverse outcomes from screening and treatment including side effects from treatment, adverse events from liver biopsy, and effects of diagnosing chronic HCV infection on quality of life.

Other reasons for screening for HCV infection might be to prevent spread of the disease or to identify those who might benefit from hepatitis A or B vaccination, alcohol cessation counseling, or other interventions. We performed an additional literature search and review to identify potential benefits from screening from these types of interventions in patients with chronic HCV.

Chapter 2. Methods

Search Strategy

We searched the topic of HCV in the MEDLINE and Cochrane Library databases from 1989 (the year HCV was characterized) through July 2002, and searched updates of these databases through February 2003. We originally performed three MEDLINE searches, one for screening for HCV infection, one for work-up of HCV infection, and one for treatment of HCV infection. For screening, the medical subject headings (MeSH) *hepatitis C* and *hepacivirus* were combined with the terms *mass screening*, *hepatitis C antibodies*, *predictive value of tests*, and *sensitivity and specificity*, and the text words *antibody testing*. For work-up, the MeSH headings *hepatitis C* and *hepacivirus* were combined with the terms *ultrasonography*, *liver function tests*, *liver biopsy*, and *viral load*. For treatment, the MeSH headings *antiviral agents*, *interferons*, and *ribavarin* were combined with the terms *hepatitis C* and *hepacivirus*. We conducted a search for controlled studies of treatment of hepatitis C infection in the Cochrane Library databases, using the phrase *hepatitis C* in title, abstract, or keywords combined with terms for clinical trials. We retrieved the complete reference list from a recent Agency for Healthcare Research and Quality (AHRQ) evidence report commissioned by the National

Institutes of Health (NIH) to update their consensus statement on management of HCV infection.[107] Periodic hand searching of hepatology, gastroenterology, and major medical journals and review of the reference lists of retrieved articles supplemented the electronic searches.

We performed an additional MEDLINE search in February 2003 for other interventions (counseling on alcohol use, immunizations, and preventing spread of disease) in patients with HCV. For this search, we combined the MeSH headings *hepatitis C, hepacivirus,* or *hepatitis C, chronic* with the MeSH headings *patient education, counseling, alcohol drinking, viral hepatitis vaccines, hepatitis A,* or *vaccination.*

A single reader reviewed all English abstracts. Papers were selected for full review if they were about HCV infection, were relevant to key questions in the analytic framework, and met other key-question specific inclusion criteria (see below). Reviews, policy statements, and other papers with contextual value were also obtained from the searches. Studies published as abstracts were not included in the search; although pertinent abstracts may be referred to in the text they are not included in evidence tables.

Inclusion Criteria

For all key questions, articles were limited to those that evaluated the general adult population with chronic HCV infection. We excluded studies that only focused on patients with end-stage liver disease, cirrhosis, or hepatocellular cancer. Although the population of interest was asymptomatic adults with chronic HCV infection who would be identified by screening, we included studies of patients with a broad spectrum of chronic HCV disease in order to get a picture of the benefits and adverse effects of

screening and treatment in patients with different degrees of liver disease. Studies on HCV populations who had undergone transplantation were excluded, as were studies of pregnant patients, children, or those with end-stage renal disease or HIV. Studies of non-human subjects were also excluded, and studies had to include original data. Foreign language papers were considered if they were clinical trials and an abstract was available in English. We searched for relevant systematic reviews for all key questions.

For individual key questions, additional inclusion criteria were as follows:

For key question 1, articles were included if they were clinical trials or observational studies that evaluated clinical outcomes in patients screened and not screened for HCV infection.

For key question 2, we included large observational studies that used appropriate statistical methods to assess associations between various risk factors and the presence of HCV infection. Representative smaller observational studies were also reviewed.

For key questions 3a, 3b, and 4, we included observational studies and systematic reviews that evaluated third-generation ELISAs (the most recent generation) and used a credible, current reference standard (third-generation RIBA or PCR). We did not include studies that evaluated third-generation ELISA only in relationship to an earlier generation ELISA test or only performed the reference standard in "discordant" samples from two screening tests. We included large population-based observational studies that reported the positive predictive value of confirmatory third-generation RIBA for viremia following third-generation ELISA.

For key question 5a, we included studies that evaluated the ability of blood tests to predict liver biopsy results, and performed liver biopsy as the reference standard.

For key question 5b, we included clinical trials and observational studies that reported the number of patients referred or considered for HCV treatment after a positive HCV antibody test, and that also provided detailed information about the reasons patients were considered ineligible for treatment.

For key question 6, we included observational studies that reported complications from percutaneous liver biopsy specifically in patients with chronic HCV infection. We also included representative large higher-quality observational studies of complications from percutaneous liver biopsy performed for a variety of indications.

For key questions 7a and 7b, we included controlled trials of antiviral treatment that evaluated relevant intermediate or clinical outcomes in treatment naïve populations. We included studies that evaluated pegylated interferon with or without ribavirin versus another treatment or placebo, and studies that evaluated non-pegylated interferon plus ribavirin compared to interferon alone or placebo. For question 7b, controlled trials of non-pegylated interferon without ribavarin were also included if they had greater than 5 years of post-treatment follow-up and evaluated clinical or histologic outcomes. We reviewed clinical trials that were previously included in good-quality systematic reviews to insure accuracy and reproducibility of the findings of the systematic reviews.

For key question 7c, we included controlled trials and observational studies that evaluated the effectiveness of counseling and immunizations in patients with HCV for improving clinical outcomes related to hepatitis A or B infection, alcohol use, or preventing spread of disease.

For key question 8, we included controlled antiviral trials and observational studies that reported adverse events in treatment naïve populations. We included studies

of pegylated interferon with or without ribavirin versus another treatment or placebo, and studies of non-pegylated interferon plus ribavirin versus another treatment or placebo.

For key question 9 we included controlled antiviral trials and observational studies in which long-term outcomes were stratified by intermediate responses to treatment.

Data Extraction

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials and observational studies, which we rated as "good," "fair," or "poor." We also rated the applicability of each study to the population that would be identified by screening. The rating system was developed by the USPTF and is described in detail elsewhere.[108] For included trials and systematic reviews, we also abstracted information about setting, patients, interventions, and outcomes. For clinical trials, when possible we recorded the difference between the probability of a response in the treatment and control groups for each outcome studied. We evaluated the applicability of reviewed studies to the population likely to be identified by screening. We developed evidence tables for those key questions related to antiviral treatment of HCV infection (key questions 7a and 7b). We rated the overall body of evidence for each key question using the system developed by the USPTF.[108]

Chapter 3. Results

Arrow 1: Does screening for hepatitis C reduce the risk or rate of harm and premature death and disability?

We identified no randomized trials or observational studies comparing outcomes between patients in the general adult population or high-risk subpopulations screened and not screened for hepatitis C. Although blood donors are routinely screened for HCV infection in order to insure the safety of transfused blood products, we also searched for studies demonstrating improvement in clinical outcomes in volunteer blood donors screened versus those not screened, and found none.

Arrow 2: Can clinical or demographic characteristics identify a subgroup of asymptomatic patients at higher risk for HCV infection?

The identification of risk factors for HCV infection could aid in the development of selective screening strategies. This approach might save resources compared to universal screening because efforts are focused on individuals who would be most likely to benefit from testing and treatment.[16] The most frequently cited risk factors for HCV infection are intravenous drug use and high-risk sexual behaviors (variably defined, but usually considered sex with multiple partners or sex with someone with HCV).[8, 10, 69, 109, 110]

Data regarding risk factors for HCV infection in the United States are available from two large cross-sectional studies that performed multivariate analyses to assess

associations between various risk factors and anti-HCV-Ab status. One study, NHANES III (n=21,241), was a nationwide household-based sample conducted from 1988 to 1994 in which the prevalence of anti-HCV-Ab positivity was 1.8% overall, and 2.3% in adults >20 years old.[9] Among adults 20 to 49 years old, the prevalence in this study was 4.1% for males and 1.6% for females. The National Hepatitis Screening Survey (NHSS) (n=13,997) was a nationwide screening program in 40 mostly urban centers in September 1992 that found a higher prevalence of 7.0%, but was targeted at persons who were at risk for HCV.[111] Data are also available from two large European population-based studies, where the epidemiology of HCV may differ slightly compared to the US. The Dionysos (Italy) study (n=6,917) found rates of 3.2% for anti-HCV antibody and 2.3% for viremia,[112] and a French study (n=6,288) found rates of 1.2% and 0.9%. [18] All studies were performed prior to 1994, when many patients with transfusion-associated HCV infection were being identified.

Independent risk factors for HCV infection found in large population-based studies are shown in Table 4. Studies varied in the risk factors assessed. In all studies that assessed intravenous drug use, this was the strongest independent risk factor (adjusted odds ratios [OR], 18.4-29.2). Most studies found an independent association between some high-risk sexual behaviors and HCV infection. Other factors (gender, race, socioeconomic status) showed less consistent or weaker associations. The European studies found similar independent risk factors as the American studies.[18, 112]

In NHANES III, the strongest independent predictors of HCV positivity were illegal drug use (cocaine and marijuana use) and high-risk sexual behaviors in the absence of illegal drug use. Weaker independent predictors of HCV positivity were

marital status, income (above or below the poverty level), and education. Race, ethnic group, and gender did not have significant independent associations with infection. Because NHANES III did not ask specific questions about intravenous drug use, it was postulated that cocaine and marijuana use were surrogate markers for this behavior.

In the National Hepatitis Screening Survey, the strongest independent risk factor for anti-HCV-Ab positivity was intravenous drug use (adjusted OR, 23.34), followed by hemodialysis, sex with an intravenous drug user, a history of blood transfusion, and male gender (Table 4). White or Hispanic race was associated with a decreased risk (adjusted OR, 0.57) for HCV infection. History of sex with multiple partners and age were not associated with HCV infection.

The strong association between HCV infection and intravenous drug use is supported by findings from numerous smaller cross-sectional studies. Intravenous drug use was the strongest risk factor for HCV infection in a variety of settings including US veterans,[113, 114] incarcerated persons,[115, 116] street youths,[117] sexual partners of patients with HCV,[118, 119] pregnant women,[120] blood donors,[121, 122] and patients attending sexually transmitted diseases clinics.[123-125] Cross-sectional studies in intravenous drug users have reported prevalence rates ranging from 50 to over 90%.[10-13, 126] In addition to being highly prevalent, HCV infection may be associated with rapid spread in intravenous drug users, though estimates of incidence have been higher in cross-sectional than in longitudinal studies. In the US, a cross-sectional study of drug users who reported injecting for 1 year or less found a prevalence of anti-HCV antibodies of 65%,[127] but a longitudinal study[12] found a 30% rate of seroconversion after a median of 6.5 years. Differences in drug use behaviors could account for some of the variation in incidence

and prevalence; one study found that the rate of anti-HCV positivity was higher among intravenous drug users who shared needles (53%) than in all intravenous drug users (38%).[123]

Sexual contact with infected patients appears to be a less efficient mode of transmitting HCV than intravenous drug use, and the relative importance of sexual transmission remains controversial.[109] Despite numerous conflicting studies[118, 119, 128-142] about the precise role of sexual *transmission*, however, it is clear that after intravenous drug use, high-risk sexual behaviors are the most important risk *marker* for HCV infection. This is probably related to either a high rate of sexual transmission in specific situations (high viral load, specific genotype, presence of other sexually transmitted diseases, or other local factors)[128-132, 143] or because high-risk sexual behaviors are a marker for unacknowledged drug use or other risk factors. The rate of unacknowledged drug use is probably higher if risk factor ascertainment is less stringent or if there is a strong stigma against this behavior in the population studied.[109]

In addition to large population-based studies[9, 111, 112] that found independent associations between HCV infection and some high-risk sexual behaviors (Table 4), a widely quoted CDC case-control study in patients who had not had blood transfusion or admitted intravenous drug use within the preceding 6 months found that multiple sexual partners and history of hepatitis in household or sexual contacts were independent risk factors for acute NANB hepatitis.[144] In a follow-up CDC study of populations from the same sentinel county surveillance project, 15% of acute HCV cases between 1991 and 1995 reported high-risk sexual practices or exposures (sex with patient with HCV infection or sex with multiple partners) during the 6 months prior to illness in the absence

of intravenous drug use; of these 2/3 had a partner positive for HCV infection.[10] In most settings with a low prevalence of acknowledged intravenous drug use, high-risk sexual behaviors are the strongest risk factor for HCV infection.[145-147] The risk of sexual transmission of HCV from an infected individual in the US has been estimated at 0% to 0.6% per year for those in monogamous relationships, and 1% per year for those with multiple sexual partners.[143]

Other risk factors for HCV infection can be divided into percutaneous and non-percutaneous risk factors. Non-percutaneous risk factors are not associated with a plausible mechanism of transmission and are probably markers for unsolicited high-risk behaviors or high background prevalence of disease in the specified setting. Studies have not consistently shown independent associations between these risk factors and HCV infection. These risk factors include low socioeconomic status, non-injection drug use, alcohol use, male gender, age 40-59, and non-white race.[9, 111, 148] The higher prevalence of HCV infection in incarcerated, emergency room, urban, and veteran populations also appears related to the presence of other risk factors, particularly injection drug use.[113, 116, 149]

Percutaneous risk factors other than illegal drug use and high-risk sexual behaviors that are plausible modes of HCV transmission in the general population include transfusions, tattoos, body piercing, and sharing razors.[150] Recently, the relative importance of transfusions has declined, and since 1990, transfusions have not been an important mode of HCV transmission.[10, 151] There is insufficient evidence to determine whether tattoos, body piercing, or sharing razors are risk factors for HCV infection.[152] Some observational studies[153, 154] in selected populations in the US have found that

tattoos are an independent risk factor for HCV infection, while others[136, 155, 156] have not. CDC data indicate that less than 1% of patients with newly acquired HCV report recent tattoos; a large CDC study is currently underway to further investigate the association.[157] Data on other percutaneous exposures in the US are scant. A study in volunteer blood donors found an association between ear piercing among men (but not women), but this has not been confirmed in other studies.[136] A large French population-based study showed no association between acupuncture and HCV infection.[18]

Other populations with a higher prevalence of HCV infection in which percutaneous exposures may be an important mode of transmission include hemodialysis patients, children of mothers with HCV infection, patients with percutaneous occupational exposures, post-transplantation patients, and HIV-positive patients.[8, 158-163] These populations were outside the scope of this review.

We identified no study that applied a selective screening strategy in the general population and measured what proportion of infected patients was identified correctly. Studies that reported the proportion of HCV patients with identified risk factors have not prospectively validated their findings.[120, 164, 165] Cross-sectional studies from several settings, including CDC sentinel county surveillance data on acute hepatitis, the National Hepatitis Screening Survey, a population-based study in Olmstead County, and US Veterans Affairs screening programs, have found that between 33 and 81% of patients with HCV reported intravenous drug use.[9, 111, 113, 114, 166] CDC data indicate that in over 50% of cases, acute HCV infection was associated with injection drug use <6 months (43%) or >6 months (16%) prior to onset, an additional 5% were associated with snorting, and another 15-25% reported high-risk sexual behaviors in the absence of

injection drug use.[10] The epidemiology of acute HCV infection, however, may differ from the epidemiology of chronic HCV. In a post-hoc analysis of data from the National Hepatitis Screening Survey, which identified patients with chronic HCV, screening patients using one of three different risk factor models would have identified between 53%-69% of patients with HCV infection.[165] Another study found that only 12% of HCV-positive individuals had no admitted risk factor.[164] Factors that may explain some of the discrepancies between studies regarding rates of patients with no identified risk factors include population differences, varying stringency of risk factor ascertainment, or broadening what is included as an HCV risk factor (e.g., tattoos, broader sexual practices, or acupuncture).[164]

Arrow 3: What are the test characteristics of HCV antibody testing?

A recent fair-quality systematic review of third-generation ELISA and RIBA found that only 10 of 150 studies used appropriate methods for evaluating a diagnostic test[167] We applied the USPSTF quality criteria to nine of these 10 studies; all nine had at least one of the following flaws: narrow patient spectrum, reference standard not performed in all samples, or unclear if reference standard interpreted independently of screening test.[161, 168-172] The tenth, a study of RIBA in 51 patients on hemodialysis, was not referenced in the systematic review and we were unable to find it.

Of these 10 studies, seven evaluated sensitivity of third-generation ELISA (n=4,674) and 3 evaluated third-generation RIBA (n=359). The seven studies on ELISA were performed in blood donors, patients with chronic liver disease, hemodialyzed patients, or from panels of sera. When compared with the results of PCR (four studies) or

RIBA (three studies), the sensitivity of third-generation ELISA ranged from 97.2% to 100%. PCR is a reference standard for chronic infection and RIBA is a reference standard for exposure. When compared with the results of PCR (two studies), the sensitivity of third-generation RIBA was 80% and 100%, and when compared with the results of ELISA (one study), the sensitivity was 100%.

We identified three studies (one good-quality) not included in the systematic review that also evaluated the sensitivity of third-generation ELISA using PCR as the reference standard.[173-175] All of these studies reported similar findings as the systematic review, with sensitivities of 94-100% for third-generation ELISA compared to PCR. The good-quality study performed third-generation ELISA and PCR tests in 1,090 patients admitted for acute liver disease or suspected chronic hepatitis, and reported the lowest sensitivity at 94% (107/114).[173] One of the fair-quality studies evaluated the false-negative rate of third-generation ELISA in blood donors with elevated transaminases (thought to be higher risk for HCV infection) and found that no patients (0/247) had hepatitis C viremia on subsequent testing.[175]

We found extremely limited data regarding specificity of third-generation ELISA. In the systematic review cited above, specificity of third-generation ELISA was evaluated in three studies using PCR as the reference standard and one study using a combination of second-generation ELISA and RIBA as the reference standard. Because approximately 15-45% of patients who are ELISA- and RIBA-positive do not have evidence of viremia, we expected to find lower specificity in studies using PCR as the reference standard, unless the prevalence of HCV infection was very low in the population tested. In the systematic review, however, the specificity was 100% for both

types of studies (84/84 using PCR and 2,099/2,099 using second-generation ELISA/RIBA). In the good-quality study that was not included in the systematic review, specificity of ELISA was 97% (946/976) using PCR as the reference standard.[173]

Arrow 4: What is the false-positive rate and what are the harms associated with screening for hepatitis C virus?

In ione good-quality study of 1,090 patients admitted to the hospital for acute liver disease or suspected chronic hepatitis (prevalence of hepatitis C viremia 10%), the false positive rate of an ELISA test (without confirmatory RIBA) was 3% when PCR was used as the reference standard. The positive predictive value of third-generation ELISA (without confirmatory RIBA) was 78% (107/137).[173] Similar data from good-quality studies are not available for lower-prevalence populations, though for second-generation ELISA positive predictive values of 50-61% have been reported.[60]

Data on positive predictive values for viremia of a positive confirmatory third-generation RIBA following a positive ELISA test are available from two large population-based cross-sectional studies from France[18] and Italy, which may include a more applicable spectrum of patients and prevalence (1.2-3.2%) than the study cited above.[112] In these studies a positive confirmatory RIBA test was associated with a likelihood of viremia of 84-86%.

Some patients who have discrepant ELISA and PCR results might be "biological false positives" who have cleared their infection, while others are "analytic" false positives that, in the absence of past infection, have a positive ELISA due to cross-reactivity or another factor that reduces the specificity of the assay. Although all patients receive the "gold standard" test for active HCV infection before they are subjected to

invasive tests (i.e., biopsy) or potentially harmful antiviral treatments, false-positive results on third-generation ELISA can result in other harms (labeling, anxiety, effects on close relationships) that are difficult to measure. There are few data regarding potential harms in patients who have false-positive tests or in patients with true-positive tests that are ineligible for or decline treatment. In one small fair-quality cross-sectional report (n=34) of intravenous drug users with chronic HCV infection, those who were aware of their HCV status reported worse quality of life compared to those who were not aware of their status.[37] Another small (n=34) controlled trial, published only in abstract form, found that a brief counseling program helped improve sense of well-being in women diagnosed with HCV.[176] We found no other studies investigating whether harms associated with HCV screening could be reduced by effective patient education and counseling.[69, 177]

Arrow 5a: What are the test characteristics of the work-up for treatable disease?

A general work up for treatable chronic HCV disease includes PCR testing for viremia, transaminase levels, and liver biopsy. PCR testing is currently the only readily available method for determining active HCV infection in clinical practice. Pretreatment liver biopsy is currently recommended by the National Institutes of Health.[178-180] Several other blood tests, however, have been proposed as less invasive methods of predicting biopsy findings.

A good-quality systematic review recently evaluated studies of blood tests used to predict biopsy results.[181] None of these blood tests appeared to predict liver biopsy findings accurately. Transaminase levels are already routinely ordered in patients with

HCV infection and 15 studies evaluated their ability to predict biopsy findings. Elevated serum alanine aminotransferase (ALT) was associated with fibrosis in 11/15 studies, and had a sensitivity ranging from 61 to 76% and specificity from 44 to 66%. The AST/aspartate aminotransferate (ALT) ratio, a combination of two transaminase tests, had a sensitivity ranging from 31 to 56% and specificity of 90 to 100% for predicting cirrhosis. The systematic review found little information on the role of the AST/ALT ratio in predicting noncirrhotic stages of fibrosis. The systematic review also evaluated the ability of extracellular matrix tests, cytokines, and panels of five or more blood tests to predict the results of liver biopsy. These tests are not currently part of a standard work-up for treatable chronic HCV infection. The review found that extracellular matrix tests (hyaluronic acid and laminin) may have value in predicting fibrosis on liver biopsy, that cytokines have less value than the extracellular matrix tests, and that panels of tests may have the greatest value in predicting cirrhosis and the absence of more than minimal fibrosis. None of the tests were able to consistently classify intermediate stages of fibrosis.

We identified no study evaluating outcomes in patients receiving antiviral therapy who had pretreatment biopsy compared to those who did not undergo biopsy.

Arrow 5b: In patients found to be positive for hepatitis C antibody, what proportion of patients would qualify for antiviral treatment?

Antiviral therapy is recommended for patients with chronic HCV who are at the greatest risk for progression to cirrhosis. These persons have detectable HCV RNA,

often have persistently elevated transaminase levels, and have liver biopsy findings showing at least portal or bridging fibrosis or at least moderate degrees of inflammation and necrosis.[8, 68, 182-185] The proportion of patients identified by a screening program who would have clear indications for treatment based on biopsy findings is unclear but is probably lower than would be seen in patients sent to a referral center for treatment. Large-population-based studies have not systematically biopsied patients with chronic HCV infection, but in two cohort studies that included patients with asymptomatic disease, the number of patients with more than minimal inflammation on biopsy (HAI score >4) was 39-56%.[32, 33]

Treatment is not appropriate for all patients with chronic HCV infection and evidence of more than minimal liver damage. Patients with decompensated cirrhosis are not treated with interferon-based therapies due to the risk of disease exacerbation. These patients, however, are likely to be identified without screening. Although patients with compensated cirrhosis can be considered for treatment, response rates might be lower than in patients without cirrhosis.[8, 69] Patients with active alcohol abuse or ongoing illicit drug use are usually not treated until these behaviors have been discontinued for 6 or more months, although new recommendations suggest treatment may be offered in conjunction with substance abuse therapy.[8, 182] In addition, patients with serious medical or psychological comorbidities may not be appropriate for treatment due to the serious side effects of current therapies.

In clinical practice, the number of patients who are referred for evaluation and receive treatment will depend on the degree of liver damage, the presence of serious co-morbid conditions or contraindications to treatment, and patient preferences regarding

treatment. The clinical trials that we reviewed provided insufficient information about the numbers of persons with anti-HCV antibodies screened, eligible, and enrolled, and the reasons persons were ineligible for treatment. We identified four observational studies that evaluated the number of patients referred for HCV infection who were eligible for and received treatment.[186-189] One study was excluded from further review because it did not define reasons for ineligibility or report numbers of patients ineligible for different reasons.[189] This study reported high rates of loss to follow-up (39%) after initial evaluation and in those patients who did follow up, a high proportion of patients declined treatment (42%), though reasons were not specified.[189] Of the 3 included studies, 2 (n=557 and 100) were performed in Veterans Affairs centers[186, 187] and one in a general liver teaching clinic (n=327).[188] Because all studies were in patients referred for treatment, these studies may overestimate the proportion of treatment-eligible patients who would be identified by screening. Two of the studies included a small proportion (10%) of patients without viremia.[187, 188] Patients were ineligible for treatment if they had psychiatric disease, active alcohol or drug abuse, or significant medical comorbidities. Other reasons for ineligibility varied between studies but included the presence of normal transaminases or nonadherence to the evaluation protocol. These studies generally considered patients with milder forms of liver disease ineligible for treatment.

In all three included observational studies, approximately 30-40% of evaluated patients were eligible for therapy and received treatment. Demographic characteristics did not predict ineligibility in one study.[187] Common reasons for ineligibility were ongoing substance abuse (13-44%) and serious co-morbid medical or psychiatric conditions (12-34%). Non-compliance with the evaluation protocol was the most

important reason for ineligibility in one study (37%).[188] Decompensated cirrhosis was an uncommon (1%) reason for ineligibility. About 10% of patients declined therapy in one study.[188] Findings appeared similar in the VA and non-VA studies.

In patients with chronic HCV infection who have minimal or no biopsy abnormalities, indications for treatment are not clear, and the decision for therapy is individualized.[68, 69, 150, 190] Many patients identified by screening are likely to be in this category. Information on the proportion of HCV patients with milder liver disease that might be identified by screening is available from community-based cohort studies and population-based cross-sectional studies. In three community-based cohort studies, the rate of chronic hepatitis of minimal grade or no inflammation (HAI score 0-3 or 0-4) was 43-61%.[32, 33, 66] In population-based studies, between one-third to one-half of patients with hepatitis C viremia had normal transaminases in population-based studies.[18, 111, 112] Biopsies were not performed systematically in these studies, but a review of 15 smaller cross-sectional studies of liver biopsies in patients with normal transaminases found 20% had a normal liver, 4% minimal chronic hepatitis, 52% mild chronic hepatitis, 23% moderate-severe chronic hepatitis, and 1.3% cirrhosis.[67]

Arrow 6: What are the harms associated with the work-up for active HCV disease?

In the work-up of patients with chronic HCV infection, percutaneous liver biopsy is the most invasive diagnostic procedure and associated with the highest risk of complications. The remainder of the work-up is non-invasive and does not appear associated with major complications, although other difficult-to-measure harms such as anxiety probably occur. Percutaneous liver biopsy can be performed "blind" or using

ultrasound guidance, and is generally an outpatient procedure with post-biopsy observation for 4-6 hours.[191] Patients who are at high risk for bleeding are generally excluded from the procedure.[192] The most common complication of percutaneous liver biopsy is pain, with around 30% of patients requiring strong analgesic medications following the procedure.[192] More serious but less common complications include bleeding, the most frequent major complication, and biliary rupture, intestinal perforation, vasovagal hypotension, or infection. There are no standardized definitions for major complications from percutaneous liver biopsy.

Most data on risks of percutaneous liver biopsy come from large series of patients undergoing liver biopsy for a variety of reasons.[191, 193-197] Recent smaller studies have evaluated the risks of percutaneous liver biopsy specifically in patients with HCV infection, including suspected cirrhosis.[198, 199] No study on percutaneous liver biopsies specifically examines asymptomatic patients with chronic HCV, who may be at lower risk for complications. Clinical trials on treatment of HCV have typically randomized patients after percutaneous biopsy and do not report biopsy complication rates.

Of the studies examining large series of patients biopsied for a variety of indications, the study which appears to be of highest quality evaluated consecutive percutaneous liver biopsies in a nationwide sample of the United Kingdom using a standard form to assess for major complications.[195] This was the only study that used independent assessment to ascertain complications. A bleeding rate of 26/1,500 (1.7%) was found, with 11/1,500 (0.7%) requiring transfusion. Death was definitely associated with liver biopsy in 2/1,500 patients and possibly in another three, giving a mortality rate of 0.13-0.33%. This report may overestimate the risk of percutaneous biopsy in

asymptomatic patients with chronic HCV, because the indication in over one third of the patients was primary or secondary malignancy, conditions that are associated with substantially higher complication rates.[197] The rates of major complications reported in this study are comparable to other large series, which reported rates of 0-3.7%.[191, 194, 200] Mortality rates in other large series have typically been <0.1%.

Two small studies (n=126 and 166) have reported complication rates from percutaneous biopsy in patients specifically with HCV infection.[198, 199] In both studies, no episodes of bleeding, perforation, or death were reported. Both studies included patients with known or suspected cirrhosis.

Small studies and trials suggest that ultrasound-guided biopsies may be associated with fewer complications than blind biopsies, including bleeding and pain.[199-203] Several studies have found that increased experience of the person performing the liver biopsy was associated with less risk of complications.

Arrow 7a: How well does antiviral treatment reduce the rate of viremia, improve transaminase levels, and improve histology?

Important clinical outcomes of treatment for chronic HCV infection include reduction in mortality, cirrhosis, and hepatocellular carcinoma, and improvement in quality of life. Because of the large numbers of patients and long duration required to demonstrate improvements in most of these outcomes, intermediate outcomes have been the most common measure of treatment benefit. Measured intermediate outcomes include normalization of liver enzymes, loss of detectable viremia, and improvement in

liver biopsy findings. Sustained virologic response rates are currently considered the best indication of successful treatment.

Antiviral treatment for non-A, non-B hepatitis began in 1986 with the use of interferon-alfa.[204] A meta-analysis of trials of interferon monotherapy versus placebo found a summary sustained biochemical response rate of 21% (95% CI, 13-28%) with 12-month courses of treatment versus 2% in controls.[205] Other meta-analyses have reported sustained virological response rates of 6-16% for interferon monotherapy.[206-208] This treatment was considered the standard of care for chronic HCV infection until 1998, when combination interferon plus ribavirin was approved as first line treatment.[8, 209] Treatment with pegylated interferon, alone or in combination with ribavirin has been used for only a few years.[182]

Three recent good-quality systematic reviews evaluated the effect of newer treatment regimens on intermediate outcomes.[206-208] One[207] evaluated the data for pegylated interferon alone or with ribavirin; all 3 evaluated data for non-pegylated interferon plus ribavirin.

The systematic review of the pegylated interferon literature identified three randomized controlled trials (RCTs) that compared pegylated interferon plus ribavirin to pegylated interferon alone. The review concluded there was grade A evidence that pegylated interferon plus ribavirin was superior to pegylated interferon alone for intermediate outcomes.[207] The review also concluded that there was grade A evidence from four RCTs that pegylated interferon alone was superior to regular interferon alone for intermediate outcomes.[207]

We independently reviewed trials of pegylated interferon plus ribavirin and for pegylated interferon monotherapy. One RCT only available as an abstract when the systematic review was written has since been published with full data.[210] The 3 RCTs are summarized in Evidence Table 1a and 1b. Two[210, 211] were large (n=1121 and 1530), multi-center, good quality RCTs and the other was a small (n=72), fair quality, dose-finding study.[212] All three studies compared pegylated interferon plus ribavirin to pegylated interferon alone. One RCT also compared pegylated interferon plus ribavirin to non-pegylated interferon plus ribavirin.[210] Treatment was for 24 to 48 weeks with a 24-week follow-up period. Patients with significant other medical or psychiatric problems, other sources of liver disease, HIV, end-stage liver disease, or active substance abuse were excluded.

The two good-quality trials found that 54% to 56% of all patients achieved a SVR with pegylated interferon plus ribavirin versus 44% to 47% with pegylated interferon alone ($p<=0.01$) using comparable dosage regimens.[210, 211] Patients with HCV genotype 1 responded more poorly (42% to 46% SVR) compared to genotypes 2 and 3 (76% to 82% SVR). In the fair-quality study, combination pegylated interferon plus ribavirin achieved a 60% SVR versus 42% with pegylated interferon alone (significance not reported), in the highest dose treatment groups.[212] Histologic outcomes were not evaluated in one trial;[210] in the other RCTs, all treatment groups demonstrated improvement in inflammation and fibrosis, but there was no significant difference between treatment arms in histologic outcomes.[211, 212]

One RCT also compared pegylated interferon plus ribavirin to non-pegylated interferon plus ribavirin.[210] In this trial, 56% of patients achieved a SVR with pegylated

interferon plus ribavirin versus 44% of patients with non-pegylated interferon plus ribavirin ($p<0.001$).

We identified the same 4 RCTs evaluating the efficacy of pegylated interferon versus non-pegylated interferon monotherapy in treatment naïve patients as the systematic review.[213-216] Data from these studies are summarized in Evidence Tables 1a and 1b. Treatment was for 48 weeks with a 24-week follow-up period in all of these studies. Inclusion and exclusion criteria were similar to the combination pegylated interferon and ribavirin studies. Each of these studies found that a greater percentage of patients achieved a SVR when treated with pegylated interferon monotherapy. The percentage of patients responding ranged from 25%[214] to 39%.[216] All of the studies also evaluated histologic responses to treatment. Between 44% and 70% of patients had histologic improvement with pegylated interferon monotherapy, but the difference between treatments was significant in only one of the studies.[213]

The three systematic reviews that evaluated interferon plus ribavirin in treatment-naïve chronic HCV patients are summarized in Evidence Table 2.[206-208] The most recent systematic review contained trials published through March 2002.[207] Each systematic review concluded that there was good evidence that there is an increased response rate for interferon-alfa plus ribavirin versus interferon alone. In one review, the relative risk of SVR was 0.75 (95% CI, 0.65-0.79) with interferon monotherapy compared to interferon plus ribavirin.[206] Another systematic review found a SVR of 33% for patients treated for 24 weeks and 41% for 48 weeks with combination therapy compared to 6% and 16% for patients with monotherapy ($p<0.05$).[208] The summary relative risk of achieving a SVR was calculated to be 4.90 (95% CI, 2.63-9.13).[208]

Table 5 summarizes the relative effects of each of the reviewed treatments. Newer combination treatments with higher-dose pegylated interferon plus ribavirin appeared superior to older combination treatments in two good-quality randomized trials, with a sustained response rate of 54% to 56%, compared to a historical sustained response rate of 2% in untreated patients in placebo-controlled trials. The number needed to treat with newer combination treatments to achieve one sustained response appears to be a little under 2 patients.

Treatment studies may not be directly applicable to the population that would be identified by screening because they evaluated patients referred for treatment who probably had more serious disease. In studies evaluating pegylated interferon, for example, 6[210, 211, 213-216] out of 7[212] used elevated transaminases as an inclusion criterion. It is difficult to further assess the applicability of treatment studies to the screening population because biopsy findings and numbers screened were not consistently reported. In trials that reported these data, mean HAI and fibrosis scores ranged from 1.5-13.4 and 1.3-5.0, and were generally higher than biopsy scores reported in cohorts that included asymptomatic patients.[107] Even if treatment is equally effective for virologic endpoints in patients identified by screening and those studied in clinical trials, the overall clinical benefit would be expected to be smaller since the underlying progression rate is lower.

Arrow 7b: How well does antiviral treatment improve health outcomes in asymptomatic patients with hepatitis C?

Several factors complicate our ability to assess the long-term benefits of treatment of HCV, including the long duration for important complications to develop and the relatively short time period that treatments have been available. There is no data showing long-term benefits after treatment with pegylated interferon, alone or in combination with ribavirin, due to the relatively recent introduction of pegylated interferon.

One recent good quality systematic review evaluated the long-term effects of non-pegylated interferon alone on chronic HCV. This review identified three RCTs and 14 cohort studies.[207] An additional 23 studies were also reviewed that assessed the natural history of HCV infection in persons without treatment. The studies reviewed were heterogeneous in design and had some methodological limitations (selection bias, variable lengths of follow-up, variable baseline rates of cirrhosis, little description of the untreated population, and variable alcohol consumption). Nonetheless, included studies were consistent in suggesting that treatment with standard interferon-based therapy produced a moderate decrease in the risk of hepatocellular cancer and cirrhosis in complete responders (persons with both a SBR and SVR). The review also concluded that there was some evidence that persons with a SBR also had a decreased risk of HCC and progression of liver disease compared to untreated patients. The data were inconsistent regarding the long-term impact of treatment on non-responders and relapsers: one long-term randomized controlled trial suggested that all patients treated with standard interferon, regardless of response, derived long-term benefit; other studies suggested that relapsers but not nonresponders may derive some long-term benefit from standard interferon therapy.

We independently reviewed the three RCTs that provided long-term outcomes data after treatment with interferon-alfa monotherapy. These studies are summarized in Evidence Tables 3a and 3b. In an unblinded, good-quality Japanese trial of 90 patients randomized to interferon-alfa for 24 weeks or to symptomatic treatment, after 8.7 years there was a significant long-term reduction in the rate of developing HCC (27% vs. 73%, $p<0.0001$) and in mortality (11% vs. 58%, $p<0.001$).[217] Cirrhosis was also decreased in the treatment group. Rates of cirrhosis, HCC, and mortality were much higher in this study than in studies in US and European populations. The relative risk of progressing to Child B cirrhosis was 0.230 (0.120-0.505) in the treatment versus the control groups.[217]

In the two other RCTs, both from Italy, 61 and 149 patients were followed for up to 5 to 6 years after randomization to treatment with either interferon-alfa or interferon-beta.[218, 219] No significant differences in long-term outcomes were seen, but one study evaluated interferon-beta[219] which has since been found to be less effective than interferon-alfa,[220, 221] and the other compared two doses of interferon-alfa to each other rather than to placebo.[218]

Long-term outcomes data for combination interferon plus ribavirin versus interferon monotherapy are not yet available. Available trials are characterized by a short duration of follow-up in a relatively young study population without cirrhosis or alcohol use. As a result, very few serious morbidities or deaths have occurred. The best data at this time come from a good quality systematic review which found that out of 6,585 patients in 48 trials, only patients patients on combination therapy and 12 on interferon monotherapy had developed histological cirrhosis (none developed clinical cirrhosis); in addition only one case of hepatocellular cancer had occurred, three deaths (one suicide

and two accidental), and no transplants.[206] There was no significant difference in liver related morbidity plus all-cause mortality after treatment with combination therapy as compared to interferon (Peto odds ratio 0.45; 95% CI, 0.19-1.06, Peto odds ratio 0.29; 95% CI, 0.04-2.10, respectively).

Quality of life outcomes have been evaluated in one randomized controlled trial of treatment-naïve patients that analyzed results according to treatment received.[222] Other clinical trials evaluating quality of life outcomes stratified results according to whether sustained virologic response occurred and are reviewed later (Arrow 9). In the trial that evaluated quality of life outcomes according to randomization group, 160 patients randomized to interferon monotherapy (n=106) or placebo (n=54) for 24 weeks were evaluated with the Sickness Impact Profile (SIP) at baseline, at the end of treatment, and 24 weeks post-treatment.[222] This study was rated poor-quality because SIP results were only available at the end of treatment for 53/106 patients randomized to interferon, baseline SIP scores appeared significantly different between treated and untreated patients, and it was unclear whether patients were blinded to viral or biochemical markers of response to treatment. Patients randomized to interferon had no significant change in total SIP score compared to baseline but did have significant improvements in 3 out of 7 domains.

The single RCT showing significantly improved long-term outcomes after interferon monotherapy was conducted in Japan.[217] Many of the cohort studies evaluating long-term outcomes have also been performed in Japan.[107] There is evidence that severe complications from HCV infection including cirrhosis and hepatocellular cancer are substantially more common in Japan.[223] Though the reason for this is unclear,

it may be related to differences in genotype, longer duration that HCV infection has been present in the country, or co-existing liver disease, including chronic hepatitis B infection. The results of these studies may not be applicable to populations screened in the United States and Europe. Cohort studies that include patients with asymptomatic infection in these settings have shown lower rates of HCC and mortality. In one study in the UK, the rate of HCC was 0.1% and the mortality rate 14% after 10 years, compared to 73% and 58% after 8.7 years in the Japanese RCT reporting improved long-term outcomes.[28, 217] In a US study the mortality rate was 41% after 45 years.[29]

Arrow 7c: How well do counseling and immunizations in asymptomatic patients with hepatitis C improve clinical outcomes or prevent spread of disease?

Asymptomatic patients with HCV infection identified through a screening program could benefit from interventions other than antiviral treatment, including counseling to avoid excess alcohol and to obtain immunizations for hepatitis A (HAV) or hepatitis B (HBV).[177] In addition, counseling patients on avoiding high-risk behaviors might help prevent spread of HCV and result in significant public health benefits.[152] All patients with viremia could benefit from these interventions.

We identified no studies evaluating the effect of counseling regarding HAV vaccinations after diagnosis of HCV on subsequent clinical outcomes. In a US study, hepatitis A vaccination resulted in a satisfactory immune response after a 2-dose regimen in >90% of patients with HCV.[224] Reactions to hepatitis A vaccinations appeared mild and self-limited, and no serious adverse events were reported. The incidence of

fulminant co-infection with HAV and HCV in the US is difficult to estimate. In a widely-publicized Italian study, 17/432 patients with HCV acquired HAV over a 7-year period, with 7/17 (43%) having a fulminant course and 6/17 (33%) dying.[225] Other studies, including other Italian studies from the same time period, have reported much lower rates of fulminant hepatitis and death from HAV coinfection, and the discrepancy remains unexplained.[226, 227] In the US, the CDC reported that between 1983 and 1988, 107 fatalities from HAV occurred in 2,311 patients (4.6%) with underlying chronic liver disease from different conditions, compared to 247/113,009 (0.2%) without chronic liver disease.[224] It is not clear how many of the deaths were associated with HCV infection, nor how many patients with HCV infection developed fulminant HAV coinfection while unaware of their status. We did not review several cost-effective analyses of HAV vaccination in patients with HCV.[228-230]

We identified no studies evaluating the effect of counseling regarding HBV vaccination after diagnosis of HCV on subsequent clinical outcomes. HBV and HCV coinfection is associated with more progressive disease and worse outcomes than HCV infection alone. In a widely publicized US study, HBV vaccination resulted in high rates of protective seroconversion (up to 100%) in patients with HCV infection, and appeared well-tolerated.[224] Because HBV and HCV are transmitted by similar routes, some patients diagnosed with HCV will have already been exposed to HBV. We did not identify studies estimating how many patients with HCV acquired HBV after becoming aware of their status.

We identified no studies evaluating the effect of counseling regarding alcohol consumption after diagnosis of HCV on subsequent clinical outcomes. We identified one

French observational study that retrospectively asked patients to compare their use of alcohol prior to diagnosis with HCV to current use.[231] This study found that out of 25 patients who reported 'excessive' alcohol consumption prior to HCV diagnosis, 9/25 had become completely abstinent and 14/25 had cut back to 'moderate' intake. The results of this study may have been affected by recall bias or unwillingness to admit to current heavy alcohol use.

We identified one US study evaluating changes in behavior after diagnosis of HCV in young injection drug users.[232] In this study, there were no significant differences between patients aware of their HCV status and intravenous drug users without HCV or unaware of their positive status with regard to high-risk behaviors including sharing needles and syringes. We identified no other studies evaluating changes in high-risk behaviors following diagnosis of HCV infection, nor any studies that estimated the risk of spreading HCV in patients aware of their status compared to patients unaware of their status.

Although simply being diagnosed with HCV could alter behaviors without any specific intervention, we identified no studies evaluating differences in rates of serious hepatitis A or B coinfection, complications from excess alcohol use, or decreased spread of infection between patients with HCV aware of their status compared to those not aware.

Arrow 8: What are the harms (including intolerance to treatment) associated with antiviral treatment?

Interferon monotherapy is associated with significant adverse effects. In a good-quality systematic review of 21 studies, interferon monotherapy was associated with

significant adverse effects (many dose-dependent) including flulike syndrome (41-76%), alopecia (16-19%), thyroid disease (2%), depression (7-10%), thrombocytopenia (4-8%), leukopenia (9-13%), stopping treatment (4-5%), and dose decreases (9-22%).[205] Serious or life-threatening side effects occurred in 1-2% of patients. Some trials have reported side effects that result in discontinuation of treatment in up to 15% of patients.[68] Because of the long duration of most interferon treatment regimens (6 months) these adverse effects can have significant (though usually self-limited) impacts on quality of life.

Two systematic reviews evaluated the adverse events with non-pegylated interferon monotherapy versus non-pegylated monotherapy plus ribavirin combination therapy.[206, 208] These results are presented in Evidence Table 2. Both reviews found the risk of treatment discontinuation and dose reduction were greater with combination therapy than with interferon alone. Approximately 21% of persons receiving interferon plus ribavirin discontinued treatment compared to 8% of those on interferon monotherapy.[208] Approximately 26% of persons receiving combination therapy reduced their treatment dose as compared to 9% on monotherapy.[208] Other adverse events were also more common, including anemia, cough, dyspepsia, dyspnea, leukopenia, pharyngitis, and pruritus, with as many as 67% of persons on combination therapy experiencing at least one adverse event.[208]

We identified four RCTs that compared adverse events in pegylated versus non-pegylated interferon monotherapy. These studies are summarized in table 1a and 1b. In all 4 studies, adverse events occurred at similar rates in the two treatment groups.[213-216] The most commonly reported events were fatigue, headache, myalgias, rigors, and fever.

The rates of injection site reactions and depression were higher in the pegylated interferon groups in 3 of the 4 studies. No deaths occurred as a result of therapy.

We identified three RCTs that provided data about adverse effects associated with pegylated interferon plus ribavirin versus pegylated interferon monotherapy.[210-212] These results are summarized in Evidence Table 1a. In all of the studies, adverse events were reported at similar rates in both groups. Between 50% and 60% of study subjects experienced some adverse events, but these were usually mild and self-limited. In the two large, good-quality trials, the most frequent adverse events were myalgias (42-56%), fatigue (54-64%), headache (47-62%), and fever (43-46%).[210, 211] Psychiatric (depression 22-31%), gastrointestinal and dermatological problems were also common. In studies that evaluated different doses of pegylated interferon and ribavirin, flu-like symptoms, headache, and asthenia increased with increasing medication doses in all treatment groups. None of the studies noted any new or unusual adverse events, nor did any serious complications or deaths occur as a result of treatment. Mild, self-limited hematologic abnormalities (decrease in hemoglobin) were noted more frequently in the combination therapy group in one study.[212] Fever, nausea, injection site reactions, and dose reductions were more common with combination therapy than with pegylated interferon monotherapy in one trial, but dose discontinuation rates were not different between groups in either study.[211] In the large, good-quality studies, the withdrawal rates on pegylated interferon plus ribavirin therapy were 14% and 22%.

In summary, the majority of patients taking interferon-based therapies alone or in combination with ribavirin experienced adverse effects. Withdrawal rates on interferon monotherapy averaged 5%, and were higher at 10-20% on combination therapy. The

most common adverse effect was a flu-like syndrome. Serious adverse effects included depression that rarely led to suicide. The addition of ribavirin for combination therapy may increase the rate of mild hematologic side effects. The addition of pegylated interferon does not appear to significantly increase the risk of adverse events, though injection site reactions may be more frequent. Few major adverse events or deaths occurred with any of the treatments.

Arrow 9: Have improvements in intermediate outcomes (liver function tests, viral remission, histologic changes) been shown to reduce the risk or rate of harm from hepatitis C?

A recent good-quality, systematic review identified four cohort studies that examined the relationship between intermediate response to interferon treatment and long-term health outcomes.[207] These studies were heterogeneous in design and had methodologic limitations. Specifically, cohort studies are not ideal for addressing this question due to potential bias from underlying population differences. For example, patients who respond to treatment may have less serious disease than those who do not. This might be evident in pre-treatment ALT levels, HCV RNA levels and in histological differences. The systematic review did not provide information about clinical, demographic, or other differences in each treatment response group. The review concluded that the studies were somewhat consistent in suggesting a moderately decreased risk of HCC and cirrhosis in complete responders to treatment, and that there

might be a decreased risk of HCC and progression of liver disease associated with a biochemical response to treatment.

We identified one additional study in which long-term outcomes were stratified by the serologic response to interferon treatment. This was a large (1,643) retrospective cohort study from Japan of patients diagnosed with chronic HCV, 72.5% (1,191) of whom received interferon therapy.[233] Of those who received treatment, 38.7% (461) were complete responders (CR), 12.2% (145) were biochemical responders (BR) only, and 49.1% (585) were non-responders. Some demographic differences were observed between these groups: patients receiving interferon treatment were younger, less likely to drink alcohol, had higher ALT levels, and were less likely to have genotype 1. The main long-term outcomes were crude and adjusted hepatocellular cancer rates and 10-year survival. Patients were observed for a total of 22.8 years. At the end of 10 years, the crude hepatocellular rates were 1.5% (CR or BR), 14.9% (NR), and 12.4% (NT) ($p=0.0011$). Ten-year survival was 98.8% (treated) and 95.6% (no treatment) ($p<0.001$). Multivariate analysis of the hepatocellular cancer rate found a hazard ratio of 0.32 (0.13-0.78), ($p=0.012$) for CR plus IR versus no treatment after adjustment for other factors.

We identified four clinical trials of treatment-naïve patients with HCV infection that analyzed quality of life outcomes according to response to treatment.[222, 234-236] Of these, no study was rated good-quality; three were rated fair-quality (Evidence Table 4)[234-236] and one[222] poor-quality (see Arrow 7). In all studies, patients could have been aware of results of biochemical or virologic testing prior to repeating quality of life testing. In one fair-quality study, patients were only notified of viral load test results at the end of treatment after completing the quality of life questionnaire, though they may

have known the results of earlier tests.[234] In another fair-quality study, patients were blinded to viral load testing but could be aware of transaminase test results.[235]

All three fair-quality studies found improvements in health-related quality of life measures in sustained responders compared to non-responders (Table 6). In two studies, a significant difference between baseline and post-treatment SF-36 scores was found in 5 of 8[235] and 8 of 8 domains.[234] In the other study, an improvement of at least 2 standard deviations was seen in 7 of 8 SF-36 domains in responders compared to non-responders.[236] The range of significant differences between responders and non-responders in SF-36 domain scores was 7 to 22 in one study[235] and 3 to 10 in another[234] Some experts have suggested that a difference in scores of 3-5 points represents a minimally clinically important change and 10 points a moderately important change.[237, 238] In all three studies, the greatest difference in pre- and post-treatment scores was seen in the domain evaluating ability to perform physical roles. In the study in which patients were blinded to viral load results but not transaminase levels, subgroup analysis of patients with normalized transaminases found that sustained virologic responders reported improved quality of life scores compared to non-responders.[235] These trials had relatively short duration of follow-up (24-weeks post-treatment); we did not identify studies evaluating whether quality of life improvements in responders are sustained.

Conclusions

There is no direct evidence on benefits of screening for HCV infection in the general adult population. Other evidence obtained for the systematic review is summarized in Table 7. It indicates the type of study design and the quality of evidence

for each key question. Table 8 estimates the yield from screening in a hypothetical cohort of 1000 adults in the general population and in a high-risk (intravenous drug use) population, using the highest-quality and most applicable available evidence. We did not include areas in this table in which reliable data to estimate the magnitude of benefit or harm were not available (harm from false-positive screening tests, harm from labeling, benefit from counseling or immunizations, benefit from improvement in long-term clinical outcomes).

Future Research Priorities

In assessing the balance of benefits and harms from screening for HCV infection in the general population from indirect evidence, we highlight several areas of key uncertainties and areas for future research:

Natural history: Important gaps remain in our understanding of the natural history of untreated patients with HCV infection who are likely to be identified by screening. Recent studies in cohorts that identified patients by screening populations with known exposures appear to show that in most patients with long-standing chronic HCV infection, there is an indolent course. If this is true, screening will identify many patients with chronic HCV infection who would not benefit from treatments aimed at preventing progression to cirrhosis. If untreated chronic HCV infection leads to important morbidity in the absence of cirrhosis, there may be other important goals from treatment. Additional studies are needed to define the progression from asymptomatic to symptomatic HCV infection and how long symptomatic patients remain unidentified without screening.

Population screened: Reasonable screening strategies might be to screen all patients with acknowledged established risk factors, patients more likely to rapidly progress to serious disease (e.g., patients with alcohol abuse, older patients), all patients in specific settings with a high prevalence of HCV infection (e.g., incarcerated persons, urban populations, VA patients, homeless persons), or all patients in the general population. Studies that adequately assess the usefulness of risk factor assessment to guide selective screening strategies, or the harms and benefits of selective versus universal screening are needed. Little is known regarding patient preferences for screening.

Work-up: Although liver biopsy is the only accurate method to assess the histologic stage of HCV infection, there is some controversy regarding the necessity of pretreatment liver biopsy in all patients. Because liver biopsy is a potentially harmful invasive procedure, studies that evaluate the outcomes of patients who receive treatment without liver biopsies would be helpful in determining whether all or selected patients should undergo pretreatment biopsy.

Interventions: Trials evaluating intermediate and long-term outcomes of treatment for HCV infection have been in referral populations and may not be completely applicable to patients found on screening. Many studies showing improvement in long-term clinical outcomes have been conducted in Japan, where chronic HCV infection appears to follow a substantially more aggressive course. The case for screening would be greatly strengthened by data showing that treatment in earlier, asymptomatic stages of disease in Western countries is associated with improved outcomes compared to treatment that is reserved for patients who have become symptomatic and could be

identified without screening. Little is known about the benefits and risks of treatment in patients typically excluded from or under-represented in randomized trials (ongoing substance abuse, co-morbid conditions, the elderly, non-white race).[239]

Harms: Many patients with anti-HCV antibodies will either have no evidence of chronic infection or chronic HCV infection with disease that is too mild to qualify for treatment. No studies have adequately assessed the harmful impacts due to anxiety, labeling, or relationships with family and sexual partners that result from screening for HCV infection in these patients, and whether these harmful impacts can be minimized by appropriate counseling. The short-term adverse effects of interferon-based therapies must be balanced against potential long-term benefits in patients who are likely to be asymptomatic and may have low potential to progress to cirrhosis.

Outcomes: Although treatments are increasingly effective in improving intermediate outcomes of HCV infection, there is still only limited evidence that this leads to better clinical outcomes. Few studies have adequately assessed the impact of treatment on quality of life or symptoms, which may be a more relevant outcome for the majority of patients who are unlikely to develop cirrhosis. Studies assessing quality of life outcomes in an intention-to-treat format (rather than according to response to treatment) are also lacking.

Screening for chronic HCV infection may have importance not only in terms of individual clinical outcomes, but also as a public health measure. Screening might help identify patients who would benefit from counseling about alcohol use, hepatitis A and B vaccinations, or on ways to avoid spreading disease. Studies demonstrating important individual or public health benefits from counseling, immunizations, and behavioral

changes following a diagnosis of HCV in asymptomatic patients would greatly strengthen the case for screening.

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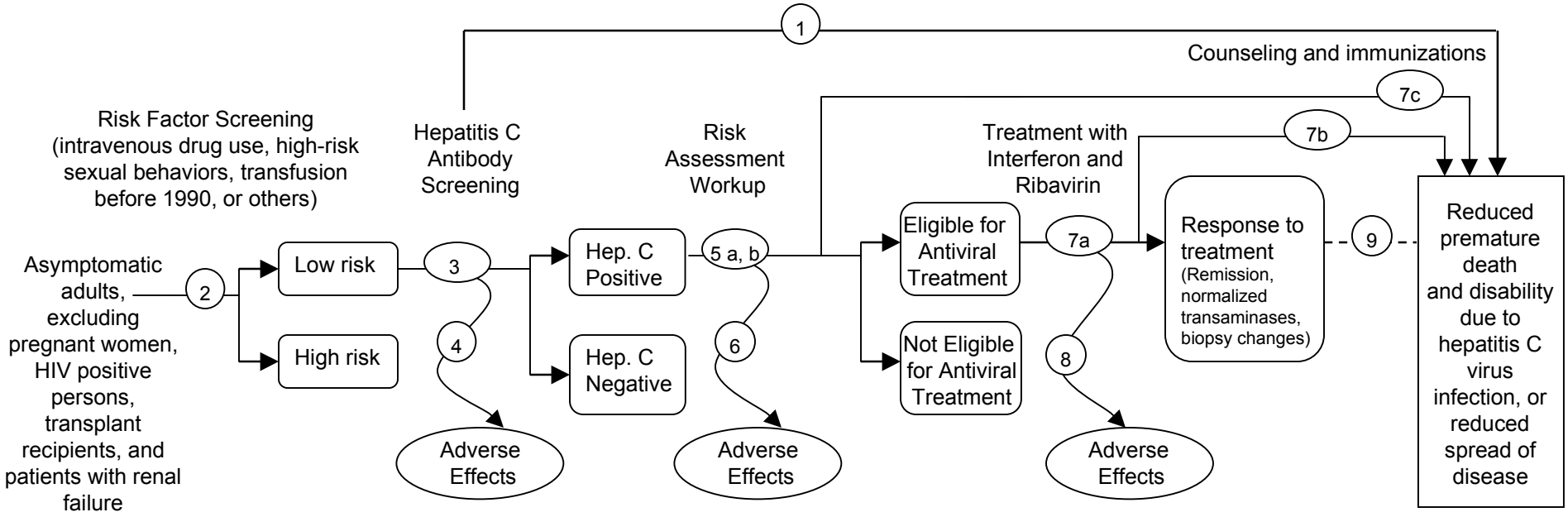
Figure 1. Screening for Hepatitis C: Analytic framework and key questions



Key Questions

Arrow 1: Does screening for hepatitis C reduce the risk or rates of harm and premature death and disability?

Arrow 2: Can clinical or demographic characteristics identify a subgroup of asymptomatic patients at higher risk for HCV infection?

Arrow 3: What are the test characteristics of hepatitis C virus antibody testing?

Arrow 4: What is the predictive value of a positive screening test and what are the harms associated with screening for hepatitis C virus?

Arrow 5: a) What are the test characteristics of the work-up for active disease?
b) In patients found to be positive for hepatitis C virus antibody, what proportion of patients would qualify for treatment?

Arrow 6: What are the harms associated with the work-up for active hepatitis C virus disease?

Arrow 7: a) How well does antiviral treatment reduce the rate of viremia, improve transaminase levels, and improve histology?
b) How well does antiviral treatment improve health outcomes in asymptomatic patients with hepatitis C?
c) How well do counseling and immunizations in asymptomatic patients with hepatitis C improve clinical outcomes or prevent spread of disease?

Arrow 8: What are the harms (including intolerance to treatment) associated with antiviral intervention?

Arrow 9: Have improvements in intermediate outcomes (liver function tests, remission, histologic changes) been shown to reduce the risk or rate of harm from hepatitis C?

Table 1. Current HCV screening recommendations

	CDC recommendations for prevention and control of HCV infection and HCV-related chronic disease	NIH consensus statement	French consensus conference
Screening recommended	• Current and former users of injection drugs • Hemodialysis patients • Recipients of clotting factor concentrates before 1987 • Patients with persistently abnormal alanine aminotransferase levels • Recipients of transfusions or organ transplants before 1992 • Occupational exposure to HCV-positive blood • Children born to HCV-positive women	• Recipient of blood transfusion before 1990 • Hemodialysis patients • Current and former users of injection drugs • Individuals with multiple sexual partners • Spouses or close household contacts of hepatitis C patients • Individuals who share instruments for intranasal cocaine use	• Recipient of blood transfusion before 1991 • Current and former users of injection drugs • Hemophiliacs • Hemodialysis patients • Nurses on hemodialysis units
Screening of uncertain need	• Recipients of transplanted tissue • Intranasal cocaine and other noninjecting illegal drug users • Persons with a history of tattooing or body piercing • Persons with a history of multiple sex partners or sexually transmitted diseases • Long-term steady sex partners of HCV-positive persons	No recommendations	Incarcerated patients
Screening not recommended	• Health-care, emergency medical, and public safety workers • Pregnant women • Household (nonsexual) contacts of HCV-positive persons • The general population	No recommendations	• Pregnant women without other risk factors • Other health care personnel
Comments	Most specific screening guidelines	Recommendations taken from 1997 consensus statement, updated June 2002	Broad guidelines, leaves a lot to individual clinical judgment

HCV=hepatitis C virus; CDC=Centers for Disease Control; NIH=National Institutes of Health

Table 2. HCV screening test results and usual interpretation

ELISA	RIBA	PCR	Interpretation
Positive	Positive or indeterminate	Positive	Active or chronic HCV infection
Positive	Positive	Negative	Cleared HCV infection if PCR persistently negative
Positive	Negative, intermediate, or not performed	Negative	Cleared HCV infection or false-positive ELISA
Positive	Negative	Not usually done if RIBA negative	False-positive ELISA
Negative	Not done if ELISA negative	Not usually done if ELISA negative (unless high suspicion for acute infection)	No evidence of past exposure to HCV
Negative	Not done if ELISA negative	Positive (not usually done in clinical settings unless high suspicion for infection)	Early (<7-8 weeks) HCV infection or false-negative

HCV=hepatitis C virus; ELISA=enzyme-linked immunoassay; RIBA=recombinant immunoblot assay; PCR=polymerase chain reaction

Table 3. Long-term outcomes of chronic HCV infection in community-based cohorts including asymptomatic patients

Study	Population studied	Sample size	Duration of follow-up	Long-term outcomes
Barrett 2001	Irish women infected with HCV genotype 1b via contaminated anti-D immunoglobulin in 1977, identified by national screening program in 1994 and evaluated at regional center	155 HCV Ab+ 87 PCR+	17-18 years following initial exposure and again 5 years later	0% (0/87) cirrhosis 0% (0/87) hepatocellular carcinoma
Harris 2002	UK transfusion recipients with HCV infection identified by national lookback program	924 HCV Ab+ 608 PCR+	10 years following initial exposure	10% (35/362) cirrhosis
Kenny-Walsh 1999	Irish women infected with HCV genotype 1b via contaminated anti-D immunoglobulin in 1977, identified by national screening program between 1994 and 1997	704 HCV Ab+ 390 PCR+	17 years following initial exposure	2% (7/390) cirrhosis
Seeff 2000	US veterans with HCV infection identified by testing stored serum specimens obtained between 1948 and 1955	17 HCV Ab+ 11 PCR+	45 years after serum samples obtained	6% (1/17) hospitalized for chronic liver disease or cirrhosis
Thomas 2000	US intravenous drug users identified by screening program	1667 HCV Ab+ 78% with persistent viremia	Median 8.8 years since diagnosis Estimated >14 years since initial exposure	3% (40/1322) with end-stage liver disease 1% (2/210) without ESLD had cirrhosis on biopsy
Wiese 2000	German women infected with HCV genotype 1b via contaminated anti-D immunoglobulin in 1978-1979, identified by national screening program in 1998/1999	917 HCV Ab+ 504 PCR+	20 years following initial exposure	1% (4/504) cirrhosis 0.4% (2/504) died from fulminant hepatitis B or alcoholism and cirrhosis

HCV=hepatitis C virus; Ab+=antibody positive; PCR=polymerase chain reaction

Table 4. Independent risk factors for HCV infection from large observational studies

Study Setting	Sample size (Prevalence of anti-HCV antibodies)	Risk factors evaluated	Independent risk factors for HCV infection		AOR (95% CI)
NHANES III	21,241	• Race or ethnic group	*Marital status:*	Divorced or separated	1.70 (1.08-2.66)
		• Gender		Never married, married or widowed	1.00
Population-based household sample	(1.80% overall and 2.3% in adults 20 years and older)	• Marital status			
		• Poverty index	*Education:*	<=12 years	1.92 (1.01-3.67)
		• Education		>12 years	1.00
		• Urban residence			
		• Region of residence	*Poverty index:*	Below poverty level	2.37 (1.50-3.75)
		• Military-service status		At or above poverty level	1.00
		• Country of birth			
		• Worker in health-care occupation	*Marijuana use:*	>=100 time	2.99 (1.69-5.27)
				1-99 times	1.15 (0.61-2.16)
		• Cocaine use		Never	1.00
		• Marijuana use			
		• Age at first sexual intercourse	*Cocaine use:*	Ever	4.70 (2.49-8.87)
				Never	1.00
		• Number of lifetime sexual partners	*No. of sexual partners:*	>=50	5.16 (1.80-14.73)
		• Herpes simplex 2 virus infection		2-49	2.54 (1.14-5.66)
				0-1	1.00
			Age at first sexual intercourse:	<18 years	2.94 (1.50-5.78)
				>= years	1.00

HCV=hepatitis C virus; AOR=adjusted odds ratio; CI=confidence interval

Table 4. Independent risk factors for HCV infection from large observational studies (continued)

Study Setting	Sample size (Prevalence of anti-HCV antibodies)	Risk factors evaluated	Independent risk factors for HCV infection		AOR (95% CI)
National Hepatitis Screening Survey Screening program at forty mostly urban centers	13,997 (7.00%)	• Age • Gender • Race • Occupation • Blood transfusion • Hemodialysis • Surgery • Intravenous drug use • Sex with intravenous drug user • Sex with multiple partners • Needle-stick injury • Borne in southeast Asia or Africa • Vaccinated for hepatitis B	*Gender:* *Race:* *Blood transfusion:* *Hemodialysis:* *Intravenous drug use:* *Sex with intravenous drug user:* *Vaccinated for hepatitis B:*	Male Female White/Hispanic Other Yes No Yes No Yes No Yes No Yes No	3.60 (2.66-4.87) 1.00 0.57 (0.39-0.83) 1.00 4.09 (2.97-5.62) 1.00 10.95 (3.85-31.13) 1.00 23.34 (15.21-35.81) 1.00 7.29 (4.74-11.21) 1.00 0.37 (0.22-0.62) 1.00
Dionysos Study Population-based study in Northern Italy	6,917 (3.2%)	• Male gender • Alcohol intake >30 g/day • Hepatitis among the cohabiting • Surgical procedure • Dental procedures • Intravenous drug use • Acupuncture • Blood transfusion • Animal bites • Homosexuality	*Hepatitis among the cohabiting:* *Intravenous drug use:* *Animal bites:* *Blood transfusion:*	Yes No Yes No Yes No Yes No	2.0 (1.4-2.8) 1.0 18.4 (5.3-64.0) 1.0 1.6 (1.0-2.5) 1.0 2.2 (1.4-3.4) 1.0

HCV=hepatitis C virus; AOR=adjusted odds ratio; CI=confidence interval

Table 4. Independent risk factors for HCV infection from large observational studies (continued)

Study Setting	Sample size (Prevalence of anti-HCV antibodies)	Risk factors evaluated	Independent risk factors for HCV infection		AOR (95% CI)
Dubois et al Population-based study throughout France	6,283 (1.2%)	• Past or present intravenous drug abuse • Unemployment • Tattoos • History of transfusions • Travel in developing countries • Voluntary abortion • Sexually transmitted disease • Casual sex partners • Sexual contact with intravenous drug users • Surgery with major blood loss • Acupuncture • Injection with reusable glass syringe • Dental surgery • Sexual contact with HCV-positive partner • Homosexual practices • Education level	*Intravenous drug use* *History of transfusion* *Unemployment*	Yes No Yes No Yes No	29.2 (3.8-225.7) 1.0 7.0 (1.7-15.1) 1.0 3.1 (1.2-8.1) 1.0

HCV=hepatitis C virus; AOR=adjusted odds ratio; CI=confidence interval

Table 5. Comparative Treatment Response Rates for HCV infection

Treatment	Sustained Virologic Response	Source
Placebo	<2%	Poynard, 1996*
Interferon monotherapy	6-16%	Poynard, 1996* Gebo, 2002* Kjaergard, 2000* Shepherd, 2000*
Interferon plus Ribavirin	33-41%	Gebo, 2002* Kjaergard, 2000* Shepherd, 2000*
Pegylated Interferon alone	25-39%	Heathcote, 2000 Lindsay, 2001 Reddy, 2001 Zeuzem, 2000
Pegylated Interferon plus Ribavirin	54-60%	Fried, 2002 Glue, 2000 Manns, 2001

* Systematic review or meta-analysis

Table 6. Differences between responders and non-responders in baseline and 24 week SF-36 scores

SF-36 Categories	Difference in SF-36 scores†		
	Studies		
	Bernstein 2002	Bonkovsky 1999	McHutchinson 2001††
Physical function	4.6*	6***	2.5
Ability to perform physical roles	9.8*	22**	5
Degree of bodily pain	2.9**	-1	1.5
Sense of general health	9.1*	7**	5
Overall sense of vitality	9.6*	8***	4.5
Social function	6.2*	9***	3
Ability to perform emotional roles	8.4**	11	3
Overall sense of mental health	4.6*	4	2.5

* $p < 0.001$

** $p < 0.01$

*** $p < 0.05$

†Reported as difference from baseline to 24 weeks after starting treatment in responders compared to non-responders

†† Difference in standard deviation of change from baseline. Statistical signicance not reported. The other studies report the difference in absolute scores.

Table 7. Summary of findings of systematic review

Arrow	Question	Level and type of evidence	Overall evidence for the link	Findings
1	Does screening for hepatitis C reduce the risk or rate of harm and premature death and disability?	None.	N/A	No controlled studies or observational studies links screening directly to health outcomes.
2	Can clinical or demographic characteristics identify a subgroup of asymptomatic patients at higher risk for infection?	II-3. Cross-sectional studies	Good for intravenous drug use, high-risk sexual behaviors, and transfusions prior to 1990. Fair other risk factors.	Intravenous drug use, the most important risk factor for HCV infection, is associated with a prevalence of 50-90%, and is present in at least 50% of infected individuals. High-risk sexual behaviors are another important risk factor. Although transfusions prior to 1990 remain a risk factor, more recent transfusions do not pose a significant risk. Other risk factors have inconsistent associations with HCV infection. No prospective study has applied a screening strategy in the general population and measured what proportion of infected patients was identified correctly.
3	What are the test characteristics of HCV antibody testing?	Studies of diagnostic test characteristics	Fair for sensitivity Fair for specificity	Using viremia as the reference standard, sensitivity of 3rd-generation ELISA testing appears to be 94% or higher. Limited data found a specificity of 97% or greater using viremia as the reference standard.
4	What is the predictive value of a positive screening test and what are the harms associated with screening for hepatitis C virus?	II-3. Large population-based cross-sectional studies. One small, poor-quality cross-sectional study on harms of screening.	Good for positive predictive values. Poor for harms.	False-positive HCV screening tests may not result in potentially harmful diagnostic tests and treatments because PCR is performed to confirm active infection, but other harms (labelling, anxiety, quality of life) that are more difficult to measure are likely to occur. In two large population-based studies the positive predictive value for viremia of positive ELISA with confirmatory positive RIBA was 84-86%. Small observational studies have found worse quality of life in patients aware of their HCV infection (true-positives); no studies are available on harms of screening in false-positives.

HCV=hepatitis C virus; ELISA: enzyme-linked immunoassay; RIBA=recombinant immunoblot assay

Table 7. Summary of findings of systematic review (continued)

Arrow	Question	Level and type of evidence	Overall evidence for the link	Findings
5a	What are the test characteristics of the work-up for treatable disease?	One good systematic review evaluated blood tests' ability to predict liver findings on biopsy.	Fair	Blood tests only have modest value in predicting fibrosis on liver biopsy. No study has evaluated outcomes between patients who had and did not have pretreatment liver biopsy.
5b	In patients found to be positive for hepatitis C antibody, what proportion of patients would qualify for antiviral treatment?	II-3. Cohort studies and cross-sectional studies	Fair	In three fair quality cohort studies, only 30% of patients referred for treatment received treatment. Co-morbid conditions and contraindications disqualified many patients. Approximately 10% of patients refused treatment despite eligibility.
6	What are the harms associated with the work-up for active HCV disease?	II-3. Cross-sectional studies	Fair	The risk of major complications (bleeding, death, perforation) from percutaneous liver biopsy was around 1-2%, with mortality less than 0.3%, in the highest-quality large trial of patients with a variety of indications for biopsy. The risks may be lower in patients undergoing liver biopsy specifically for evaluation of HCV infection.
7a	How well does antiviral treatment reduce the rate of viremia, improve transaminase levels, and improve histology?	I. Well-designed randomized clinical trials	Good	Treatment improves intermediate outcomes. Newer treatments have achieved higher rates of success (54-69% with pegylated interferon + ribavirin) than older treatments. Trials were performed in patients referred for treatment of HCV infection who probably had more severe illness than would be seen in patients identified by screening.

HCV=hepatitis C virus; ELISA: enzyme-linked immunoassay; RIBA=recombinant immunoblot assay

Table 7. Summary of findings of systematic review (continued)

Arrow	Question	Level and type of evidence	Overall evidence for the link	Findings
7b	How well does antiviral treatment improve health outcomes in asymptomatic patients with hepatitis C?	I, II-2. Cohort studies and clinical trials	Fair	One good quality RCT from Japan found a reduction in HCC and mortality after INF treatment. Cohort studies found similar results, but baseline characteristics between patients receiving and not receiving treatment may have differed. Many of these studies were performed in Japan, where chronic HCV infection appears associated with more frequent severe complications. Data on long-term quality of life outcomes according to treatment received is sparse.
7c	How well do counseling and immunizations in asymptomatic patients with hepatitis C improve outcomes or prevent spread of disease?	II-3. Case-control and cross-sectional studies	Poor	There are no studies evaluating whether counseling HCV patients or administering appropriate immunizations improves clinical outcomes or prevents spread of disease. One small retrospective study from France found that patients drinking excess alcohol cut down their intake after brief counseling. One small cross-sectional study found that intravenous drug users did not alter high-risk behaviors after becoming aware of having HCV. In one study, hepatitis A and B immunization series resulted in seroconversion in over 90% of patients with HCV and was tolerated well.
8	What are the harms (including intolerance to treatment) associated with antiviral intervention?	I. Well-designed randomized clinical trials	Good	Antiviral treatment frequently causes a wide array of adverse symptoms, however, these are usually mild and self-limiting. The most common adverse events are flu-like symptoms. In addition, depression, gastrointestinal, and dermatological effects are common. The overall rate of serious or life-threatening adverse events has been 1-2%. In trials specifically of pegylated interferon plus ribavirin, myalgias occurred in 42-56%, fatigue 54-64%, headache 47-62%, and depression 22-31%. No serious complications or deaths occurred. Withdrawals due to adverse events occurred in 14-22%.

HCV=hepatitis C virus; ELISA: enzyme-linked immunoassay; RIBA=recombinant immunoblot assay

Table 7. Summary of findings of systematic review (continued)

Arrow	Question	Level and type of evidence	Overall evidence for the link	Findings
9	Have improvement in intermediate outcomes been shown to reduce the risk or rate of harm from hepatitis C?	II-2. Fair-quality cohort studies and clinical trials	Fair	A limited number of cohort studies have shown that patients who achieve intermediate outcomes after treatment are less likely to develop HCC than those who do not achieve intermediate outcomes and than those who do not receive treatment. Three fair-quality clinical trials found that patients who are sustained responders to treatment have signficant improvements in health-related quality of life.

HCV=hepatitis C virus; ELISA: enzyme-linked immunoassay; RIBA=recombinant immunoblot assay

Table 8. Estimated yield of screening for hepatitis C virus

Base case assumptions		Source	Number out of 1000 average-risk adults screened	Number out of 1000 adults screened who report IVDU
Prevalence of anti-HCV antibodies in population	2% in general U.S. population	NHANES III (1.8% in general population, 2.3% in adults >20 years old)	20	500-900
	50 to >90% in U.S. patients with past or current IVDU	Numerous cross-sectional studies		
Proportion of anti-HCV antibody positive patients with viremia	72-84%	NHANES III, Dionysos study (Italy), French population-based study (Dubois)	14	360-765
Proportion of patients with viremia that will develop cirrhosis after 10-20 years	0-10%	6 community-based cohorts of patients exposed to HCV infection	0-1.4	0-76
Proportion of patients with viremia that has abnormal transaminases	60-66%	Dionysos study (Italy), French population-based study	8-9	216-505
Proportion of patients undergoing liver biopsy who have major complications	1-2% for major complications (bleeding, death, perforation)	1 large fair-quality observational study with independent ascertainment of complications in patients referred for biopsy for a variety of indications; numerous other poor- and fair-quality observational studies (small randomized trials of patients with HCV infection suggest a lower rate of complications)	0.14 major complications and <0.04 deaths if all patients with viremia undergo biopsy	4-15 major complications and 0-2 deaths
	<0.3% mortality		0.08-0.18 major complications and <0.03 deaths if only patients with abnormal transaminases undergo biopsy	2-10 major complications and 0-1.5 deaths

Table 8. Estimated yield of screening for hepatitis C virus

Base case assumptions		Source	Number out of 1000 average-risk adults screened	Number out of 1000 adults screened who report IVDU
Proportion of patients referred for evaluation of HCV infection that received therapy	30%	3 fair-quality observational studies of patients referred for evaluation of HCV infection	4, if all patients with viremia referred	108-230
			2-3, if only patients with abnormal transaminases referred	65-152
Proportion of patients who received interferon-based therapy that completed treatment course	80-90%	Numerous good-quality randomized trials and systematic reviews	3.2-3.6, if all patients with viremia referred	86-207
			1.6-2.7, if only patients with abnormal transaminases referred	52-137
Proportion of patients who received interferon-based therapy that had a serious or life-threatening adverse event	1-2%	Numerous good-quality randomized trials and systematic reviews	0.04-0.08, in all patients with viremia referred	1-5
			0.02-0.06, if only patients with abnormal transaminases referred	0.6-3
Proportion of patients who receive treatment that have a sustained virologic response to best available therapy (pegylated interferon and ribavirin)	54-60% for pegylated interferon and ribavirin combination therapy	3 randomized clinical trials (2 good-quality, 1 fair-quality) for pegylated interferon and ribavirin	2, if all patients with viremia referred	46-124
			0.9-1.6, if only patients with abnormal transaminases referred	28-82

Evidence Table 1a. Intermediate outcomes

Author Year	Type of study, Setting	Aims	Study Duration	Eligibility Criteria	Exclusion Criteria	Screened/ Eligible/ Enrolled Population	Withdrawals or lost to follow-up (%) Analyzed
Pegylated Interferon plus Ribavarin							
Fried 2002[210]	RCT Multicenter (81) in USA, Europe, Austraila, Brazil	To assess the efficacy of peginterferon alfa-2a plus ribavirin as compared to interferon alfa-2b plus ribavirin or to peginterfeon alfa-2a alone	48 wks treatment 24 wks follow-up	Adults with ≥ 2000 copies of HCV RNA by PCR, elevated ALT levels within 6 mo., liver biopsy consistent with chronic HCV, no previous interferon treatment	Neutropenia, thrombocytopenia, anemia, HIC, decomensatied liver disease, serum creatinine > 1.5 x normal, poorly controlled psychiatric disease, alcohol or drug dependence within one year, substantial coexisting medical condition	1459/ NR/ 1149 Male: 71% Mean age: 42.5 years Range: NR Race: 84% White	28 randomized but did not receive any study medication for multiple reasons including ineligibility and refusal of treatment. All persons receiving one dose of medicine included in final analysis. If <20 weeks follow up, counted as having no response to treatment 1121 analyzed
Glue 2000[212]	RCT France	To assess the safety, tolerability, pharmacokinetics and pharmaco-dynamics of combined pegylated interferon and ribavirin	24 wks treatment 24 wks follow-up	Adults with compensated chronic HCV, postive HCV RNA by PCR, recent liver biopsy consistent with chronic hepatitis	HIV, Hep B, significant other medical or psychiatric illness, substance abuse, uncompensated liver disease, other causes of liver disease, previous treatment for HCV	NR/ NR/ 72 Male: 49% Mean age: 39.8 years Range: 20-68 Race: NR	5 withdrawals: 1 neutropenia 2 alcohol abuse 2 personal reasons 72 analyzed

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus; IVDU=intravenous drug use®

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Baseline liver disease	Method of Outcome Assessment and Timing of Assessment	Intervention + Control	Biochemical Response		Virologic Response		Histologic Response	
Pegylated Interferon plus Ribavarin				***ETR***	***SR***	***TR***	***SR***	***Inflam***	***fibro***
Fried 2002[210]	*Genotype 1* : 62% *ALT:* 90 U/L *HCV RNA:* 6.0 x 10*6 *Cirrhosis or bridging fibrosis:* 13% *Source:* *Transfusion:* 20% *IVDU* : 40%	HCV RNA: weeks 12, 72 Safety assessment at weeks 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60, 72	a. INF alfa-2b 3 MU 3x/wk + RIB 1000-1200 mg/d b. PEG INF alfa-2a 180 ug/kg q wk c. PEG INF alfa-2a 180 ug/kg q wk + RIB 1000-1200 mg/d	N/A	N/A	52% 59% 69% (a vs c p<0.001) (b vs c p=0.001)	44% 29% 56% (a vs c, b vs c p<0.001)	N/A	N/A
Glue 2000[212]	*Genotype 1* : 44%	HCV-RNA: weeks 0, 1, 4, 12, 24, 28, 36, 48	a. PEG INF 2b 0.35 ug/gk q wk b. PEG INF 2b 0.70 ug/kg q wk c. PEG INF 2b 1.40 ug/kg q wk d. PEG INF 2b 0.35 ug/kg q wk + RIB 600-800 mg/d e. PEG INF 2b 0.70 ug/kg q wk + RIB 600-1200 mg/d f. PEG INF 2b 1.40 ug/kg q wk + RIB 600-1200 mg/d	N/A	N/A	50% 63% 50% 58% 69% 81%	0% 44% 42% 17% 53% 60%	N/A	N/A

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Variables associated with response	Adverse Events	Funding Source and Role	Internal Validity Rating	Relevance to screening	Comments
Pegylated Interferon plus Ribavarin						
Fried 2002[210]	Best treatment results if genotype other than 1, age of 40 or less, body weight 75 kg or less	*Dose Reduction:* 83+181/68+48/159+203(???) *Dose Discontinuation:* 140 (22%)/72(32%)/100(32%) *Fatigue:* 55/44/54% *Headache:* 52/51/47% *Fever:* 56/38/43% *Myalgia:* 50/42/42% *Nausea*: 33/26/29% *Depression:* 30/20/22% *Dermatitis:* 22/11/21% *Deaths:* 3, none thought to be related to treatment	Hoffman-LaRoche, Univ. of N. Carolina Gen. Clin. Rsrch. Cntrs., and NIH. Sponsors involved in analysis of data. Authors had full access to the data and the decision to publish was not limited by the sponsor.	Good	Good	Sponsor, investigators, and patients blind to whether patients receiving PEG INF received RIB or placebo. Randomization stratified by country and by genotype (1 vs. other). Genotype 1 SVR 36% vs 21% vs 46% (a/b/c)
Glue 2000[212]	N/A	*Dose Reduction:* NR *Dose Discontinued:* 1 *(tx group not specified)* *Flu symptoms:* 17-44% *Headache:* 50-56% *Asthenia:* 0-22% *Mean Hgb reduction:* 1.5/2/2.5 g/dL	Schering Plough Research Institute, employer of lead author	Fair	Unclear	Drug dosing study

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Type of study, Setting	Aims	Study Duration	Eligibility Criteria	Exclusion Criteria	Screened/ Eligible/ Enrolled Population	Withdrawals or lost to follow-up (%) Analyzed
Manns 2001[211]	RCT Multicenter (62) in Europe, Canada, Argentina, USA	To assess the safety and efficacy of two regiments of PEG INF and ribavirin, and to identify predictors of response	48 wks treatment 24 wks follow-up	Adults, previously untreated, positive HCV RNA by PCR, recent liver biopsy consistent with chronic hepatitis, elevated ALT	Decompensated cirrhosis, other causes of liver disease, HIV, organ transplantation, significant other medical or psychiatric conditions, unable to take contraception	2316/ NR/ 1530 Male: 66% Mean age: 43 years Range: 21-68 Race: NR	1530 analyzed
Pegylated Interferon							
Heathcote 2000[213]	RCT Multicenter (30) in USA, Canada, Austraila, UK	To compare the efficacy and safety of two doses of PEG INF alfa-2a with standard INF theray in HCV patients with cirrhosis or bridging fibrosis	48 wks treatment 24 wks follow-up	Adults, chronic HCV, biopsy-proven cirrhosis or bridging fibrosis, not perviously treated, ALT abnormal 2x in past 6 mo, biopsy done within past year	Presence of other liver diseases, decompensated cirrhosis, HIV, medical or psychiatric conditions	397/ 271/ 271 Male: 72% Mean age: 47 yrs Range: NR Race: 88% White Weight: 79 kg	50 withdrew (18.5%) 271 analyzed

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus; IVDU=intravenous drug use®

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Baseline liver disease	Method of Outcome Assessment and Timing of Assessment	Intervention + Control	Biochemical Response		Virologic Response		Histologic Response	
Manns 2001[211]	*Genotype 1*: 68% *ALT:* 2.3 x nl *HCV RNA:* 2.7 x 10*6 *Histology:* 7.9 (Knodell) *Cirrhosis:* 29% *Source:* *Transfusion:* 22% *IVDU:* 65%	HCV RNA: weeks 0, 4, 12, 24, 36, 48, 12, 24 Liver biopsy: Knodell index, at the end of the follow-up period	a. INF 2b 1.5 ug/kg 3x/wk + RIB 1000-1200 mg/d b. PEG INF 2b 1.5 ug/kg q wk x 4 wks then 0.5 ug/kg x 44 wks + RIB 1000-1200 mg/day x 48 wks c. PEG INF 2b 1.5 ug/kg q wk+ RIB 800 mg/d x 48 wks	69% 63% 65%	47% 48% 54%	54% 56% 65% (a vs c p<0.001)	47% 47% 54% (a vs c p=0.01)	69% 70% 68%	20% 19% 21%
Pegylated Interferon									
Heathcote 2000[213]	*Genotype 1:* 56% *ALT:* 110 U/L *HCV RNA:* 6.1x10*6 *Histology:* 13 (HAI) *Cirrhosis:* 78% *Source:* *Transfusion:* 25% *IVDU:* 48%	HCV RNA: weeks 1, 2, 4, 6, 8, and q 4 wks till end ALT levels viral genotyping Histologic eval: biopsy at 72 wks, Histological Activity Index Safety assessment	a. INF alfa-2a 3 MU 3x/wk b. PEG INF 90 ug q wk c. PEG INF 180 ug q wk	22% 35% 39% (a vs c p = 0.02)	15% 20% 34% (a vs c p=0.004)	14% 42% 44% (a vs c p=0.001)	8% 15% 30% (a vs c p=0.001)	31% 44% 54% (a vs c p=0.02)	N/A

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Variables associated with response	Adverse Events	Funding Source and Role	Internal Validity Rating	Relevance to screening	Comments
Manns 2001[211]	Best treatment result with genotype other than 1, lower viral, lighter weight, female gender, younger age, absence of cirrhosis	*Dose Reduction:* 34/36/42% *Dose Discontinued:* 13/13/14% *Fatigue:* 60/62/64% *Headache:* 58/58/62% *Myalgia:* 50/48/56% *Fever:* 33/44/46% *Diarrhea:* 17/16/22% *Depression:* 34/29/31% *Injection site reaction:* 36/59/58% *Deaths:* 0	Schering Plough sponsor; role not specified	Good	Fair	
Pegylated Interferon						
Heathcote 2000[213]	Best result with genotype other than 1	*Dose Reduction:* 14/2/14% *Dose Discontinued:* 8/7/13% *Fatigue:* 52/51/53% *Headache:* 46/52/43% *Myalgia:* 33/35/44% *Fever:* 31/28/33% *Diarrhea:* 16/20/21% *Depression:* 18/20/21% *Injection site reaction:* 12/14/27% *Death:* 0/1/3(#)	Hoffmann-LaRoche designed trial, monitored adherence to guidelines, and monitored analysis	Fair	Unclear	Emphasis on cirrhotic patients may not apply to asymptomatic general population

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Type of study, Setting	Aims	Study Duration	Eligibility Criteria	Exclusion Criteria	Screened/ Eligible/ Enrolled Population	Withdrawals or lost to follow-up (%) Analyzed
Lindsay 2001[214]	RCT Multicenter (53) USA, Europe, Australia	To evaluate the safety and efficacy of PEG INF as compared to INF in adult patients with chronic HCV not previously treated	48 wks treatment 24 wks follow-up	Adults, chronic HCV, compensated liver disease, positive HCV RNA, liver biopsy within past year, abnormal ALT 1x in past 6 mo	Any other cause for liver disease, HIV, substance abuse, preexisting medical condition that might interfere with tx, hemophilia, hemoglbnpths, breastfeeding, nonpregnant, using contraception	NR/ NR/ 1224 Male: 63% Mean age: 43 yrs Range: 18-73 Race: 91% White Weight: 80 kg	1219 analyzed 5 withdrew before receiving treatment for reasons unrelated to study 23% withdrew
Reddy 2001[215]	RCT Multicenter, USA	To evaluate the safety and efficacy of 4 doses of PEG INF alfa-2a as compared to INF alfa-2a. Primary intent is to establish the most appropriate dose of PEG INF for future trials	48 wks treatment 24 wks follow-up	Adults, chronic HCV, not previously treated, without cirroshis or bridging fibrosis on biopsy, ALT abnormal 2x at least 2 wks apart, biopsy within past year, positive HCV Ab test	Liver disease from other causes, neutropenia, thrombocytopenia, renal damage, hx of preexisting medical or psychiatric illness, current pregnancy or breastfeeding, alcohol or drug dependence within previous 12 months, administration of antineoplastic, immunomodulatory, antiviral, investigational compounds	NR/ NR/ 159 Male: 76% Mean age: 42 Range: NR Race: 88% white Weight: 86 kg	159 analyzed

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus; IVDU=intravenous drug use®

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Baseline liver disease	Method of Outcome Assessment and Timing of Assessment	Intervention + Control	Biochemical Response		Virologic Response		Histologic Response
Lindsay 2001[214]	*Genotype 1:* 70% *ALT:* 2.3 x nl *HCV RNA:* 3.4x10*6 *Histology:* 6.9 (HAI) *Cirrhosis:* 3.5% *Source:* *Transfusion:* 21% *IVDU:* 48% *Years since exposed:* 19	HCV RNA: weeks 4, 12, 24, 36, 48, 52, 60, 72 ALT levels Histologic eval: biopsy at 72 wks, Histological Activity Index Safety assessment	a. INF alfa-2b 3MU 3x/wk b. PEG INF alfa-2b 0.5 ug/kg q wk c. PEG INF alfa-2b 1.0 ug/kg q wk d. PEG INF alfa-2b 1.5 ug/kg q wk	20% * 25% 31% 33% (a vs d, p<0.001, a vs c, p=0.002, a vs b, p=0.14)	12% * 17% 24% 23% (a vs d, a vs c, p<0.001, a vs b, p=0.13)	24% 33% 41% 49% (a vs d, a vs c p<0.001, a vs b p=0.01)	12% 18% 25% 23% (a vs d, a vs c p<0.001, a vs b p=0.04)	47% 49% 50% 48% (NS) (61% of all subjects)
Reddy 2001[215]	*Genotype 1:* 73% *ALT:* 96 *HCV RNA:* 2.2x10*6 *Cirrhosis:* 10% *Source:* NR	HCV RNA: wks 1, 2, 4, 6, 8 and every 4 wks until end ALT levels Viral Genotype Histologic eval: biopsy at 72 wks, HAI score Safety assessment	a. INF alfa-2a 3 MU 3x/wk b. PEG INF alfa-2a 45 ug q wk c. PEG INF alfa-2a 90 ug q wk d. PEG INF alfa-2a 180 ug q wk e. PEG INF alfa-2a 270 ug q wk	15% 20% 20% 38% 27% (a vs d, p=0.04)	9% 10% 25% 38% 27% (a vs d p=0.004)	12% 30% 45% 60% 56% (a vs c, p=0.01, a vs d, a vs e, p<0.0001)	3% 10% 30% 36% 29% (a vs c, p=0.009, a vs d, p=0.0006, a vs e p=0.004)	57% 47% 59% 63% 66%

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Variables associated with response	Adverse Events	Funding Source and Role	Internal Validity Rating	Relevance to screening	Comments
Lindsay 2001[214]	Best result with genotype other than 1, baseline HCV RNA < 2 million copies	*Dose Reduction:* 6/9/14/19% *Dose Discontinued:* 6/9/11/9% *Fatigue:* 50/43/51/45% *Headache:* 58/61/64/64% *Myalgia:* 53/48/54/61% *Fever:* 30/31/45/44% *Nausea:* 20/21/26/25% *Irritability:* 24/19/18/17% *Injection site reaction:* 16/44/42/40% *Deaths:* 0	Schering Plough, U of Southern California	Good	Unclear	
Reddy 2001[215]	NR	*Dose Reduction: "similar" except for treatment d* (12%) *Dose D/C:* 10/0/22/20% *Fatigue:* 21/14/12/30/28% *Headache:* 18/8/7/26/19% *Myalgia:* 19/8/13/14/19% *Fever:* 9/3/2/11/11% *Diarrhea:* 6/5/5/14/13% *Depression:* 3/6/7/12/15% *Injection site reaction:* 6/7/6/11/10% *Deaths:* 0	Hoffmann-La Roche, role not specified	Fair	Unclear	Dosing study; design permitted differences in treatment group characteristics, limiting the validity of the results

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Type of study, Setting	Aims	Study Duration	Eligibility Criteria	Exclusion Criteria	Screened/ Eligible/ Enrolled Population	Withdrawals or lost to follow-up (%) Analyzed
Zeuzem 2000[216]	RCT Multicenter (36) Australia, Canada, Germany, Mexico, New Zealand, Spain, Switzerland, Taiwan, and the UK	To compare the efficacy and safety of PEG INF and INF, and establish equivalent doses	48 wks treatment 24 wks follow-up	Adults, not previously treated with interferon, positive HCV Ab, HCV RNA > 2000 copies, ALT abnl 2x in past 6 mo, liver biopsy consistent with chronic hepatitis, biopsy performed within past year	Neutropenia, thrombocytopenia, abnormal kidney function, evidence of other liver disease, HIV, decompensated liver disease, organ transplant, cancer, severe cardiac or pulmonary disease, or other significant medical problem, not on contraception	613/ 531/ 531 Male: 67% Age: 41 yrs Range: NR Race: 85.5% White Weight: 75 kg	61 (23%) withdrew from PEG INF 110 (42%) withdrew from INF 531 analyzed

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Baseline liver disease	Method of Outcome Assessment and Timing of Assessment	Intervention + Control	Biochemical Response		Virologic Response		Histologic Response
Zeuzem 2000[216]	*Genotype 1:* 30% *ALT:* 139 *HCV RNA:* 7.8x10*6 *Histology:* 8.8 HAI score *Cirrhosis:* 13.5 (includes bridging fibrosis) *Source:* *Transfusion:* 23% *IVDU:* 37%	HCV RNA, 0, 2, 4, 6, 8, then q 4 wks until 72 wks ALT Genotype Histology from biosy at 72 wks, HAI score used Adverse events	a. INF alfa-2a 6 MU 3x/wk x 12 wks, then 3 MU 3x/wk x 36 wks b. PEG INF alfa-2a 180 ug q wk x 48 wks	39% 46% (NS)	24% 45% (p=0.001)	28% 69% (p=0.001)	19% 39% (p=0.001)	55% 63%

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1a. Intermediate outcomes (continued)

Author Year	Variables associated with response	Adverse Events	Funding Source and Role	Internal Validity Rating	Relevance to screening	Comments
Zeuzem 2000[216]	Yonger age, smaller body surface area, lower HCV RNA, higher ALT, not cirrhotic, HCV genotype other than 1	*Dose Reduction:* 51/47% *Dose Discontinued:* 10/7% *Fatigue:* 60/65% *Headache:* 60/66% *Myalgia:* 42/43% *Fever*: 37/52% *Diarrhea:* 19/20% *Depression:* 16/23% *Injection site reaction:* 5/11% *Deaths:* 1 (unrelated to tx)	Hoffmann-LaRoche designed study, analyzed data in conjunction with the authors	Fair	Unclear	Large, differential withdrawal, substantial number of INF withdrawals for "insufficient therapeutic response"

* Combined biochemical and virological response

ETR=end of treatment response; SR=sustained response; Inflam=inflammation; Fibro=fibrosis; NR=not reported; RCT=randomized controlled trial; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; PCR=polymerase chain reaction; ALT=alanine aminotransferase; RIB=ribavirin; PEG INF=pegylated interferon; INF=interferon; HIV=human immunodeficiency virus

Evidence Table 1b . Quality of RCTs for treatment--intermediate outcomes

Author Year	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Patient unaware of treatment?
Pegylated Interferon plus Ribavarin						
Fried 2002[210]	Yes, in blocks of 5	Not reported	Yes	Yes	For PEG INF (RIB vs. Placebo) but not for PEG INF vs. INF	For PEG INF (RIB vs. Placebo) but not for PEG INF vs. INF
Glue 2000[212]	Yes, by individual	No	Not stated, were not similar % genotype 1 or viral load	Yes	No	No
Manns 2001[211]	Yes, in blocks of 3	Yes, centralized	Yes	Yes	Pathologist blinded for post treatment biopsy evaluation	No
Pegylated Interferon						
Heathcote 2000[213]	Yes, in blocks of 6	Yes, centralized	Yes	Yes	Pathologist blinded for post treatment biopsy evaluation	No
Lindsay 2001[214]	Yes, method not clarified	Not clarified	More genotype 1 in PEG INF 1.5 group, (p=0.09), otherwise similar	Yes	Yes	Yes
Reddy 2001[215]	Yes, by individual	Not clarified	Gender, race, % genotype 1, ALT levels, HCV RNA levels, cirrhosis % differences	Yes	Pathologist blinded for post treatment biopsy evaluation	No
Zeuzem 2000[216]	Yes, by individual	Not clarified	Difference in HCV RNA levels, otherwise similar	Yes	No	No

HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; ALT=alanine aminotransferase; PEG INF=pegylated interferon; INF=interferon

Evidence Table 1b . Quality of RCTs for treatment--intermediate outcomes (continued)

Author Year	Intention to treat analysis?	Maintenance of comparable groups?	Reporting of attrition, crossovers, adherence, and contamination?	Differential loss to follow up or high loss?	Statistical analysis appropriate?	Internal Validity Rating
Pegylated Interferon plus Ribavarin						
Fried 2002[210]	Yes	Yes	Yes	High overall loss (22% PEG+RIB, 32% INF+RIB, 32% PEG alone)	Yes	Good
Glue 2000[212]	Not done, but calculable	Groups maintained, however not certain if similar at baseline	Yes	No	No	Fair
Manns 2001[211]	Yes	Yes	Yes	No	Yes	Good
Pegylated Interferon						
Heathcote 2000[213]	Yes, except for histology	Yes	Yes	No	Yes	Fair
Lindsay 2001[214]	Yes, except for histology	Yes	Partially	Non differential, high loss (23%)	Yes	Good
Reddy 2001[215]	Yes, except for histology	Not similar at baseline	No	Non differential, high loss (23%)	OK	Fair
Zeuzem 2000[216]	Yes, except for histology	Uncertain	Partially	Large, differential loss (23% PEG, 42% INF)	Yes	Fair

HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; ALT=alanine aminotransferase; PEG INF=pegylated interferon; INF=interferon

Evidence Table 2. Interferon plus ribavirin intermediate outcomes

Author Year	Aims	Time period covered and sources used in literature search	Eligibility Criteria	Exclusion Criteria	Funding Source and Role	Method of appraisal	Characteristics of identified articles
Interferon plus Ribavarin							
Reviews							
Gebo 2002[107]	To determine the most effective therapy for HCV	Used data from Kjaergard, added additional articles found from September 2000 - March 2002 MEDLINE, Biological Abstracts, Science Citation Index, Manual Alternative and Natural Therapy, Allied and Complementatry Medicine Database, CAB Health, PsychINFO, Sociological Abstracts, manual searches	RCTs with planned follow up at least 24 weeks after the end of treatment, written in English, human, original data	Meeting abstracts and other incomplete reports	US government	Used standardized template. All article titles read and assessed by two reviewers. All articles read and assessed by two reviewers.	Kjaergard, 2000, used to summarize material prior to September 2000. 4 additional articles identified after that date.

CI=confidence interval; HCV=hepatitis C virus; ; INF=interferon; RIB=ribavirin; HIV=human immunodeficiency virus; RCT=randomized controlled trial; RR=relative risk; ETBR=end of treatment biochemical response; SBR=sustained biochemical response; SVR=sustained virological response; HAI=histologic activity index; HCC=hepatocellular carcinoma; tx=treatment

Evidence Table 2. Interferon plus ribavirin intermediate outcomes (continued)

Author Year	Population Characteristics	Results (95% CI)	Variables associated with response	Adverse Events	Internal Validity Rating	Relevance to screening
Interferon plus Ribavarin						
Reviews						
Gebo 2002[107]	4 additional articles heterogenous with respect to treatment regemen, dose, and duration.	In general, there is good data to support an increased benefit from combination therapy over interferon alone. There were some inconsistencies in the additional four studies reviewed independently of the Kjaergard review, however, these studies were heterogenous with respect to patient population and study design. The magnitude of the relative treatment effect may depend on the dose and duration of treatment.		See Kjaergard	Good	Good

CI=confidence interval; HCV=hepatitis C virus; ; INF=interferon; RIB=ribavirin; HIV=human immunodeficiency virus; RCT=randomized controlled trial; RR=relative risk; ETBR=end of treatment biochemical response; SBR=sustained biochemical response; SVR=sustained virological response; HAI=histologic activity index; HCC=hepatocellular carcinoma; tx=treatment

Evidence Table 2. Interferon plus ribavirin intermediate outcomes (continued)

Author Year	Aims	Time period covered and sources used in literature search	Eligibility Criteria	Exclusion Criteria	Funding Source and Role	Method of appraisal	Characteristics of identified articles
Kjaergard 2001[206]	To assess the efficacy and safety of interferon with and without ribavirin for naïve patients, relapsers, and non-repsonders with chronic HCV.	1966-August 2000 Cochrane Hepato-Biliary Group, Cochrane Library, EMBASE, MEDLINE, hand search of specialist journals and bibliographies, authors of included trials, pharmaceutical companies	Trials in which patients with chronic HCV were randomized to INF-alfa plus RIB versus INF-alfa alone; patients were naïve, non-responders, or relapsers.	Hep B, HIV, hepatic decompensation	Danish governmental grants	Used standard template. All articles read and assessed by two reviewers.	15 RCTs of naïve patients.
Shepherd 2000[208]	To review the clinical and cost-effectiveness of combination therapy in patients with HCV	1993-1999 Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, MEDLINE, PreMEDLINE, EMBASE, reference lists	RCTs or systematic reviews of RCTs evaluating interferon alfa and ribavirin compared with interferon alfa alone or with placebo	Non-randomized studies, abstracts only	Governmental grant	Used standized template. Quality assessment assigned by one reviewer. Another reviewer checked these results and disagreements were resolved through discussion.	19 RCTs identified, 2 meta-analyses.

CI=confidence interval; HCV=hepatitis C virus; ; INF=interferon; RIB=ribavirin; HIV=human immunodeficiency virus; RCT=randomized controlled trial; RR=relative risk; ETBR=end of treatment biochemical response; SBR=sustained biochemical response; SVR=sustained virological response; HAI=histologic activity index; HCC=hepatocellular carcinoma; tx=treatment

Evidence Table 2. Interferon plus ribavirin intermediate outcomes (continued)

Author Year	Population Characteristics	Results (95% CI)	Variables associated with response	Adverse Events	Internal Validity Rating	Relevance to screening
Kjaergard 2001[206]	Articles heterogenous in terms of treatment regemens, dose, and duration of treatment.	*RR no ETBR:* 0.63 (0.58-0.70) *RR no SBR:* 0.78 (0.64-0.94) *RR no SVR:* 0.75 (0.65-0.79) *RR no HAI improvment:* 0.83 (0.74-0.93)	Not cirrhotic, longer treatment duration more likely to improve.	*Dose Reduction:* 2.44 1.58-3.75 *Dose Discontinued:* 1.28 (1.07-1.52) *Anemia:* 16.67 (5.68-48.89 *Cough:* 1.66 (1.19-2.37) *Dyspepsia:* 1.72 (1.17-2.54) *Leukopenia:* 4.52 (1.55-13.23) *Cirrhosis:* 6 combo and 12 INF *HCC:* 0 combo, 1 INF *Transplants:* none *Deaths:* 2 INF pts died (1 suicide, 1 accidental), 1 combo died (accidental)	Good	Good
Shepherd 2000[208]	Quality of studies variable, though larger studies were of high quality.	*SVR, 24 wks tx combo vs INF*: 33% vs. 6% (p<0.05) *SVR, 48 wks tx combo vs INF*: 41% vs 16% (p<0.05) *RR SVR:* 4.90 (2.63-9.13)		*Dose Reduction:* 9-26% (NS) *Dose Discontinued:* 8-21% (NS) *Flu symptoms:* 63-67% (NS) *GI symptoms:* 19-25% (NS) *Psychiatric symptoms*: 32-37% (NS) *Respiratory symptoms:* 9-15% (NS) *Dermatalogic symptoms:* 28-32% (NS)	Good	Fair

CI=confidence interval; HCV=hepatitis C virus; ; INF=interferon; RIB=ribavirin; HIV=human immunodeficiency virus; RCT=randomized controlled trial; RR=relative risk; ETBR=end of treatment biochemical response; SBR=sustained biochemical response; SVR=sustained virological response; HAI=histologic activity index; HCC=hepatocellular carcinoma; tx=treatment

Evidence Table 3a. Long term outcomes

Author Year	Type of study, Setting	Aims	Duration of follow up after study	Eligibility Criteria	Exclusion Criteria	Screened/Eligible/ Enrolled Population
Interferon only RCTs						
Bernardinello 1999[219]	RCT Italy	To describe the long-term results of an RCT done to evaluate INF-beta.	Up to 5 years	Chronic HCV, anit-HCV positive, HCV-RNA positive, 2x normal ALT, liver biopsy consistent with activer cirrhosis, 18-65 years old, informed consent	Portal HTN with varices at risk of bleeding, Child C cirrhosis, previous episode of hepatic decompensation, ascites, thrombocytopenia, WBC<2000, alcohol abuse, cardiac/renal dysfunction, autoimmune/thyroid disease	NR/NR/61 Male: 54% Mean Age: 57 yrs Range: NR Race: NR
Chemello 1999[218]	RCT Itally	To describe the long-term results of an RCT done to evaluate INF-alfa tiw vs. daily	Up to 6 years	18-60 years old, ALT > 2x normal on 3 occasions 6 months prior to randomization, chronic HCV, HCV RNA positive, histologic features consistent with chronic HCV, with or without cirrhosis (Child A), a liver biopsy during 12 months prior to enrollment, no previous INF tx	other causes of liver disease, active alcohol or IVDU, autoimmune or thyroid disease, pregancy, cytopenia, cirrhosis Child B or C, history of liver decompensation or presence of portal HTN, ascites, varicies, variceal bleeding, hepatic encephalopathy, or other serious medical condition	NR/NR/149 Male: 66% Mean Age: 48 yrs Range: NR Race: NR
Nishiguchi 2001[217]	RCT Japan	To describe the long-term results of an RCT done to evaluate INF-alfa	8.7 years	Chronic active hepatitis, with compensated Child A cirrhosis, abnormal ALT > 1 year, detectable HCV in serum	Liver disease of another etiology, thrombocytopenia, HIV, immunosuppression, autoimmune hepatitis, HCC, Hep B, alcohol use.	136/108/90 Male: 57% Mean Age: 56 yrs Range: NR Race: NR

*p<0.05

ETR=end of treatment response; SR=sustained response; tx=treatment; HCC=hepatocellular carcinoma; sx=symptoms; rdx=reduction; Child C=measure of abnormalities of liver histology; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; WBC=white blood cell; NR=not reported; ALT=alanine aminotransferase

Evidence Table 3a. Long term outcomes (continued)

Author Year	Withdrawals or lost to follow-up (%) Analyzed	Baseline liver disease	Method of Outcome Assessment and Timing of Assessment	Intervention + Control	Biochemical Response		Virological response	
Interferon only RCTs					***ETR***	***SR***	***ETR***	***SR***
Bernardinello 1999[219]	Analyzed: 61	*Genotype 1:* 73% *ALT:* 161 UI/L HCV RNA: NR *Histology:* 84% Child A *Cirrhosis:* 100% *Source:* NR *Duration of cirrhosis (presumed):* 41 months	Assessed hematological, biochemical and virological parameters q month x 3 months then q 6 months. Also had an US of liver q 6 months, and had an EGD q 6 months during tx and q 12 months until end of study.	a) INF-beta IM 6 MU/tiw x 6 m then 3 MU/tiw x 6 mo b) no treatment	13% 9%	11% 9%	11% 0%	3% 0%
Chemello 1999[218]	Analyzed: 149 60 (49%) had follow up liver biopsy	Genotype 1: 56% ALT: 223 IU/L HCV RNA: NR Cirrhosis: 16% Duration of disease: 119 mo	Evaluated 1, 3, 6, 9 , 12 months during treatment, then anually therafter.	a) INF-alfa 3 MU/tiw x 6 m IM b) INF-afla 3 MU qd x 3 m then tiw x 3 mo IM	47% 37%	13% 20%	36% 9%	31% 9%
Nishiguchi 2001[217]	Analyzed: 90	Genotype 1: 2% ALT: 108 IU/L HCV RNA: NR Cirrhosis: 100%	Evaluated q 3 months	a) INF-alfa 6 MU/tiw x 24 wks b) symptomatic tx.			35%	16%*

*p<0.05

ETR=end of treatment response; SR=sustained response; tx=treatment; HCC=hepatocellular carcinoma; sx=symptoms; rdx=reduction; Child C=measure of abnormalities of liver histology; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; WBC=white blood cell; NR=not reported; ALT=alanine aminotransferase

Evidence Table 3a. Long term outcomes (continued)

Author Year	Long term outcomes	Adverse Effects	Funding Source and Role	Internal Validity Rating	Relevance to screening	Comments
Interferon only RCTs						
Bernardinello 1999[219]	Probability of developing clinically significant liver related events: NS Cumulative probability of decompensation: 24% vs. 35% (*tx* vs. no tx.) *Risk of death:* 9% vs. 4.4% (tx vs. no tx) *HCC:* 5.3 % (2 cases) tx vs. 4.3% (1 case) no tx *SR:* at 60 months 5% tx vs 4% no tx had SVR, and 16% tx vs. 17% no tx had SBR.	*Drop out:* none due to *sx* *Dose redx:* none *Fatigue:* 24% *Depression:* 21% *Myalgias:* 21% *Headache:* 21% *Flu sx:* 16%	Grant from Regione Veneto, Ricerca Sanitaria Finalizzata	Fair	Unclear	Author notes that INF-beta has been found to be less efficacious when given i.m. as it was in this study.
Chemello 199[218]	Histologic improvement: NS between groups 73% SR, 35% TR and 15% NR had improvement 0% SR, 29% TR and 43% NR had worsening SR: at 72 mo 9% group a and 14% group b had continued biochemical response and 9% of group a and 12% of group b had continued virological response	*Drop out:* 9 vs 3 *Dose redx:* NR *Flu sx:* 29% *Myalgias:* 39% *Fatigue:* 55% *Irritability:* 26% *Depression:* 5% *Headache:* 17%	Grant from the Regione Veneto, Ricerca Sanitaria Finalizzata, Italy	Fair	Unclear	
Nishiguchi 2001[217]	*HCC:* 27% (a) vs. 73% (b) (p<0.001) *Death* : 11% (a) vs. 58% (b) (p<0.001) *Univariate* : *RR of progression to Child B:* 0.302 (0.156-0.583) *RR of development of HCC:* 0.244 (0.126-0.475) *RR of death:* 0.169 (0.065-0.440) *Multivariate:* *RR progression to Child B:* 0.250 (0.124-0.505) *RR development of HCC:* 0.256 (0.125-0.522) *RR death:* 0.135 (0.049-0.372)	Fever, flu sx, thrombocytopenia, all resolved once end of treatment reached	Ministry of Welfare, Japan	Good	Unclear	

*p<0.05

ETR=end of treatment response; SR=sustained response; tx=treatment; HCC=hepatocellular carcinoma; sx=symptoms; rdx=reduction; Child C=measure of abnormalities of liver histology; HCV=hepatitis C virus; HCV RNA=hepatitis C ribonucleic acid; WBC=white blood cell; NR=not reported; ALT=alanine aminotransferase

Evidence Table 3b. Quality of RCTs for long term outcomes

Author Year	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Patient unaware of treatment?
Interferon						
Bernardinello 1999[219]	Yes, by computer	Not clarified	Yes	Yes	Not clarified	Not clarified, but unlikely as no placebo
Chemello 1999[218]	Yes, by computer	Not clarified	Yes	Yes	Pathologist blinded for post treatment biopsy evaluation	Not clarified
Nishiguchi 1995[217]	Yes, by computer	No	Yes	Yes	No	No

RCT=randomized controlled trial

Evidence Table 3b. Quality of RCTs for long term outcomes (continued)

Author Year	Intention to treat analysis?	Maintenance of comparable groups?	Reporting of attrition, crossovers, adherence, and contamination?	Differential loss to follow up or high loss?	Statistical analysis appropriate?	Internal Validity Rating
Interferon						
Bernardinello 1999[219]	Yes	Not clarified	No	Not reported	Yes	Fair
Chemello 1999[218]	Yes	Not clarified	No	Not reported	Yes	Fair
Nishiguchi 1995[217]	Yes	Not clarified	Yes	No	Yes	Good

RCT=randomized controlled trial

Evidence Table 4. Quality of Life

Author Year	Study Type	Sample Size	Quality of Life Measure	Treatment	Results	Blinded to treatment response	Internal Validity Rating
Pegylated Interferon versus Interferon							
Bernstein 2002[234]	Pooled analysis from 3 RCTs Open label study	1441	SF-36 FFS	a) Peg INF 180 ug x 48 wks b) INF 3 MU tiw x 48 wks or 6MU tiw x 12 wks then 3MU tiw x 36 wks	FSS SVR NR Diff p TS -0.4 0.1 -0.5 <0.001 VAS -9.1 2.4 -11.5 <0.001 SF-36 PF 2.4 -2.2 4.6 <0.001 PR 8.2 -1.6 9.8 <0.001 BP 2.8 -0.1 2.9 <0.01 GH 8.5 -3.6 9.1 <0.001 VT 9.2 -0.4 9.6 <0.001 SF 4.6 -1.6 6.2 <0.001 RE 4.5 -3.9 8.4 <0.01 MH 2.5 -2.1 4.6 <0.001 PCS 2.2 -0.6 2.8 <0.001 MCS 2.0 -1.0 3.0 <0.001	Blinded to 24 week treatment response until after completed questionaire, but could have known prior response status	Fair (open label, loss to follow up appears high but difficult to tell; no references for trials pooled; not clear if all 1441 patients included in analysis)
Interferon + Ribavirin versus Interferon alone							
McHutchinson 2001[236]	Double blind placebo controlled RCT	828	HQLQ SF-36	a) INF 3 MU tiw + Placebo for 24 or 48 wks b) INF 3 MU tiw + Ribavirin 100-1200 mg/day for 24 or 48 wks	SVR PF 2.5 RP 5.0 BP 1.5 GH 5.0 VT 4.5 SF 3.0 RE 3.0 MH 2.5 SLP 3.5 DIS 5.0 HHD 5.5 (Values shown are the standard deviation of change from NRs.)	Could have been aware of results of biochemical or virologic testing	Fair (not blinded to treatment results)

Evidence Table 4. Quality of Life

Author Year	Study Type	Sample Size	Quality of Life Measure	Treatment	Results	Blinded to treatment response	Internal Validity Rating
Interferon alone							
Bonkovsky 1999[235]	Multicenter double blind RCT	642	HRQOL SF-36 MOS	a) INF Consensus 3-9 ug tiw x 24 wks b) INF alfa-2b 15 ug tiw x 24 wks	SVR NR Diff p PF +8 +2 +6 <0.05 RP +26 +4 +22 <0.01 BP +3 +4 -1 NS GH +7 0 +7 <0.01 VT +12 +4 +8 <0.05 SF +12 +3 +9 <0.05 RE +15 +4 +11 NS MH +6 +2 +4 NS APT +8 +2 +6 <0.01 COG +3 +1 +2 NS CUR +16 +2 +14 <0.01 DIS +8 +3 +5 NS SEX +8 +4 +4 <0.05 SLP +4 +3 +1 NS	Blinded to viral load testing but could have been aware of transaminase test results	Fair (22% loss to follow up; not blinded to treatment results)

ug = micrograms
MU = million units
tiw = three times per week
wks = weeks
pts = patients
RCT = Randomized controlled trial
PF = Physical function
RP = Ability to perform physical roles
BP = Degree of bodily pain
GH = Sense of general health
COG = Cognitive function
DIS = Feeling of health distress
SLP = Sleep quality
PCS = Physical component summary
HHD = Hepatitis specific health distress
SF = Short form
FFS = Fatigue Severity Scale
HQLQ = Hepatitis Quality of Life Questionaire
HRQOL = Health Related Quality of Life
MOS = Medical Outcomes Study
VT = Overal sense of vitality
SF (results) = Social function
RE = Ability to perform emotional roles
MH = Overal sense of mental health
APT = Appetite
CUR = Perception of current health
SEX = Sexual functioning
Diff = Difference
MCS = Mental component summary