World Health Organization

WHO/HIV/2014.32

Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries

PICO 6: Treatment

Pegylated interferon plus ribavirin versus standard interferon plus ribavirin for chronic hepatitis C infection: a meta-analytical systematic review

Conducted by the Burnet Institute, Melbourne and Health Protection Scotland, Glasgow
23 June 2013

Review Members

Dr Brendan Quinn	Burnet Institute, Melbourne
Dr Jess Howell	Royal Melbourne Hospital, Melbourne
Dr SweeLin Mei	St Vincent's Hospital, University of Melbourne
Dr Joseph Doyle	Burnet Institute, Melbourne
Dr Esther Aspinall	Health Protection Scotland, Glasgow
Prof Sharon Hutchinson	Caledonian University, Glasgow
Prof Margaret Hellard	Burnet Institute, Melbourne

Review Advisory Group

Dr Mark Stoove	Burnet Institute, Melbourne
Prof David Goldberg	Health Protection Scotland
Prof Stanley Luchters	Burnet Institute, Melbourne
Dr Alexander Thompson	St Vincent's Hospital, University of Melbourne
Dr Stefan Wiktor	WHO Global Hepatitis Program
Mr Tim Nguyen	WHO Global Hepatitis Program
Dr Bryce Smith	Centre for Disease Control and Prevention, Atlanta
Dr Yngve Falck-Ytter	Case Western Reserve University,
Ms Rebecca Morgan	Centre for Disease Control and Prevention, Atlanta

Table of Contents

BACKGROUND

The World Health Organization (WHO) estimates that between 130 and 150 million people are chronically infected with hepatitis C virus (HCV) worldwide [1]. People with untreated HCV are at increased risk of liver cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality [2]. According to the most recent guidelines of the European Association for the Study of the Liver (EASL) [3], the combination of pegylated interferon and ribavirin therapy is the approved standard of care for treating individuals with chronic HCV. This review assessed the available evidence to determine whether pegylated interferon is more effective at treating chronic HCV compared to standard interferon with respect to maximising the chance of achieving a sustained virological response (SVR), and reducing morbidity (i.e., decompensated liver disease/hepatocellular carcinoma), mortality and other serious adverse events.

METHODS

Narrative review question:

Among people with chronic HCV and receiving antiviral treatment, is treatment with pegylated interferon and ribavirin therapy more effective than treatment with standard interferon and ribavirin therapy?

PICO question:

Population: Treatment-naïve adults and children with chronic HCV infection

Intervention*:* Treatment with pegylated interferon and ribavirin therapy

Comparison*:* Treatment with standard interferon and ribavirin therapy

Outcomes: Rates of SVR, decompensated liver disease, hepatocellular carcinoma, all-cause mortality and treatment-related adverse events leading to discontinuation of therapy; quality of life. Cost outcomes will require economic modelling which will be conducted separately from this protocol.

Study type/limits*:* Experimental studies (human) published between 1994 and the present

Search strategy

A systematic review was conducted using the following electronic databases and information sources:

- OVID MEDLINE, OVID EMBASE, LILACS, and the Cochrane Library (CENTRAL and DARE) (without language restrictions);
- Unpublished/ongoing research presented at relevant international conferences;
- Conference proceedings and clinical trials registries from EASL, AASLD, APASL, and ClinicalTrials.gov;
- Reference lists of all relevant articles and reviews;
- Recommendations from Guideline Development Group (GDG) members and other experts in the field;
- Relevant articles identified during the conduct of the other systematic reviews.

Search terms are listed in Appendix I, briefly summarized as: Hepatitis C/HCV AND pegylated interferon.

Conduct of the review

- The review was conducted using *GRADE profiler* (version 3.6; GRADE working group) software, and complied with Cochrane methodology and PRISMA guidelines on reporting (Prospero registration number CRD42013004482);
- Due to the large number of citations, the primary reviewer removed all obviously irrelevant articles on citation screening. The primary reviewer and secondary reviewers subsequently screened abstracts and full-text articles. A third reviewer was consulted on any points of difference;
- Although cost-effectiveness was not included as an outcome of this review, relevant cost effectiveness studies were reviewed to check for any previously unpublished empirical data that met the PICO criteria;
- Foreign language articles were translated online using Google Translate, with additional interpretation sought from the primary authors as required;
- Missing data on outcomes of interest were requested from primary authors, with each author contacted twice in the case of non-response.

Quality appraisal

Studies were assessed as having low, high, or unclear level of bias using the Cochrane Risk of Bias assessment tool.

Data extraction

Data were extracted from each study by the primary reviewer and two secondary reviewers. The following data were extracted, where available:

- Study characteristics (country, study design, study objectives, funding source);
- Study population (adults vs. children, people who inject drugs [PWID], genotype);
- Setting (community clinic, hospital clinic; harm reduction and community services, low- and middle-income country [LMIC] vs. high-income country [HIC] setting);
- Participant details (age, sex, ethnicity);
- Inclusion/exclusion criteria for study;
- Sample size;
- Intervention (type of HCV treatment);
- Control (selection and characteristics of control group);
- Analysis (number offered intervention, number accepted intervention, reason for refusal, time to follow-up, study data collection method, statistical analyses, primary and secondary outcomes of study);
- Results (SVR, decompensated cirrhosis, hepatocellular carcinoma, all-cause mortality, treatment-related serious adverse events, quality of life);
- Additional comments.

GRADE process

The quality of the body of evidence as a whole was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. GRADE rates the quality of evidence for each outcome of interest (i.e., SVR, mortality, morbidity, cost-effectiveness, serious adverse events) as high, moderate, low or very low, depending on a number of criteria. These include study design, study quality, study consistency (the similarity of estimates of effect across studies) and study directness (the extent to which the evidence is relevant to the population, intervention, and outcome of interest).

Data synthesis

Where sufficient data relating to any of the outcomes of interest was available, pre-specified meta-analyses were attempted as follows:

- What is the relative risk of the outcomes of interest (SVR, morbidity, mortality, adverse events, quality of life) among chronic HCV populations administered pegylated interferon vs. interferon?

- Depending on the availability of data, subgroup meta-analyses were considered for the following:
    - Outcomes (as above) of administering treatment in adults vs. children;
    - Outcomes (as above) of administering treatment by genotype (GT 1, 2/3 vs 4);
    - Outcomes (as above) of administering treatment by HIV infection status;
    - Outcomes (as above) of administering treatment by PWID/IDU status;
    - Outcomes (as above) of administering treatment by fibrosis stage;
    - Outcomes (as above) of administering treatment in GP/community-based settings vs. HCV-specialist treatment settings;
    - Outcomes (as above) of administering treatment in LMIC vs. HIC settings.

RESULTS

The literature search identified 3877 citations. Figure 1 details the process undertaken to identify articles that satisfied the PICO criteria outlined above. Following the removal of 1230 duplicates, further clearly irrelevant citations were excluded based on the screening of article titles (n=2120) and abstracts (n=445). Eighty-two full-text articles were reviewed, of which 58 were excluded.

Twenty-five articles were included in the final analysis. The characteristics of each study are listed in Table 1. Only one study [4] was from a low-middle income region (Egypt). The identification of one systematic review [5] and one meta-analysis [6], which both addressed similar PICOs to this review, were published in 2007 and included studies up until the beginning of 2005, enabled valuable comparisons between the findings of this review and theirs. While their eligibility criteria for study inclusion were somewhat broader in scope (e.g., studies involving treatment of non-responders or relapsers were deemed eligible but excluded from this review), there is a degree of cross-over between this report and those two articles.

Two additional systematic reviews and meta-analyses were identified that were not included in the final review because they did not address the same PICO (specifically the comparison between pegylated and standard interferon); however, their findings are worth mentioning due to their focus on SVR as an outcome among crucial sub-groups identified in the 'Data extraction' section above that were not well represented in the findings of this review. The first assessed clinical trials to investigate the safety and efficacy of pegylated interferon plus ribavirin for the treatment of chronic HCV in children and adolescents [7]. Eight trials were included in the review, with results indicating that over half (58%; 95% CI: 53-64) of patients aged 3-18 years who were administered pegylated interferon alpha-2a or 2b achieved SVR. SVR was higher for those with HCV genotypes 2 or 3 compared to 1 or 4. Four percent of patients discontinued treatment due to adverse events. Overall, the review findings indicated that pegylated interferon plus ribavirin is effective and safe in treating children and adolescents with HCV. The second article investigated HCV treatment outcomes among PWID [8]. The findings of six studies (comprising 314 drug users, of whom 141 (45%) were PWID) resulted in a pooled SVR of approximately 61% (95% CI: 51-72) among PWID, which was comparable to SVR rates among studies of former or non-PWID.

Outcome and sub-group analyses

Sustained virological response

The findings of the reviewed experimental studies (n=25), with a total of 6350 study participants (3492 administered pegylated interferon plus ribavirin, 2858 administered standard interferon plus ribavirin) indicated that the use of pegylated interferon and ribavirin is more effective at achieving SVR among people with chronic HCV compared to standard interferon and ribavirin (Figure 2; overall RR: 0.81; 95% CI: 0.76-0.86; I^2=48.2%). One study [9] was an exception, indicating a higher rate of SVR among participants administered standard interferon and ribavirin versus pegylated interferon and ribavirin; however, this finding was not significant (RR: 1.12; 95% CI: 0.75-1.66). Sub-group analyses involving the findings of six studies [10-15] suggested that the effect of treatment was more pronounced among non-genotype 1 HCV patients in particular (Figures 2 and 3). In comparison, there was very little difference observed in sub-group analyses involving cirrhotic and non-cirrhotic patients administered pegylated versus standard interferon (Figures 5 and 6) [10, 11, 16, 17].

Terminated study due to adverse events

Sixteen of the 25 studies [4, 10-24] provided data on study discontinuation due to adverse events (Figure 7). Findings suggested that there was no significant difference between patients administered pegylated interferon versus conventional interferon (both plus ribavirin) regarding treatment discontinuation resulting from adverse events (RR: 1.01; 95% CI: 0.79-1.29; I^2=37.4%).

All-cause mortality among study participants

Five articles [4, 13, 15, 16, 18] provided data on all-cause mortality among patients during study participation (Figure 8). This evidence was considered to be of moderate quality due to imprecision resulting from the occurrence of only a few events (Table 2). Nevertheless, analyses of the available data indicated that there was no significant difference in rates of all-cause mortality among patients administered pegylated versus standard interferon (RR: 1.26; 95% CI: 0.52-3.07; I^2=0.0%).

Liver-related mortality among study participants

Only two articles [15, 16] included findings on liver-related mortality among study participants. This evidence was considered to be of moderate quality due to imprecision (i.e., few events). Analyses indicated no significant difference between study participants administered pegylated interferon plus ribavirin and conventional interferon plus ribavirin regarding liver-related mortality (RR: 0.63; 95% CI: 0.12-3.24; I^2=0.0%).

Hepatic decompensation

Two studies [13, 15] provided data on hepatic decompensation among patients; the evidence was considered to be only of low quality due to imprecision and risk of bias. There was no significant difference between patients administered pegylated versus standard interferon regarding hepatic decompensation (RR: 0.84; 95% CI: 0.20-3.64; I^2=15.7%).

Development of HCC

Only one article provided data on the development of HCC among patients during the study period. The available evidence was considered to be low due serious imprecision due to few events and only short term follow up.

CONCLUSION

The available evidence indicates that the use of pegylated interferon and ribavirin is more effective at achieving SVR among people with chronic HCV compared to standard interferon and ribavirin, particularly among individuals with non-genotype 1 HCV. Overall, there was no significant difference in the rate of study termination due to adverse events among patients administered pegylated versus conventional interferon (both plus ribavirin). Limited data prevented adequate investigation of the rate of liver-related mortality, hepatic decompensation and HCC development among people treated with pegylated versus standard interferon. There is indirect evidence from other systematic reviews that HCV treatment among children or PWID is effective. There was a considerable lack of studies examining these outcomes in low-middle income countries, which impacts on the relevance of this review's findings to such areas.

Implications for practice

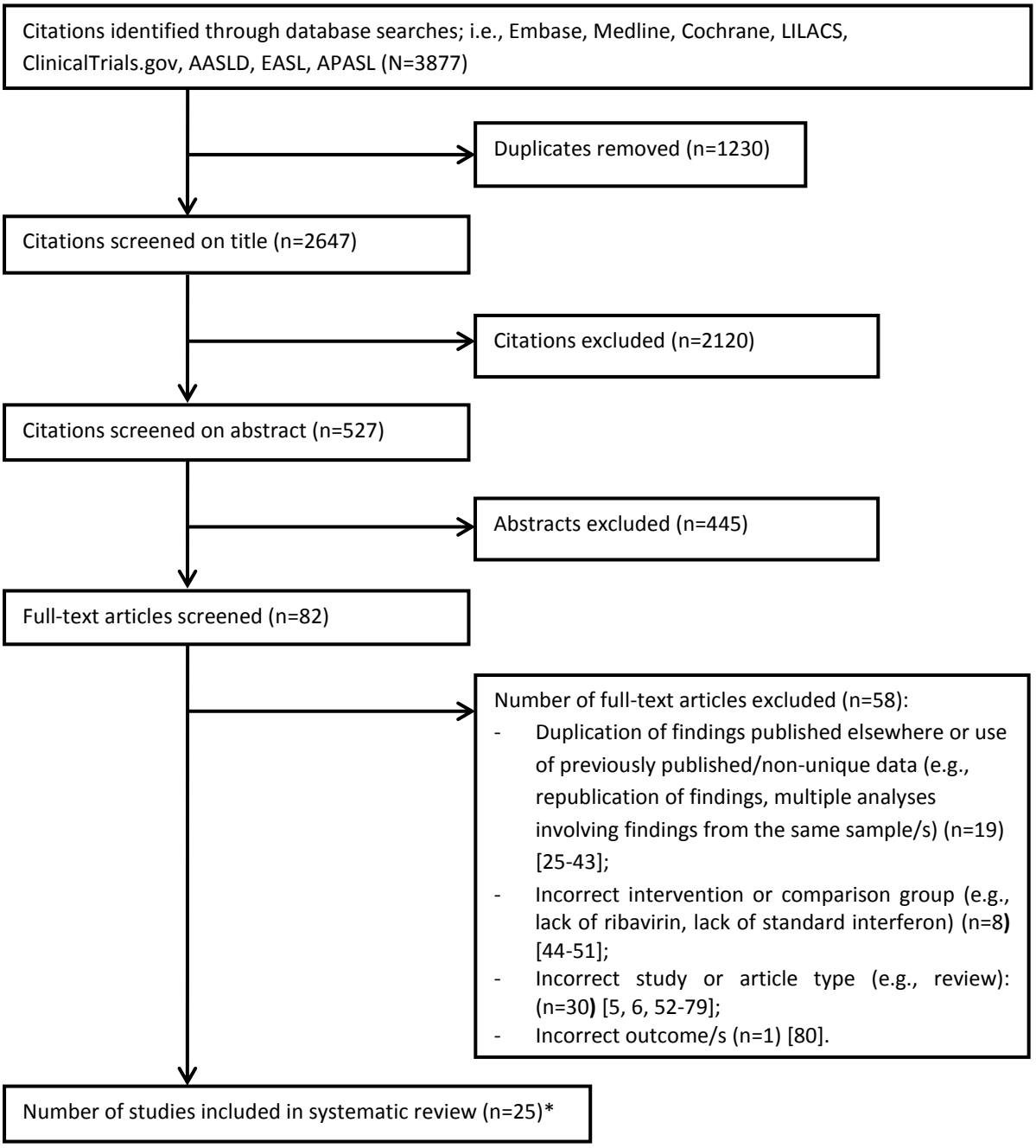
Pegylated interferon plus ribavirin is more effective than standard interferon and ribavirin at achieving SVR among patients with chronic HCV. However, decisions regarding treatment must consider treatment cost in particular (i.e., pegylated interferon can be more expensive than standard interferon and therefore might be prohibitive for treatment of HCV in low-middle income countries).

Implications for research

There is a lack of research examining the safety and efficacy of pegylated versus standard interferon (both plus ribavirin) in low-middle income countries.

FIGURES AND TABLES

Figure 1: Systematic Review Flowchart



*Refer to Table 1 below for a description of each study included in the review.

Table 1: Summaries of included studies

STUDY	**Alfaleh, F.S. et al., 2004 [18]**
OBJECTIVE/S	Compare the efficacy and safety of PEG-IFN alpha-2b vs. IFN alpha-2b (both plus RBV) in patients with chronic HCV genotype 4
PARTICIPANT CHARACTERISTICS	56% male; mean/median age of 47 years
SETTING/LOCATION	Four hospitals in Saudi Arabia
INTERVENTION PERIOD	June – October 2001
STUDY POPULATION	Saudi Arabian adults with chronic HCV (all genotypes)
INCLUSION	Persistently raised aminotransferases for >6 months; serum antibodies to HCV; HCV RNA found by PCR; chronic hepatitis diagnosis via liver biopsy last 12 months
EXCLUSION	<18 years or >70 years; previous IFN or RBV treatment; neutropenia; thrombocytopenia; anaemia; serum creatinine >1.5 times upper normal limit; serum α-fetoproteins concentration >25ng/ml; history of alcohol or haemolytic disease; decompensated cirrhosis; autoimmune hepatitis; HBV or HIV; current IDU; severe depressive illness; severe comorbid disease; organ transplant; pregnant or unwilling to use contraception; HCC
INTERVENTION	N=48; 100µg of PEG-IFN alpha-2b weekly + RBV (800mg/day) for 48 weeks
CONTROL	N=48; 3MU IFN alpha-2b TIW + RBV (800mg/day) for 48 weeks
OUTCOME/S	Biochemical and virologic responses
HEADLINE FINDING OF STUDY	Treatment with PEG-IFN resulted in a higher (although not statistically significant) rate of SVR
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Almeida, F.S. et al., 2009 [81]**
OBJECTIVE/S	Evaluate rate of SVR for PEGIFN vs. IFN (both plus RBV) in coinfected HCV/HIV patients with HCV genotype 1 in a Brazilian Health Ministry program
PARTICIPANT CHARACTERISTICS	78% male; mean/median age of 41 years
SETTING/LOCATION	Brazil
INTERVENTION PERIOD	IFN/RBV pre-2002; PEG-IFN/RBV from 2002 onwards
STUDY POPULATION	Brazilian adults coinfected with HCV/HIV (genotype 1) attending a public health program
INTERVENTION	N=59; PEG-IFN alpha-2a (180mcg) or PEG-IFN alpha-2b (1.5 mcg/kg) weekly + weight-based RBV for 48 weeks
CONTROL	N=22; IFN-alpha (3MIU) 3 TIW + weight-based RBV for 48 weeks
OUTCOME/S	Virologic response
HEADLINE FINDING OF STUDY	HCV/HIV coinfected patients (genotype 1) treated with PEG-IFN and RBV were 1.9 times more likely to obtain a SVR than those treated with standard IFN and RBV
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: No Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Unclear Free of other bias: Unclear
SUMMARY	UNCLEAR RISK OF BIAS

STUDY	**Arizcorreta, A. et al., 2004 [19]**
OBJECTIVE/S	Analyse the evolution of haematological population counts during and after IFN and RBV therapy for chronic HCV infection in coinfected HCV/HIV patients
PARTICIPANT CHARACTERISTICS	71% male; mean/median age of 34 years
SETTING/LOCATION	Hospital in Cadiz, Spain
STUDY POPULATION	Coinfected HCV/HIV adults attending a hospital's Infectious Disease Unit
INCLUSION	HCV/HIV coinfection
EXCLUSION	Decompensated cirrhosis; HBV; other infectious, autoimmune, tumoural, biliary or vascular-associated liver disease; AOD dependence; Karnofsky index <80; low neutrophil or platelet counts or haemoglobin concentration; poorly controlled psychiatric disease; substantial coexisting medical conditions; inability to use contraception; previous IFN or RBV treatment
INTERVENTION	N=11; PEG-IFN alpha-2a (180µg /week) + 800mg RBV daily for 48 weeks
CONTROL	N=10; IFN alpha-2a 3MIU TIW + 800mg RBV/day
OUTCOME/S	Changes in haematological series, SVR
HEADLINE FINDING OF STUDY	The reduction in all haematological series was higher in patients treated with PEG-IFN. SVR was achieved in 64% of patients administered PEG-IFN vs. 20% of those administered standard IFN.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: No Allocation concealment: No Blinding of participants, personnel and outcome assessors: No Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Bruno, S. et al., 2004 [20]**
OBJECTIVE/S	Assess the efficacy and safety of an initial induction period of 'crudely weight-based' dose of PEG-IFN alpha-2b in treatment-naïve patients with chronic HCV genotype 1, and identify predictors of treatment response
PARTICIPANT CHARACTERISTICS	62% male; mean/median age of 50 years
SETTING/LOCATION	8 Italian tertiary referral liver units
INTERVENTION PERIOD	January – June 2000
STUDY POPULATION	Adults with chronic HCV genotype 1
INCLUSION	Treatment-naïve HCV RNA positive patients; 18-65 years; ALT values >1.5 times upper normal limit; liver biopsy last 6 months with chronic HCV diagnosis (any degree of fibrosis); high haemoglobin, WBC, granulocyte and platelet counts; bilirubin, albumin and serum creatinine levels within normal limits
EXCLUSION	Advanced cirrhosis (>F2); history of gastrointestinal bleeding, ascites or encephalopathy; HCC, anti-HIV or HBsAg positivity; alcohol abuse; parenteral drug addiction if not abstaining for at least 2 years; other contraindications to IFN or RBV
INTERVENTION	N=163; weight-based PEG-IFN alpha-2b (80-100µg/week) for 8 weeks followed by 50µg/week for 40 weeks (+ weight-based RBV)
CONTROL	N=160; IFN alpha-2b 6MIU on alternate days + weight-based RBV/day for 48 weeks
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	Treatment with PEG-IFN was more effective and better tolerated among naïve patients with genotype 1 compared to standard IFN
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: Yes Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Cappiello, G. et al., 2003 [82]**
OBJECTIVE/S	Characterise the IFN sensitivity determining region (ISDR) mutation pattern and its changes at 4 weeks of treatment in patients infected with HCV genotype 1b receiving standard or PEG-IFN (both plus RBV) to find early correlates of therapy outcome
PARTICIPANT CHARACTERISTICS	76% male; median/mean age of 51 years
SETTING/LOCATION	Italy
INTERVENTION PERIOD	2000-2001
STUDY POPULATION	Adults infected with chronic HCV genotype 1b
INCLUSION	Chronic HCV; median METAVIR score grade 2, stage 2
EXCLUSION	No laboratory signs of other causes of hepatitis; HIV
INTERVENTION	N=23; weight-based PEG-IFN alpha-2b (80–100µg/week) for 8 weeks, followed by 50µg/week for 40 weeks (+ weight-based RBV)
CONTROL	N=22; IFN alpha-2b (6 MIU/day) + weight-based RBV for 48 weeks
OUTCOME/S	ISDR pattern/evolution, virological response
HEADLINE FINDING OF STUDY	The baseline pattern of ISDR was unrelated to treatment outcome among study participants. SVR was achieved in 39% of participants administered PEG-IFN vs 32% in those administered standard IFN.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	UNCLEAR RISK OF BIAS

STUDY	**Carrat, F. et al., 2004 [16]**
OBJECTIVE/S	Compare the efficacy and safety of a 48 week course of RBV and either IFN alpha-2b or PEG-IFN alpha-2b in HCV/HIV coinfected patients
PARTICIPANT CHARACTERISTICS	74% male; median/mean age of 40 years
SETTING/LOCATION	71 French hospitals
INTERVENTION PERIOD	February 2000 – February 2002
STUDY POPULATION	Adult, IFN-naïve patients with HCV/HIV coinfection
INCLUSION	IFN-naïve; aged 18+; second-generation enzyme-linked immunosorbent assay positive for anti-HCV antibodies and polymerase chain reaction-based assay positive for HCV-RNA in serum; liver biopsy last 18 months showing at least mild activity or fibrosis; HIV; stable plasma HIV-1 RNA level; stable antiretroviral treatment last 3 months; CD4 cell count > $200x10^6$/L
EXCLUSION	Neutropenia; thrombocytopenia; anaemia; serum creatinine level > 1.70mg/dL; circulating HBV surface antigen positivity; decompensated cirrhosis; biliary, tumoral or vascular liver disease; psychiatric disorders; history of seizures; cardiovascular disease; poorly controlled diabetes mellitus; autoimmune disorders; IDU last 3 months; excessive daily alcohol intake; unwilling to use contraception
INTERVENTION	N=205; PEG-IFN alpha-2b (1.5µg/kg/week) + 800mg RBV/day
CONTROL	N=207; IFN alpha-2b (3MIU TIW) + 800mg RBV/day
OUTCOME/S	Virological and histological responses
HEADLINE FINDING OF STUDY	Treatment with PEG-IFN and RBV was more effective than standard IFN for HCV infection in HIV-infected patients
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: No Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Chung, R.T. et al., 2004 [12]**
OBJECTIVE/S	Compare PEG-IFN to IFN (both plus RBV) in treating HCV/HIV coinfected patients
PARTICIPANT CHARACTERISTICS	82% male; median/mean age of 45 years
SETTING/LOCATION	21 Adult AIDS Clinical Trials Group sites in the USA
INTERVENTION PERIOD	December 2000 – June 2001
STUDY POPULATION	HIV-infected adults with chronic HCV
INCLUSION	Aged18+; HIV; chronic HCV (i.e., HCV RNA level >600 IU/mL); IFN-naïve; liver biopsy showing abnormal histologic findings consistent with chronic HCV last 48 weeks; individuals with normal or elevated serum ALT levels. Cirrhotic subjects required no evidence of hepatic decompensation (i.e., ascites, encephalopathy, jaundice, hypoalbuminemia, or coagulopathy).
EXCLUSION	Clinically significant anemia; neutropenia; thrombocytopenia; renal disease; HBV; uncontrolled cardiopulmonary disease; poorly controlled psychiatric disease; active HIV-related opportunistic infection
INTERVENTION	N=66; PEG-IFN alpha-2a (180 µg/week) + RBV (600-1000mg/day)
CONTROL	N=67; IFN alpha-2a (6MIU TIW for 12 weeks, 3 MIU for 36 weeks) + RBV (600-1000mg/day)
OUTCOME/S	Histological and virological responses
HEADLINE FINDING OF STUDY	PEG-IFN plus RBV is superior to IFN plus RBV in the treatment of chronic HCV in HIV-infected persons
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Crespo, M. et al., 2007 [15]**
OBJECTIVE/S	Assess the safety and efficacy of PEG-IFN alpha-2b vs. IFN alpha-2b (both plus RBV) for chronic HCV in HIV-infected patients
PARTICIPANT CHARACTERISTICS	77% male; median/mean age of 38 years
SETTING/LOCATION	A tertiary hospital in Spain
INTERVENTION PERIOD	January 2001 – April 2003
STUDY POPULATION	Adults with HCV/HIV coinfection
INCLUSION	Aged 18–60 years; serum ALT >44 IU/L in men & >34 IU/L in women; serum HCV RNA >1000 IU/mL; CD4+ T-cell count >200 cells/mm^3; serum HIV RNA <80 copies/mL for patients on HAART or <10 000 copies/mL for HAART-naïve patients
EXCLUSION	Prior IFN treatment; HBV; active AOD use and/or opportunistic infection last 6 months; decompensated cirrhosis; serum creatinine >1.5 times upper normal limit; haemoglobin <11g/dL in women or <12g/dL in men; neutrophil count <1500/mm^3; platelet count <70 000/mm^3; history of major psychiatric illness; active autoimmune disease
INTERVENTION	N=60; PEG-IFN alpha-2b (1.5 mcg/kg/week) + RBV (800mg/day)
CONTROL	N=61; IFN alpha-2b (3 MIU TIW) + RBV (800mg/day)
OUTCOME/S	Virological response, changes in mitochondrial DNA
HEADLINE FINDING OF STUDY	PEG-IFN alpha-2b plus RBV was more effective than IFN alpha-2b plus RBV in treating HCV/HIV coinfected patients
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**D'Ambrosio, R. et al., 2011 [9]**
OBJECTIVE/S	Assess whether successful IFN therapy modifies the development and/or progression of esophageal varices in patients with HCV-related compensated cirrhosis
PARTICIPANT CHARACTERISTICS	62% male; median/mean age of 59 years
SETTING/LOCATION	Italian liver clinic
INTERVENTION PERIOD	January 2000 – March 2006
STUDY POPULATION	Treatment-naïve Child-Pugh A patients with either no or small (F1) esophageal varices
INCLUSION	Compensated liver disease (Child-Pugh A); no previous clinical decompensation (e.g., jaundice, ascites, encephalopathy, variceal bleeding); willing to undergo endoscopic surveillance independently of treatment outcome
EXCLUSION	HCC; HBV; HIV; drug dependence; >40g/day alcohol intake; previous medical or endoscopic treatment for esophageal varices; F2 or F3 varices and/or moderate or severe PHG; poorly controlled diabetes; severe depression; autoimmune diseases; concomitant malignant neoplastic diseases
INTERVENTION	N=91; PEG-IFN alpha-2b (1.5µg/kg/week) + weight-based RBV *or* PEG-IFN alpha-2a (180µg/week) + weight-based RBV in HCV-1 and HCV-4 patients or fixed RBV in HCV-2 and HCV-3 patients
CONTROL	N=36; IFN alpha-2b (3MIU TIW) + RBV (800-1200mg/day)
OUTCOME/S	Portal hypertension-related events, other cirrhosis-related complications, mortality, virological response
HEADLINE FINDING OF STUDY	Successful IFN therapy prevents or delays the *de novo* onset of esophageal varices in patients with compensated cirrhosis due to HCV. SVR was more common in patients administered standard IFN (53%) vs. those administered PEG-IFN (47%)
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: No Allocation concealment: No Blinding of participants, personnel and outcome assessors: Yes Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Dimitroulopoulos, D. et al., 2009 [21]**
OBJECTIVE/S	Assess compliance rates of patients on methadone maintenance therapy (MMT) administered PEG-IFN vs. IFN (both plus RBV) and evaluate treatment efficacy
PARTICIPANT CHARACTERISTICS	80% male; median/mean age of 38 years
SETTING/LOCATION	Gastroenterology-Hepatology departments of two tertiary care state hospitals in Greece
INTERVENTION PERIOD	2000-2003
STUDY POPULATION	Chronic HCV patients naïve to IFN on MMT
INCLUSION	Adults with chronic HCV on MMT; anti-HCV positive; detectable HCV-RNA level in a polymerase chain reaction-based assay for more than 6 months; liver biopsy within last 6 months; elevated ALT levels
EXCLUSION	Active AOD use; severe or untreated psychiatric illness; decompensated cirrhosis; HIV; HBV; severe cardiac or neurologic disease; HCC; history of other malignancy or active malignant disease; autoimmune disorders; pregnancy or lactation; previous IFN treatment; neutrophil count <1500/mm^3; platelet count <75000/mm^3
INTERVENTION	N=45; PEG-IFN alpha-2b (1.5μ/kg/week) + weight-based RBV
CONTROL	N=65; IFN alpha-2b (6 MIU TIW) + weight-based RBV
OUTCOME/S	Patient compliance rate, virological response
HEADLINE FINDING OF STUDY	PEG-IFN achieved a significantly higher compliance rate than IFN in patients undergoing MMT. SVR was achieved in 51% of patients on PEG-IFN, compared to 32% of those on IFN.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: No Allocation concealment: No Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: No Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Esmat, G.H. et al., 2003 [4]**
OBJECTIVE/S	Assess the effect of PEG-IFN vs. IFN (both plus RBV) in treatment-naïve subjects with chronic HCV
PARTICIPANT CHARACTERISTICS	79% male; median/mean age of 40 years
SETTING/LOCATION	Egypt
STUDY POPULATION	Treatment-naïve adults with chronic HCV in Egypt
INCLUSION	Chronic HCV documented by liver biopsy; detectable HCV RNA in serum
INTERVENTION	N=100; PEG-IFN alpha-2b (100 mcg/week) + weight-based RBV (800-1000mg) for 48 weeks
CONTROL	N=100; IFN alpha-2b (3 MU TIW) + weight-based RBV (800-1000mg) for 48 weeks
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	Subjects with chronic HCV and genotype 4 infection have a similar antiviral response to standard IFN and PEG-IFN (both plus RBV)
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Unclear Free of other bias: Unclear
SUMMARY	UNCLEAR RISK OF BIAS

STUDY	**Fried, M.W. et al., 2002 [11]**
OBJECTIVE/S	Assess the efficacy and safety of PEG-IFN vs. standard IFN (both plus RBV)
PARTICIPANT CHARACTERISTICS	72% male; median/mean age of 43 years
SETTING/LOCATION	81 centres worldwide
INTERVENTION PERIOD	February 1999 – April 2001
STUDY POPULATION	IFN-naïve adults with chronic HCV
INCLUSION	Treatment-naïve; >2000 copies of HCV RNA/ml of serum; serum ALT activity > upper limit of normal last 6 months; chronic HCV
EXCLUSION	Neutropenia; thrombocytopenia; anaemia; HIV; decompensated liver disease; serum creatinine level <1.5 times the upper limit of normal; poorly controlled psychiatric disease; AOD dependence last 12 months; substantial coexisting medical conditions
INTERVENTION	N=453; PEG-IFN alpha-2a (180µg/week) + daily weight-based RBV
CONTROL	N=444; IFN alpha-2a (3 MIU TIW) + weight-based RBV
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	Weekly PEG-IFN was tolerated as well as standard IFN and produced significant improvements in the rate of SVR.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Gedik, H. et al., 2008 [83]**
OBJECTIVE/S	Evaluate the efficacy and adverse events of standard IFN vs. PEG-IFN (both plus RBV) in treating patients with chronic HCV
PARTICIPANT CHARACTERISTICS	43% male; median/mean age of 48 years
SETTING/LOCATION	Turkey
STUDY POPULATION	Treatment-naïve patients with chronic HCV
INCLUSION	Treatment-naïve; biopsy-proven chronic HCV; elevated ALT levels; positive HCV-RNA
INTERVENTION	N=42; PEG-IFN alpha-2a (135µg or 180µg/week) or PEG-IFN alpha-2b (1.5µg/kg/week) + RBV for 52 weeks
CONTROL	N=56; IFN alpha-2a or 2b (3 MIU TIW) + RBV for 52 weeks
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	No significant differences in efficacy and rates of adverse events were observed between the two treatment schedules. Nevertheless, a higher rate of SVR was observed in patients administered PEG-IFN (74%) vs. standard IFN (63%)
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Unclear Free of other bias: Unclear
SUMMARY	UNCLEAR RISK OF BIAS

STUDY	**Hinrichsen, H. et al., 2002* [84]**
SETTING/LOCATION	Germany
STUDY POPULATION	Treatment-naïve patients with genotype 2 or 3 HCV
INTERVENTION	N=28; PEG-IFN alpha-2b + RBV for 24 weeks
CONTROL	N=26; IFN alpha-2b + RBV for 24 weeks
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	SVR was achieved in 86% of patients administered PEG-IFN plus RBV vs. 85% of those administered standard IFN plus RBV
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Unclear Free of other bias: Unclear
SUMMARY	UNCLEAR RISK OF BIAS

*No abstract or publication was available for this study. Data was extracted from the systematic review presented in Simin et al. (2007) [5]

STUDY	**Horsmans, Y. et al., 2008 [22]**
OBJECTIVE/S	Evaluate the differences between PEG-IFN and standard IFN (both plus RBV) by conducting a multi-centre RCT
PARTICIPANT CHARACTERISTICS	55% male; median/mean age of 46 years
SETTING/LOCATION	60 centres in Belgium
INTERVENTION PERIOD	October 2000 – March 2002
STUDY POPULATION	Treatment-naïve adults with chronic HCV infection
INCLUSION	Aged 18-70 years; chronic HCV (elevated ALT activity, presence of HCV RNA in the serum); treatment-naïve
EXCLUSION	Decompensated liver cirrhosis or other chronic liver diseases; HIV; active alcohol or IDU; contraindications to RBV
INTERVENTION	N=114; PEG-IFN alpha-2b (100mcg/week) + RBV for 48 weeks
CONTROL	N=65; IFN alpha-2b (3MIU TIW) + RBV for 48 weeks
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	Daily IFN and PEG-IFN (both plus RBV) offer the same efficacy and safety rates. SVR was achieved in 45% of patients administered PEG-IFN vs. 35% of those administered standard IFN
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Yes Free of selective outcome reporting: No Free of other bias: Yes
SUMMARY	UNCLEAR RISK OF BIAS

STUDY	**Izumi, N. et al., 2004 [85]**
OBJECTIVE/S	Assess the viral dynamics of HCVRNA during 12 weeks of therapy with IFN vs. PEG-IFN (both plus RBV) in patients with chronic HCV genotype 1b and a high viral load
PARTICIPANT CHARACTERISTICS	88% male; median/mean age of 54 years
SETTING/LOCATION	Japanese hospital
INTERVENTION PERIOD	November 2001 – May 2002
STUDY POPULATION	Adults with Chronic HCV genotype 1b and a high viral load
INCLUSION	Biopsy-proven HCV genotype 1b; high viral load (HCVRNA >100kIU/ml)
EXCLUSION	Cirrhosis; autoimmune hepatitis; alcoholic liver injury
INTERVENTION	N=23; PEG-IFN alpha-2b (1.5µg/kg/week) + weight-based RBV for 48 weeks
CONTROL	N=26; IFN alpa-2b (6MIU daily for 2 weeks, 6MIU TIW for 46 weeks) + weight-based RBV
OUTCOME/S	HCVRNA dynamics, virological response
HEADLINE FINDING OF STUDY	In chronic HCV patients (genotype 1b) with a high viral load administered PEG-IFN plus RBV, elimination of infected cells may be pronounced following an increase in serum ribavirin concentration. SVR was achieved in 43% of patients administered PEG-IFN vs. 31% of those administered standard IFN.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Unclear Free of other bias: Yes
SUMMARY	UNCLEAR RISK OF BIAS

STUDY	**Kraus, M.R. et al., 2005 [86]**
OBJECTIVE/S	Assess incidence, spectrum and extent of psychiatric symptoms associated with IFN therapy in patient subgroups treated with conventional or PEG-IFN
PARTICIPANT CHARACTERISTICS	53% male; median/mean age of 40 years
SETTING/LOCATION	Hospital university clinic, Germany
INTERVENTION PERIOD	August 1998 – May 2003
STUDY POPULATION	Adults with chronic HCV
INCLUSION	Aged 18-65 years; documented antibody to HCV and serologic confirmation of active HCV
EXCLUSION	HBV; HIV; severe internal diseases (e.g., cancer); major depressive disorder; psychosis; active AOD use; obvious intellectual impairment; insufficient knowledge of the German language
INTERVENTION	N=50; peg alpha-2b (80-150µg/week) + weight-based RBV
CONTROL	N=48; IFN alpha-2b (5 MIU TIW) + weight-based RBV
OUTCOME/S	Psychiatric symptoms, virological response
HEADLINE FINDING OF STUDY	Therapy with PEG-IFN produces comparable scores for depression compared to conventional IFN. SVR was achieved in 56% of patients administered PEG-IFN vs. 50% of those administered IFN.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: No Allocation concealment: No Blinding of participants, personnel and outcome assessors: No Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Laguno, M. et al., 2004 [17]**
OBJECTIVE/S	Evaluate the efficacy and safety of IFN vs. PEG-IFN (both plus RBV)
PARTICIPANT CHARACTERISTICS	68% male; median/mean age of 40 years
SETTING/LOCATION	Hospital in Spain
INTERVENTION PERIOD	April 2001 – October 2002
STUDY POPULATION	HIV-HCV coinfected patients receiving medical care for their HIV infection
INCLUSION	Treatment-naïve for HCV; HCV RNA positive in plasma;, ALT >1.5 times the upper limit of normal and histological modifications in liver biopsy (fibrosis >1 and/or necroimflammatory activity); control of HIV infection with a viral load <10000 copies/ml and a CD4 cell count >250 x 10^6 cells/l, in response to a stable ART or without ART if it was not required
EXCLUSION	Other causes of hepatopathy; decompensated cirrhosis; pregnancy and potential contraindications for IFN or RBV therapy such as haemoglobinopathies, cardiopathy, autoimmune diseases, major depression or other severe psychiatric pathologies; active illicit drug use last 12 months
INTERVENTION	N=52; PEG-IFN alpha-2b (100-150µg/week) + daily RBV for 48 weeks
CONTROL	N=43; IFN alpha-2b (3 MIU TIW) + daily RBV for 48 weeks
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	PEG-IFN was significantly more effective than IFN (both plus RBV) for treating chronic HCV in HIV coinfected patients, mainly of genotype 1 or 4.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: No Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Lee, S.-D. et al., 2005 [14]**
OBJECTIVE/S	Compare the virological, biochemical, histological responses and safety profiles after administration of a 24 week course of PEG-IFN or IFN (both plus RBV), and examine factors that can predict SVR
PARTICIPANT CHARACTERISTICS	69% male; median/mean age of 44 years
SETTING/LOCATION	Five major Taiwanese medical centres
INTERVENTION PERIOD	August 2001 – December 2002
STUDY POPULATION	Treatment-naïve adults with chronic HCV
INCLUSION	Treatment-naïve; Chinese chronic HCV patient; aged 18-65 years; HCV RNA detectable in serum PCR assay; liver biopsy during the past year consistent with chronic hepatitis; elevated serum ALT ($\geq$2 times the upper limit of normal for at least two measurements during the past 6 months)
EXCLUSION	HBV; previous liver transplantation; neutropenia; thrombocytopenia; anaemia; HIV; decompensated liver disease; other causes liver disease; abnormal serum creatinine or α-fetoprotein level; abnormal thyroid function test; pre-existing psychiatric disorders; haemoglobinopathies; autoimmune-type disease; poorly controlled coexisting medical conditions; unable to use contraception
INTERVENTION	N=76; PEG-IFN alpha-2b (1.5 mcg/kg/week) + weight-based RBV for 24 weeks
CONTROL	N=77; IFN alpha-2b(3 MIU TIW) + weight-based RBV
OUTCOME/S	Virological, biochemical, histological responses
HEADLINE FINDING OF STUDY	PEG-IFN plus RBV had significantly better SVR and lower relapse rate compared to IFN plus RBV in Chinese patients with chronic HCV genotype 1. However, higher rates of adverse events and treatment discontinuation were observed in patients treated with PEG-IFN plus RBV.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: Yes Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Manns, M.P. et al., 2001 [10]**
OBJECTIVE/S	Assess the safety and efficacy of two different regimens of PEG-IFN alpha-2b vs. IFN (all plus RBV), and identify predictors of response to PEG-IFN plus RBV
PARTICIPANT CHARACTERISTICS	66% male; median/mean age of 43 years
SETTING/LOCATION	62 centres in Europe, Canada, Argentina, USA
INTERVENTION PERIOD	March 1998 – October 2000
STUDY POPULATION	Treatment-naïve adults with chronic HCV
INCLUSION	Treatment-naïve adults; HCV RNA detectable in serum by PCR; liver biopsy last 12 months consistent with chronic HCV; high serum values of ALT; minimum haematological and biochemical values of: haemoglobin, white-blood-cell count, neutrophil count, platelet count; bilirubin, albumin and creatinine within normal limits
EXCLUSION	Decompensated cirrhosis; serum-fetoprotein concentration >50µg/L; HIV; previous organ transplantation; other causes of liver disease; pre-existing psychiatric disease; seizure disorders; cardiovascular disease; haemoglobinopathies; haemophilia; poorly controlled diabetes; autoimmune-type disease; unable to use contraception
INTERVENTION	N=1025; PEG-IFN alpha2b (1.5µg/kg/week) + RBV (800mg/day) for 48 weeks *or* PEG-IFN alpha-2b (1.5µg/kg/week) for 4 weeks, followed by PEG-IFN alpha-2b (0.5µg/kg/week) for 44 weeks, + RBV (100-200mg/day)
CONTROL	N=505; IFN alpha-2b (3MIU TIW) + RBV (1000-1200mg/day) for 48 weeks
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	In patients with chronic HCV, the most effective therapy is the combination of PEG-IFN alpha-2b 1.5µg/kg/week plus RBV. The benefit is mostly achieved in patients with HCV genotype 1 infections.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: Yes Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Nevens, F. et al., 2010 [87]**
OBJECTIVE/S	Examine the efficacy and safety of PEG-IFN vs. IFN (both plus RBV) in treatment-naïve patients
PARTICIPANT CHARACTERISTICS	52% male; median/mean age of 47 years
SETTING/LOCATION	Belgium
INTERVENTION PERIOD	October 2000 – January 2003
STUDY POPULATION	Treatment-naïve adults with chronic HCV
INCLUSION	Aged 18 years or more; high ALT activity; treatment-naïve; chronic HCV; compensated liver disease; use of two forms of contraception during and after (six months) treatment
EXCLUSION	Pregnant; therapy with any systemic antineoplastic or immunomodulatory treatment during the last 6 months; history of a medical condition associated with chronic liver disease other than HCV; HCC; HIV; low haemoglobin or neutrophil count
INTERVENTION	N=178; PEG-IFN alpha-2a (40KD; 180µg/week) + weight-based RBV for 48 weeks
CONTROL	N=166; IFN alpha-2a (6 MIU TIW) for first 8 weeks, followed by 3 MIU TIW thereafter, plus weight-based RBV
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	SVR was achieved in 54% of the PEG-IFN group vs. 49% of the standard IFN group.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: No Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: Yes Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Pol, S. et al., 2005 [88]**
OBJECTIVE/S	Compare the safety and efficacy of standard IFN vs. PEG-IFN (both plus RBV) among HCV/HIV coinfected patients
PARTICIPANT CHARACTERISTICS	74% male; median/mean age of 40 years
STUDY POPULATION	HCV/HIV coinfected patients
INCLUSION	HCV-RNA positive and abnormal liver histology; CD4 > 200; stable HIV-RNA; off or stable HAART
INTERVENTION	N=205; PEG-IFN alpha-2b (1.5 mg/kg/week) + RBV (800mg/day) for 48 weeks
CONTROL	N=207; IFN alpha-2b (3 MIU TIW) + RBV (800mg/day) for 48 weeks
OUTCOME/S	Virological and histological response
HEADLINE FINDING OF STUDY	In HCV/HIV coinfected patients, the combination of PEG-IFN plus RBV is associated with a superior HCV virologic response than standard IFN plus RBV, with a similar adverse-event profile
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Unclear Free of other bias: Unclear
SUMMARY	UNCLEAR RISK OF BIAS

STUDY	**Scotto, G. et al., 2005 [23]**
OBJECTIVE/S	Compare the efficacy and safety of PEG-IFN vs. IFN (both plus RBV) in treatment-naïve patients with chronic genotype 1b HCV
PARTICIPANT CHARACTERISTICS	46% male; median/mean age of 37 years
SETTING/LOCATION	Italy
INTERVENTION PERIOD	August 2001 – June 2002
STUDY POPULATION	Adults with chronic genotype 1b HCV
INCLUSION	Treatment-naïve patients with chronic HCV; serum ALT levels >twice the upper normal limit for >6 months pre-treatment; anti-HCV antibodies; measurable serum HCV RNA; HCV genotype 1b; leukocyte counts >3000/mm^3;;platelet counts >75000/mm^3; haemoglobin concentration >13g/dl for males and >12g/dl for females
EXCLUSION	Previous episodes of decompensated liver disease; HIV; active IDU or potential cause of liver disease other than HCV
INTERVENTION	N=26; PEG-IFN alpha-2b (1.5mcg/kg/week) + weight-based RBV
CONTROL	N=52; IFN alpha-2b (3 MIU daily or 6 MIU TIW) + weight-based RBV
OUTCOME/S	Virological and histological response
HEADLINE FINDING OF STUDY	SVR was achieved in 50% of the PEG-IFN group vs. 37% in the IFN group. PEG-IFN was better tolerated and resulted in significantly fewer treatment discontinuations.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Shobokshi, A. et al., 2003 [24]**
OBJECTIVE/S	Determine and compare the efficacy and safety of PEG-IFN vs. IFN (both plus RBV) for treating chronic genotype 4 HCV patients
SETTING/LOCATION	Multicentre clinical trial in Saudi Arabia
STUDY POPULATION	Saudi adults with chronic HCV
INTERVENTION	N=60; PEG-IFN alpha-2a (180µg/week) + RBV (800mg/day)
CONTROL	N=60; IFN alpha-2a (4.5 MIU TIW) + RBV (800mg/day)
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	An SVR of 50% was achieved in the PEG-IFN group vs. 30% in the IFN group. A comparatively low relapse rate was observed in patients administered PEG-IFN.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Unclear Allocation concealment: Unclear Blinding of participants, personnel and outcome assessors: Unclear Incomplete outcome data addressed: Unclear Free of selective outcome reporting: Unclear Free of other bias: Unclear
SUMMARY	UNCLEAR RISK OF BIAS

STUDY	**Torriani, A. et al., 2004 [13]**
OBJECTIVE/S	Study the efficacy and safety of PEG-IFN plus RBV in HCV/HIV coinfected people
PARTICIPANT CHARACTERISTICS	81% male; median/mean age of 40 years
SETTING/LOCATION	95 centres in 19 countries
INTERVENTION PERIOD	June 2000 – September 2003
STUDY POPULATION	IFN and RBV-naïve adults coinfected with HCV/HIV
INCLUSION	Aged 18 years or more; coinfected with HIV and HCV; anti-HCV antibodies in serum; detectable serum levels of HCV RNA (>600 IU/mL); elevated serum ALT levels on more than two occasions during the last 12 months; findings on liver biopsy within past 15 months consistent with presence of chronic HCV infection; compensated liver disease; been receiving stable ART at least six weeks before study entry with no changes expected for first 8 weeks of study, or not to have received ART for at least eight weeks before randomization and be able to delay ART for six or more weeks
EXCLUSION	Active HIV-related opportunistic infection or cancer; absolute neutrophil count <1500/cubic mL; platelet count <70000/cubic mL; haemoglobin level <11g/dL for women, or <12 g/dL for men; serum creatinine level >1.5 times the upper limit of normal; concurrent infection with HAV or HBV; decompensated liver disease; severe psychiatric disease; clinically significant co-existing medical conditions; pregnancy or unwillingness to practice contraception; previous IFN or RBV treatment
INTERVENTION	N=289; PEG-IFN alpha2a (180µg/week) + daily RBV for 48 weeks
CONTROL	N=285; IFN alpha2a (3MIU TIW) + daily RBV for 48 weeks
OUTCOME/S	Virological response
HEADLINE FINDING OF STUDY	PEG-IFN was significantly more effective than IFN (both plus RBV) among patients coinfected with HCV/HIV.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation: Yes Allocation concealment: Yes Blinding of participants, personnel and outcome assessors: Yes Incomplete outcome data addressed: Yes Free of selective outcome reporting: Yes Free of other bias: Yes
SUMMARY	LOW RISK OF BIAS

Figure 2: Failure to achieve SVR among patients with chronic HCV administered PEG versus standard IFN (both plus RBV)

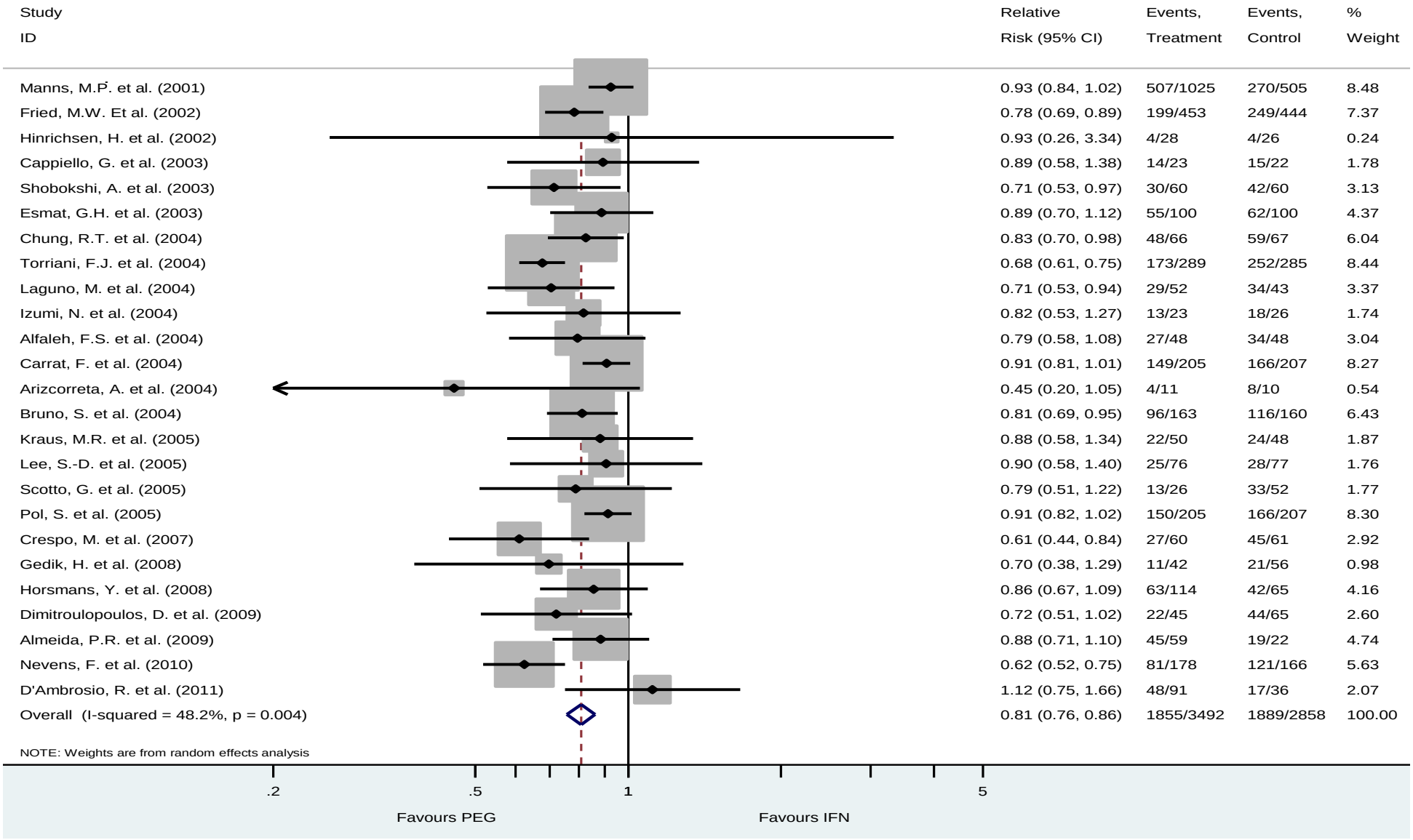


Figure 3: Sub-group analysis: Failure to achieve SVR among HCV genotype 1 patients administered PEG versus standard IFN (both plus RBV)

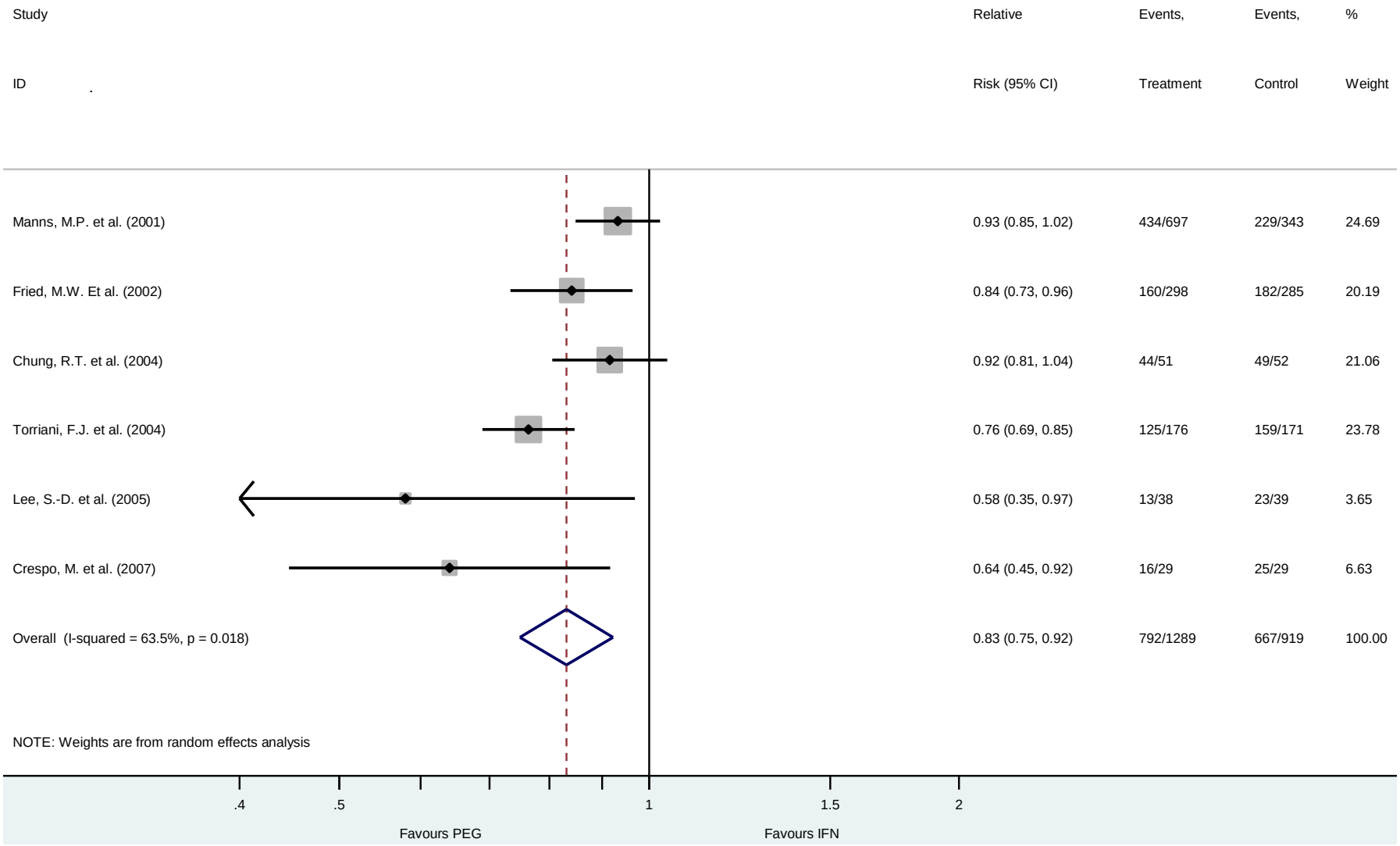


Figure 4: Sub-group analysis: Failure to achieve SVR among non-genotype 1 HCV patients administered PEG versus standard IFN (both plus RBV)

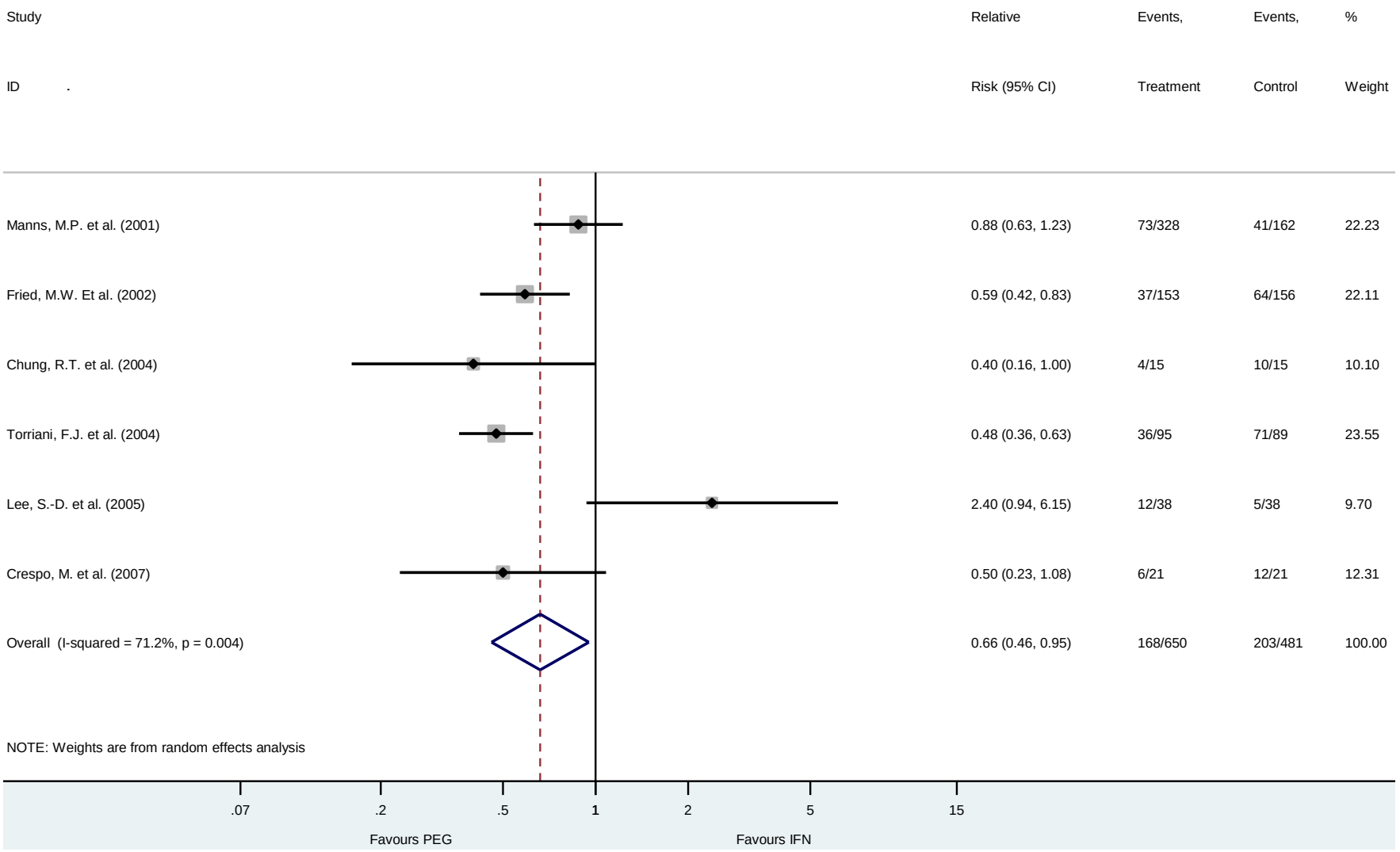


Figure 5: Sub-group analysis: Failure to achieve SVR among cirrhotic patients administered PEG versus standard IFN (both plus RBV)

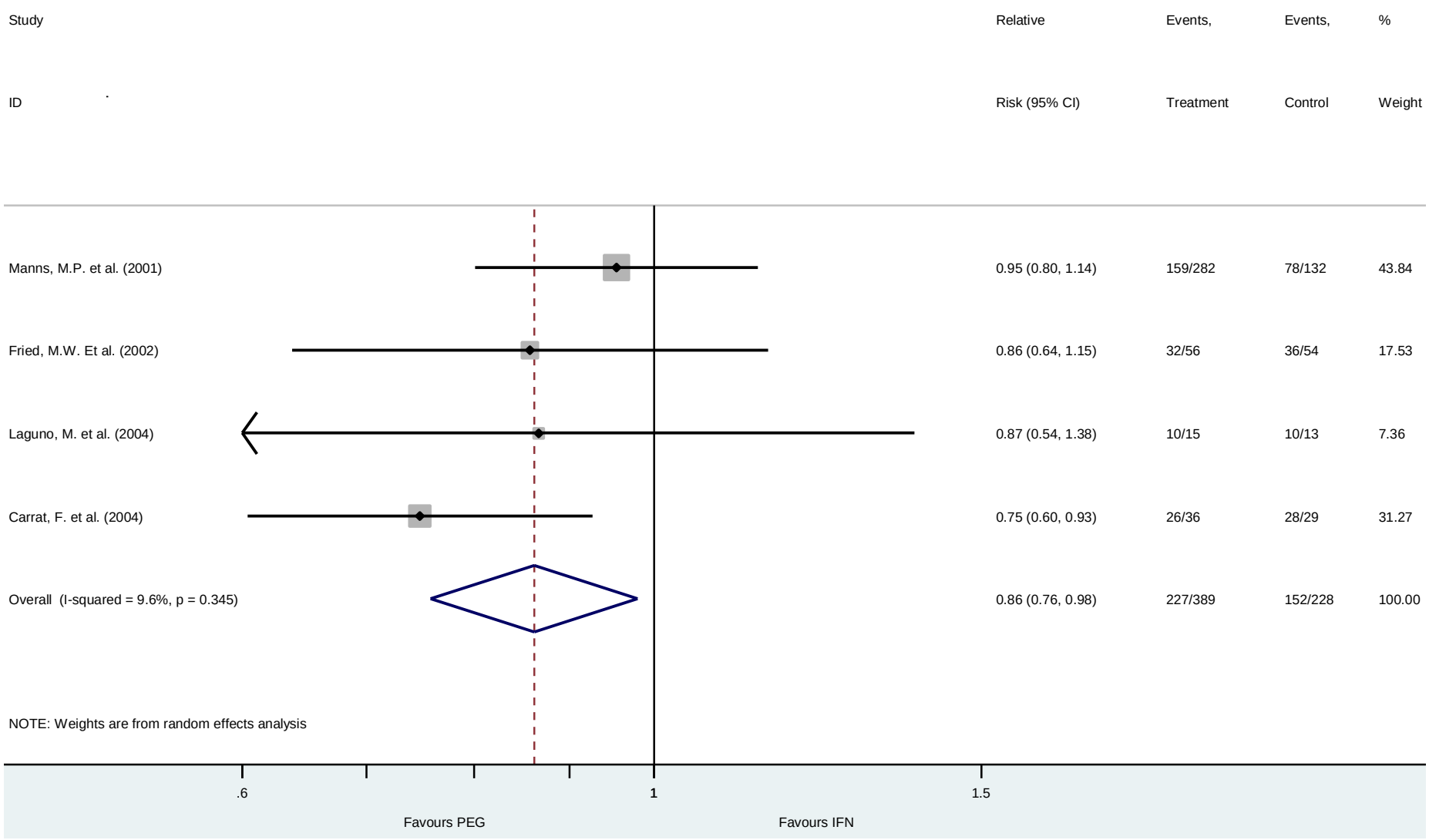


Figure 6: Sub-group analysis: Failure to achieve SVR among non-cirrhotic patients administered PEG versus standard IFN (both plus RBV)

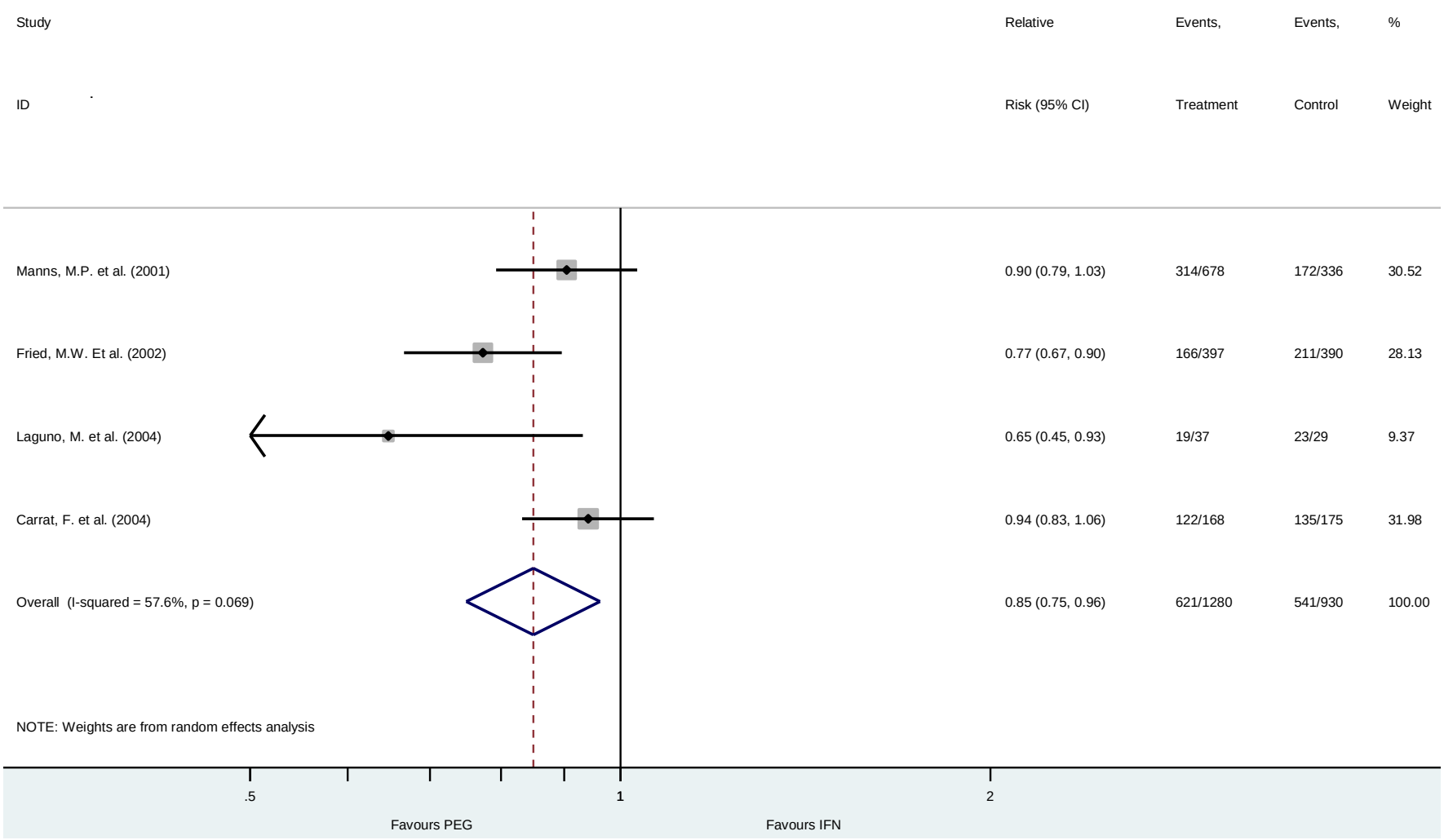


Figure 7: Treatment discontinuation due to adverse events among chronic HCV administered PEG versus standard IFN (both plus RBV)

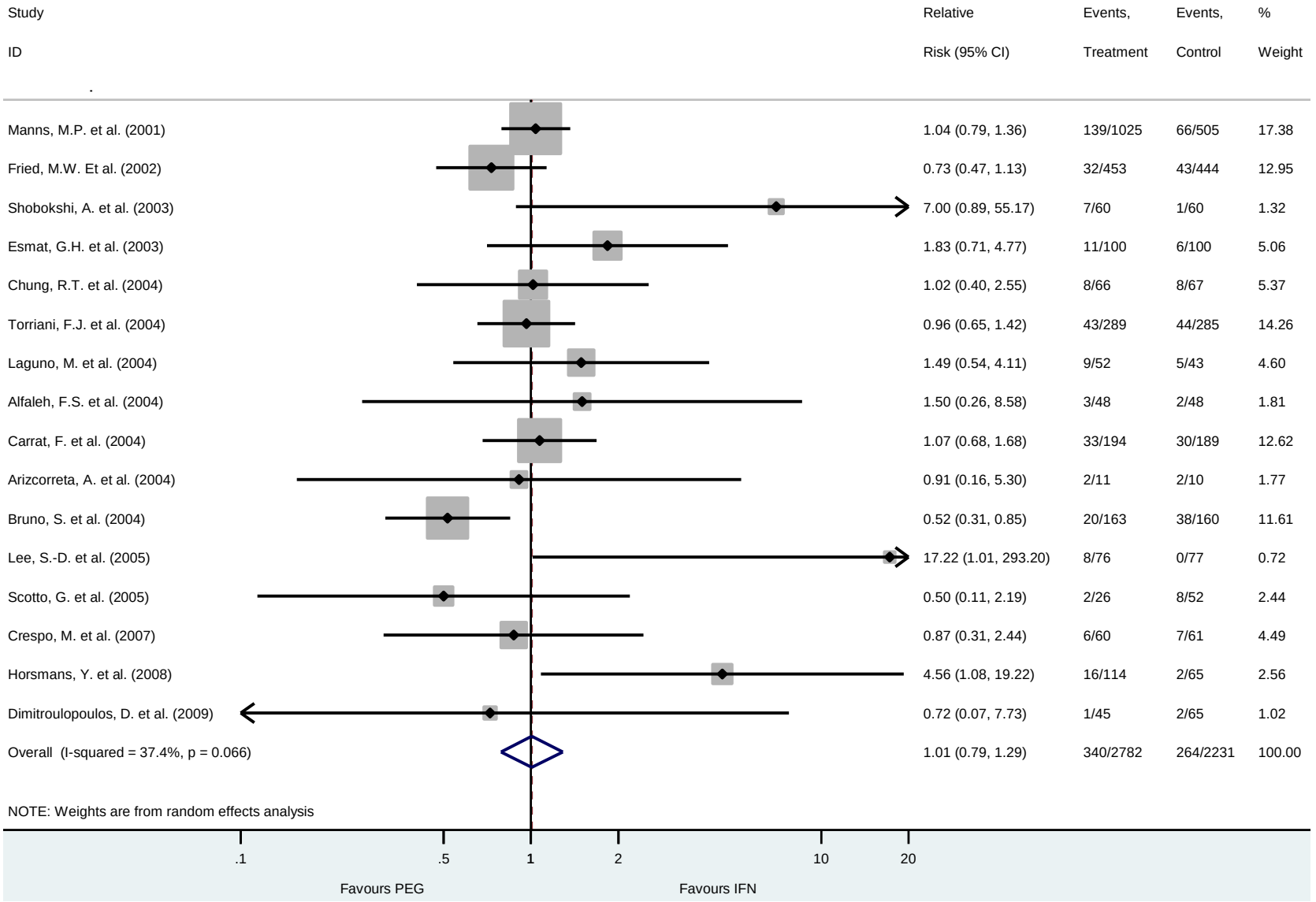


Figure 8: All-cause mortality among patients with chronic HCV administered PEG versus standard IFN (both plus RBV)

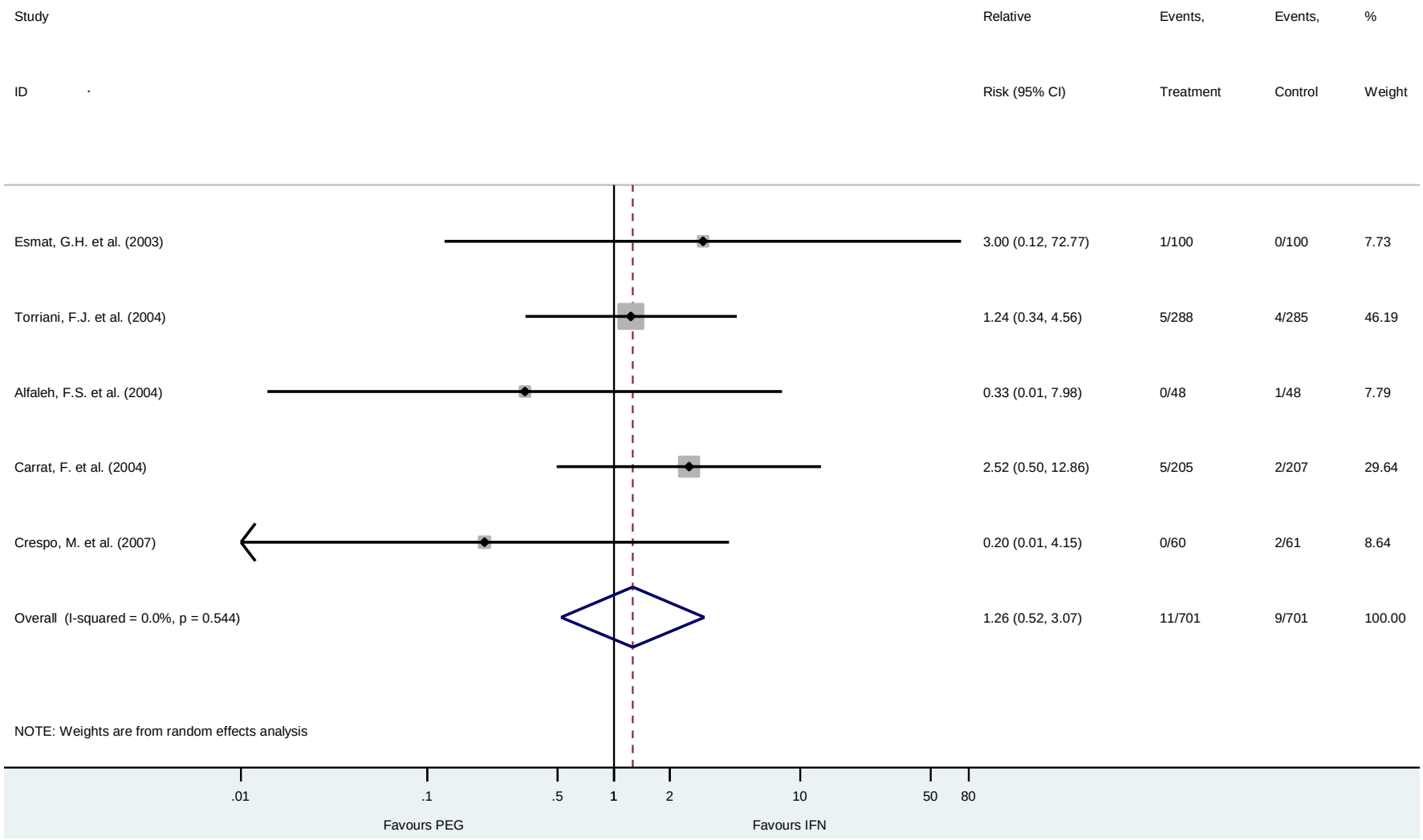


Figure 9: Liver-related mortality among patients with chronic HCV administered PEG versus standard IFN (both plus RBV)

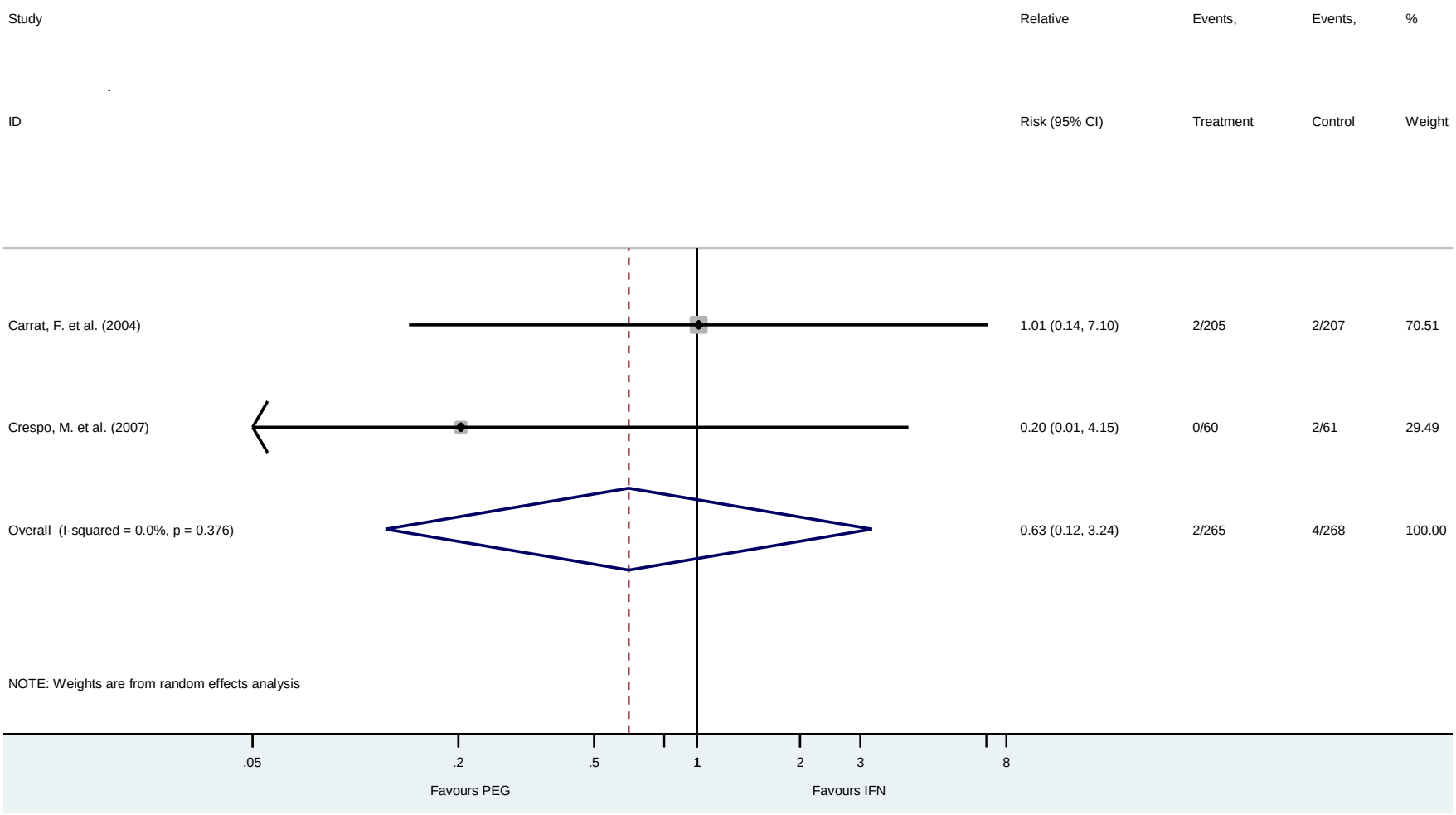


Figure 10: Hepatic decompensation among patients with chronic HCV administered PEG versus standard IFN (both plus RBV)

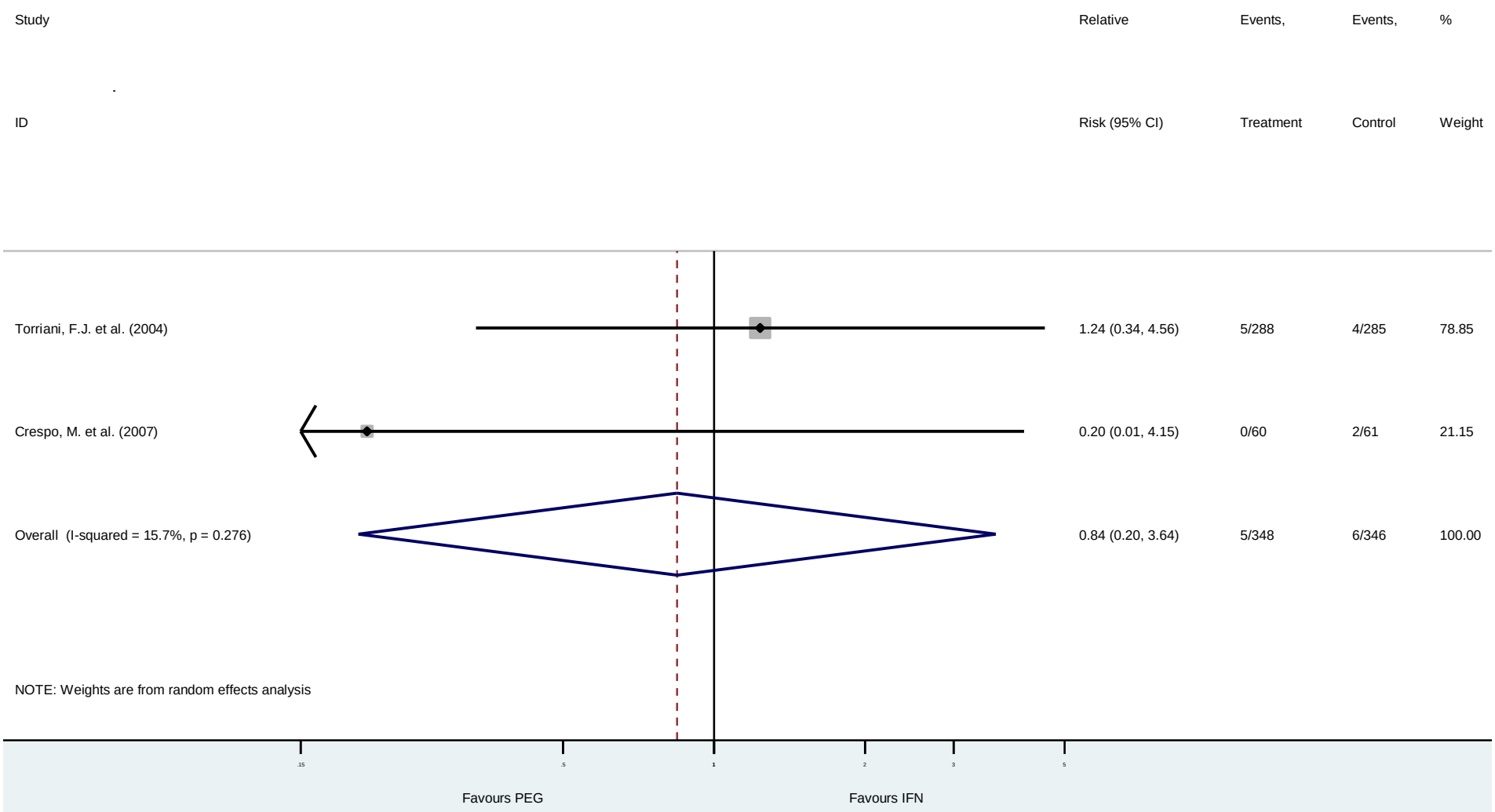


Table 2: GRADE summary of findings

Question: Should pegylated interferon and ribavirin vs standard interferon and ribavirin be used for HCV?											
Quality assessment							**Summary of Findings**				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Standard interferon and ribavirin	**With Pegylated interferon and ribavirin**		**Risk with Standard interferon and ribavirin**	**Risk difference with Pegylated interferon and ribavirin** (95% CI)
Failure to achieve sustained virological response (CRITICAL OUTCOME)											
6350 (25 studies) 72 weeks	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**[1]	1889/2858 (66.1%)	1855/3492 (53.1%)	**RR 0.81** (0.76 to 0.86)	**661 per 1000**	**126 fewer per 1000** (from 93 fewer to 159 fewer)
Terminated study due to adverse events (CRITICAL OUTCOME)											
5013 (16 studies) 72 weeks	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to inconsistency	264/2231 (11.8%)	340/2782 (12.2%)	**OR 1.01** (0.79 to 1.29)	**118 per 1000**	**1 more per 1000** (from 22 fewer to 29 more)
All-cause mortality during study (CRITICAL OUTCOME)											
1402 (5 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	9/701 (1.3%)	11/701 (1.6%)	**OR 1.26** (0.52 to 3.07)	**13 per 1000**	**3 more per 1000** (from 6 fewer to 26 more)
Liver-related mortality during study (CRITICAL OUTCOME)											
533 (2 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	4/268 (1.5%)	2/265 (0.75%)	**OR 0.63** (0.12 to 3.27)	**15 per 1000**	**5 fewer per 1000** (from 13 fewer to 32 more)
Hepatic decompensation during study (IMPORTANT OUTCOME)											
694 (2 studies) 72 weeks	serious[5]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊖⊖ **LOW**[4,5] due to risk of bias, imprecision	6/346 (1.7%)	5/348 (1.4%)	**OR 0.84** (0.19 to 3.74)	**17 per 1000**	**3 fewer per 1000** (from 14 fewer to 45 more)
Development of hepatocellular carcinoma during study (IMPORTANT OUTCOME)											
96 (1 study) 72 weeks	no serious risk of bias[6]	serious[6]	no serious indirectness	very serious[6]	undetected	⊕⊖⊖⊖ **VERY LOW**[6] due to inconsistency, imprecision	1/48 (2.1%)	0/48 (0%)	**OR 0.33** (0.01 to 8.22)	**21 HCC per 1000**	**14 fewer HCC per 1000** (from 21 fewer to 128 more)

[1] Most information is from studies at low risk of bias. However, some studies were at bias associated with sequence generation and allocation concealment (e.g., the randomization process was not always explicitly described (see Simin et al., 2007, and Kim et al., 2007))
[2] There is significant heterogeneity between studies in findings regarding patients administered PEG-IFN + RBV vs. IFN-RBV.
[3] Few events, wide confidence interval.
[4] Some imprecision due to few events.
[5] These two studies only involve HCV/HIV coinfected participants (i.e., results cannot be generalised to individuals with chronic HCV without HIV).
[6] One study of Saudi Arabian patients (with a focus on those with HCV genotype 4 and a relatively small sample size) limits the representativeness of findings.

Table 3: Indirect evidence from systematic reviews of HCV treatment in Children and PWID

Study, methods	No of studies (numbers and population)	Intervention Outcomes	Summary of primary findings (95% confidence interval)	Review conclusions
Druyts *et al. (*2013) Systematic review Cochrane/PRISMA compliant	1 RCT, 7 non-randomised trials (n=438, 3-18 year children/adolescents)	PEG+RBV for all patients Measured SVR, treatment discontinuation due to AE	Among children: • SVR: 58% (95%CI 53-64) • Treatment discontinuation due to AE: 4% (1-7%)	Treatment is effective and safe in treating children and adolescents with HCV
Aspinall *et al.* (2013) Systematic review Cochrane/PRISMA compliant	6 observational studies (n=314 PWID, 45% active PWID in last month)	PEG+RBV for all patients Measured SVR, adherence, treatment discontinuation (all-cause)	Among PWID: • SVR 61% (51-72%) • Adherence 82% (74-89%) • Treatment discontinuation (all-cause, not AE specific) 22% (16-27%)	Treatment among active PWID has a comparable SVR and adherence rates among studies to former or non-PWID.

APPENDICIES

Appendix 1: Search syntax

#	SEARCH SYNTAX
1	*Hepatitis C/ or *Hepatitis C, Chronic/
2	HCV.ti,ab.
3	hepatitis c.ti,ab.
4	1 or 2 or 3
5	peg.ti,ab.
6	pegylated.ti,ab.
7	5 or 6
8	interferon*.ti,ab.
9	IFN.ti,ab.
10	interferon-alpha/
11	8 or 9 or 10
12	7 and 11
13	peginterferon.ti,ab.
14	12 or 13
15	4 and 14
16	limit 15 to yr="1994 -Current"
17	limit 16 to humans
18	**Medline only:** limit 17 to (clinical trial, all or clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)
18	**Embase only:** limit 17 to (meta analysis or "systematic review")
18	**Embase only:** limit 17 to (clinical trial or randomized controlled trial or controlled clinical trial or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
	LILACS and COCHRANE search: ("hepatitis c" OR "HCV" OR "hepatitis C, chronic") AND ((("pegylated" OR "peg") AND (“interferon” OR “IFN” OR “interferon-alpha/”)) OR "peginterferon”)

Appendix 2: Cochrane Collaboration's tool for assessing risk of bias.

Domain	Description	Review authors' judgement
Sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to Allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Appendix 3: GRADE approach to assessing the quality of evidence across studies

<table>
<tr><th>Quality of Evidence (summary score)</th><th>Study Design</th><th>Downgrading Factors</th><th>Upgrading Factors</th></tr>
<tr><td>High (4) =Further research is very unlikely to change our confidence in the estimate of effect.</td><td>Randomized trials or valid accuracy studies for diagnostic tests begin with a score of High (4)</td><td rowspan="4">Study Limitations:
-1 Serious
-2 Very serious

Consistency:
-1 Serious
-2 Very serious

Directness:
-1 Serious
-2 Very serious

Precision:
-1 Serious
-2 Very serious

Publication Bias:
-1 Serious
-2 Very serious</td><td rowspan="4">Large effect
+1 Large
+2 Very large

Plausible confounding would change the effect
+1

Dose-response gradient
+1 if Present</td></tr>
<tr><td>Moderate (3) = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td><td></td></tr>
<tr><td>Low (2) = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td><td>Observational studies or indirect accuracy studies for diagnostic tests begin with a score of low (2).</td></tr>
<tr><td>Very low (1) = Any estimate of effect is very uncertain.</td><td></td></tr>
</table>

REFERENCES

1. World Health Organization. Hepatitis C (Fact sheet No. 164). 2012 [accessed 14 February 2013]; Available from: http://www.who.int/mediacentre/factsheets/fs164/en/.
2. Grebely, J. and Dore, G.J. *What is killing people with hepatitis C virus infection?* Semin Liver Dis, 2011. 31(4): p. 331-9.
3. European Association for the Study of the Liver. *EASL Clinical Practice Guidelines: management of hepatitis C virus infection.* J Hepatol, 2011. 55(2): p. 245-64.
4. Esmat, G.H., Abouzied, A., Abdel-Hamid, M., Mohamed, M.K., Zalata, K., El Raziky, M.S., Ismail, S.A., Said, M., Hasan, A., Anwar, M., Shaheen, A., Abdel-Aziz, F., Mikhail, N.N., and Ismail, A. *Results of a randomized clinical trial of genotype-4 infected subjects when treated with standard or pegylated interferon alfa-2b in combination with ribavirin [Abstract].* Hepatology, 2003. 38(Suppl. S4): p. 314A.
5. Simin, M., Brok, J., Stimac, D., Gluud, C., and Gluud, L.L. *Cochrane systematic review: pegylated interferon plus ribavirin vs. interferon plus ribavirin for chronic hepatitis C.* Alimentary Pharmacology & Therapeutics, 2007. 25(10): p. 1153-62.
6. Kim, A.I., Dorn, A., Bouajram, R., and Saab, S. *The treatment of chronic hepatitis C in HIV-infected patients: a meta-analysis.* HIV Medicine, 2007. 8(5): p. 312-21.
7. Druyts, E., Thorlund, K., Wu, P., Kanters, S., Yaya, S., Cooper, C.L., and Mills, E.J. *Efficacy and safety of pegylated interferon alfa-2a or alfa-2b plus ribavirin for the treatment of chronic hepatitis C in children and adolescents: a systematic review and meta-analysis.* Clin Infect Dis, 2013. 56(7): p. 961-7.
8. Aspinall, E., Corson, S., Doyle, J., Grebely, J., Hutchinson, S.J., Dore, G., Goldberg, D., and Hellard, M. *Peginterferon and ribavirin treatment for chronic hepatitis C virus in people who inject drugs: A systematic review and meta-analysis.* Clinical Infectious Diseases, In press.
9. D'Ambrosio, R., Aghemo, A., Rumi, M.G., Primignani, M., Dell'Era, A., Lampertico, P., Donato, M.F., De Nicola, S., Prati, G.M., de Franchis, R., and Colombo, M. *The course of esophageal varices in patients with hepatitis C cirrhosis responding to interferon/ribavirin therapy.* Antiviral Therapy, 2011. 16(5): p. 677-84.
10. Manns, M.P., McHutchison, J.G., Gordon, S.C., Rustgi, V.K., Shiffman, M., Reindollar, R., Goodman, Z.D., Koury, K., Ling, M.-H., and Albrecht, J.K. *Peginterferon alfa-2b plus ribavirin compared with interferonalfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial.* Lancet, 2001. 358(9286): p. 958-965.
11. Fried, M.W., Shiffman, M.L., Reddy, K.R., Smith, C., Marinos, G., Goncales Jr., F.L., Haussinger, D., Diago, M., Carosi, G., Dhumeaux, D., Craxi, A., Lin, A., Hoffman, J., and Yu, J. *Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection.* New England Journal of Medicine, 2002. 347(13): p. 975-82.
12. Chung, R.T., Andersen, J., Volberding, P., Robbins, G.K., Liu, T., Sherman, K.E., Peters, M.G., Koziel, M.J., Bhan, A.K., Alston, B., Colquhoun, D., Nevin, T., Harb, G., van der Horst, C., and Aids Clinical Trials Group A Study Team. *Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons.* New England Journal of Medicine, 2004. 351(5): p. 451-9.
13. Torriani, F.J., Rodriguez-Torres, M., Rockstroh, J.K., Lissen, E., Gonzalez-Garcia, J., Lazzarin, A., Carosi, G., Sasadeusz, J., Katlama, C., Montaner, J., Sette, H., Jr., Passe, S., De Pamphilis, J., Duff, F., Schrenk, U.M., Dieterich, D.T., and Apricot Study Group. *Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. APRICOT Study.* New England Journal of Medicine, 2004. 351(5): p. 438-50.
14. Lee, S.D., Yu, M.L., Cheng, P.N., Lai, M.Y., Chao, Y.C., Hwang, S.J., Chang, W.Y., Chang, T.T., Hsieh, T.Y., Liu, C.J., and Chen, D.S. *Comparison of a 6-month course peginterferon alpha-2b plus ribavirin and interferon alpha-2b plus ribavirin in treating Chinese patients with chronic hepatitis C in Taiwan.* Journal of Viral Hepatitis, 2005. 12(3): p. 283-91.

15. Crespo, M., Sauleda, S., Esteban, J.I., Juarez, A., Ribera, E., Andreu, A.L., Falco, V., Quer, J., Ocana, I., Ruiz, I., Buti, M., Pahissa, A., Esteban, R., and Guardia, J. *Peginterferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin for chronic hepatitis C in HIV-coinfected patients.* Journal of Viral Hepatitis, 2007. 14(4): p. 228-38.
16. Carrat, F., Bani-Sadr, F., Pol, S., Rosenthal, E., Lunel-Fabiani, F., Benzekri, A., Morand, P., Goujard, C., Pialoux, G., Piroth, L., Salmon-Ceron, D., Degott, C., Cacoub, P., Perronne, C., and Team, A.H.R.S. *Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial.* JAMA, 2004. 292(23): p. 2839-48.
17. Laguno, M., Murillas, J., Blanco, J.L., Martinez, E., Miquel, R., Sanchez-Tapias, J.M., Bargallo, X., Garcia-Criado, A., de Lazzari, E., Larrousse, M., Leon, A., Lonca, M., Milinkovic, A., Gatell, J.M., and Mallolas, J. *Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients.* AIDS, 2004. 18(13): p. F27-36.
18. Alfaleh, F.Z., Hadad, Q., Khuroo, M.S., Aljumah, A., Algamedi, A., Alashgar, H., Al-Ahdal, M.N., Mayet, I., Khan, M.Q., and Kessie, G. *Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C in Saudi patients commonly infected with genotype 4.* Liver International, 2004. 24(6): p. 568-74.
19. Arizcorreta, A., Brun, F., Fernandez-Gutierrez, C., Garcia Juarez, R., Guerrero, F., Perez-Guzman, E., and Giron-Gonzalez, J.A. *Modifications of haematological series in patients co-infected with human immunodeficiency virus and hepatitis C virus during treatment with interferon and ribavirin: differences between pegylated and standard interferon.* Clinical Microbiology & Infection, 2004. 10(12): p. 1067-74.
20. Bruno, S., Camma, C., Di Marco, V., Rumi, M., Vinci, M., Camozzi, M., Rebucci, C., Di Bona, D., Colombo, M., Craxi, A., Mondelli, M.U., and Pinzello, G. *Peginterferon alfa-2b plus ribavirin for naive patients with genotype 1 chronic hepatitis C: a randomized controlled trial.* Journal of Hepatology, 2004. 41(3): p. 474-81.
21. Dimitroulopoulos, D., Petroulaki, E., Manolakopoulos, S., Anagnostou, O., Tsaklakidou, D., Xinopoulos, D., Tsamakidis, K., Tzourmakliotis, D., and Paraskevas, E. *Peginterferon/ribavirin treatment achieves a higher compliance rate than interferon/ribavirin combination in patients chronically infected with HCV on methadone maintenance.* European Journal of Gastroenterology & Hepatology, 2009. 21(12): p. 1407-12.
22. Horsmans, Y., Colle, I., Van Vlierberghe, H., Langlet, P., Adler, M., Bourgeois, N., Brenard, R., Michielsen, P., Goossens, A., Bruckers, L., and Belgian Assocation for the Study of the Liver. *Weekly pegylated interferon alpha-2b vs daily interferon a-2b versus standard regimen of interferon a-2b in the treatment of patients with chronic hepatitis C virus infection.* Acta Gastroenterologica Belgica, 2008. 71(3): p. 293-7.
23. Scotto, G., Fazio, V., Palumbo, E., Cibelli, D.C., Saracino, A., and Angarano, G. *Treatment of genotype 1b HCV-related chronic hepatitis: efficacy and toxicity of three different interferon alfa-2b/ribavirin combined regimens in naive patients.* New Microbiologica, 2005. 28(1): p. 23-9.
24. Shobokshi, O.A., Serebour, F.E., Skakni, L., Al-Jasser, N., Tantawi, A.O., Sabah, A., Dinish, T., Al-Quaiz, M., Qahtani, K., Sandokji, A., Al-Blowi, A., Al-Karawi, M., Al-Kayyal, B., Al-Momen, S., Akbar, H., Ayoola, A., El-Hazi, M., Humaida, A., El-Hazmi, I., Eissa, H., Khawajah, F., and Al-Khalifa, M. *Combination therapy of peginterferon alfa-2A (40KD) (Pegasys (R)) and ribavirin (Copegus (R)) significantly enhance sustained virological and biochemical response rate in chronic hepatitis C genotype 4 patients in Saudi Arabia [AASLD abstract]*. Hepatology, 2003. 38, 636a.
25. Annemans, L., Warie, H., Nechelput, M., and Peraux, B. *A health economic model to assess the long term effects and cost-effectiveness of PEG IFN alpha-2a in hepatitis C virus infected patients.* Acta Gastro Enterologica Belgica, 2004. 67(1): p. 1-8.

26. Bernstein, D., Kleinman, L., Barker, C.M., Revicki, D.A., and Green, J. *Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients.* Hepatology, 2002. 35(3): p. 704-708.
27. Bosques-Padilla, F., Trejo-Estrada, R., Campollo-Rivas, O., Cortez-Hernandez, C., Dehesa-Violante, M., Maldonado-Garza, H., Perez-Gomez, R., and Cabrera-Valdespino, A. *Peginterferon alfa-2a plus ribavirin for treating chronic hepatitis C virus infection: analysis of Mexican patients included in a multicenter international clinical trial.* Annals of Hepatology, 2003. 2(3): p. 135-9.
28. Buti, M., Medina, M., Casado, M.A., Wong, J.B., Fosbrook, L., and Esteban, R. *A cost-effectiveness analysis of peginterferon alfa-2b plus ribavirin for the treatment of naive patients with chronic hepatitis C.* Alimentary Pharmacology and Therapeutics, 2003. 17(5): p. 687-694.
29. Crespo, M., Esteban, J.I., Sauleda, S., and al., e. *Early prediction of sustained virological response in patients with chronic hepatitis C and HIV infection treated with IFN + RBV.* Hepatology, 2004. 40(Supplement S4): p. 350A.
30. Hassanein, T., Cooksley, G., Sulkowski, M., Smith, C., Marinos, G., Lai, M.-Y., Pastore, G., Trejo-Estrada, R., Horta E Vale, A., Wintfeld, N., and Green, J. *The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C.* Journal of Hepatology, 2004. 40(4): p. 675-81.
31. Herrmann, E., Lee, J.-H., Marinos, G., Modi, M., and Zeuzem, S. *Effect of ribavirin on hepatitis C viral kinetics in patients treated with pegylated interferon.* Hepatology, 2003. 37(6): p. 1351-8.
32. Lin, W.-A., Tarn, Y.-H., and Tang, S.-L. *Cost-utility analysis of different peg-interferon alpha-2b plus ribavirin treatment strategies as initial therapy for naive Chinese patients with chronic hepatitis C.* Alimentary Pharmacology and Therapeutics, 2006. 24(10): p. 1483-1493.
33. Mauss, S., Valenti, W., DePamphilis, J., Duff, F., Cupelli, L., Passe, S., Solsky, J., Torriani, F.J., Dieterich, D., and Larrey, D. *Risk factors for hepatic decompensation in patients with HIV/HCV coinfection and liver cirrhosis during interferon-based therapy.* AIDS, 2004. 18(13): p. F21-5.
34. Nevens, F., Vlierberghe, H., D'Heygere, F., Delwaide, J., Adler, M., Henrion, J., Henry, J.P., Hendlisz, A., Michielsen, P., Bastens, B., Brenard, R., and Meeren, O. *Peginterferon alfa-2a (40 kDa) plus ribavirin is as effective in patients relapsing after conventional interferon based therapy as in naive patients: results from the BERNAR-1 trial*. Journal of Hepatology, 2005. 42, 214.
35. Payan, C., Pivert, A., Morand, P., Fafi-Kremer, S., Carrat, F., Pol, S., Cacoub, P., Perronne, C., and Lunel, F. *Rapid and early virological response to chronic hepatitis C treatment with IFN alpha2b or PEG-IFN alpha2b plus ribavirin in HIV/HCV co-infected patients.* Gut, 2007. 56(8): p. 1111-1116.
36. Pialoux, G. *Efficacy of peginterferon plus ribavirin for HIV-HCV co-infection. Results of Apricot study.* Presse Medicale, 2005. 34(20 II): p. 1589-1591.
37. Pol Sr, S., Carrat Sr, F., Bani-Sadr, F., Rosenthal, E., Lunel, F., Morand, P., Salmon, D., Pialoux, G., Patrice, C., and Christian, P. *Final results of ANRS HC02 - RIBAVIC: a randomized controlled trial of pegylated-interferon alfa-2B plus ribavirin vs interferon alfa-2B plus ribavirin for the initial treatment of chronic hepatitis C in HIV co-infected patients*. Hepatology, 2004. 40, 315a.
38. Poynard, T., Ratziu, V., McHutchison, J., Manns, M., Goodman, Z., Zeuzem, S., Younossi, Z., and Albrecht, J. *Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C.* Hepatology, 2003. 38(1): p. 75-85.
39. Shobokshi, O., Serebour, F., Skakni, L., Tantawi, A., Dinish, T., Al Quaiz, M., Sandokji, A., Al-Kayyal, B., Al Momen, S., Akbar, H., Ayoola, A., Amer, H., Hussein, E., Khawaja, F., and Al-Jasser, N. *Efficacy of pegylated (40 kda) ifn alfa-2a (pegasys) plus ribavirin in the treatment*

of hepatitis c genotype 4 chronic active patients in saudi arabia [abstract]. Journal of Hepatology, 2002. 36, 129.

40. Siebert, U., Sroczynski, G., Rossol, S., Wasem, J., Ravens-Sieberer, U., Kurth, B.M., Manns, M.P., McHutchison, J.G., Wong, J.B., German Hepatitis C. Model Group, and International Hepatitis Interventional Therapy Group. *Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C.* Gut, 2003. 52(3): p. 425-32.
41. Torriani, F.J., Ribeiro, R.M., Gilbert, T.L., Schrenk, U.M., Clauson, M., Pacheco, D.D.M., and Perelson, A.S. *Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) dynamics during HCV treatment in HCV/HIV coinfection.* Journal of Infectious Diseases, 2003. 188(10): p. 1498-507.
42. Wong, J.B., Davis, G.L., McHutchison, J.G., Manns, M.P., Albrecht, J.K., and International Hepatitis Interventional Therapy Group. *Economic and clinical effects of evaluating rapid viral response to peginterferon alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C.* American Journal of Gastroenterology, 2003. 98(11): p. 2354-62.
43. Wong, J.B. and Nevens, F. *Cost-effectiveness of peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin as initial treatment of chronic hepatitis C in Belgium.* Acta Gastro Enterologica Belgica, 2002. 65(2): p. 110-111.
44. Cicinnati, V.R., Iacob, S., Klein, C.G., Baba, H.A., Sotiropoulos, G.C., Hilgard, P., Erim, Y., Broelsch, C.E., Gerken, G., and Beckebaum, S. *Ribavirin with either standard or pegylated interferon to treat recurrent hepatitis C after liver transplantation.* Alimentary Pharmacology and Therapeutics, 2007. 26(2): p. 291-303.
45. Ferreira, S.C., Carneiro, M.V., Souza, F.F., Teixeira, A.C., Villanova, M.G., Figueiredo, J.F.C., Passos, A.D.C., Ramalho, L.N.Z., Zucoloto, S., and Martinelli, A.L.C. *Long-term follow-up of patients with chronic hepatitis C with sustained virologic response to interferon.* Braz J Infect Dis, 2010. 14(4): p. 330-334.
46. Tao, J., Liu, J., Pu, D., and Lei, H. *[Efficacy of interferon alpha with ribavirin for treatment of chronic Hepatitis C].* Chung Hua Kan Tsang Ping Tsa Chih, 2011. 19(9): p. 683-5.
47. Trepo, C., Maynard-Muet, M., Pradat, P., Causse, X., Larrey, D., Marcellin, P., Bourliere, M., Guest, M., and Kravtzoff, R. *Intermediate analysis of a phase IIA study of a new sustained release interferon-alpha-2B (IFN-alpha-2BXL) confirms improved safety profile versus marketed pegylated IFN-alpha-2b during a 3-month course of combined therapy with weight-based ribavirin.* Hepatology, 2011. Conference: p. 62nd Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2011 San Francisco.
48. Trepo, C., Maynard-Muet, M., Pradat, P., Larrey, D.G., Marcellin, P., Pol, S., De Ledinghen, V., Causse, X., Ribard, D., Serfaty, L., Bourliere, M., Berthillon, P., Guest, M., and Kravtzoff, R. *Interim report on efficacy results of a new sustained release interferon-alpha-2b (IFNalpha-2bXL) compared with Pegylated IFN-alpha-2b during a 3-month course of combined therapy with ribavirin in hepatitis C patients (Phase 2 study: ANRS HC23 COAT-IFN).* Hepatology, 2012. Conference: p. 63rd Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2012 Boston.
49. Tsubota, A., Arase, Y., Someya, T., Suzuki, Y., Suzuki, F., Saitoh, S., Ikeda, K., Akuta, N., Hosaka, T., Kobayashi, M., and Kumada, H. *Early viral kinetics and treatment outcome in combination of high-dose interferon induction vs. pegylated interferon plus ribavirin for naive patients infected with hepatitis C virus of genotype 1b and high viral load.* Journal of Medical Virology, 2005. 75(1): p. 27-34.
50. Vigani, A.G., Gonçales, E.S., Pavan, M.H.P., Genari, F., Tozzo, R., Lazarini, M.S.K., Fais, V., Feltrin, A., Gonçales, N.S.L., and Gonçales Jr, F.L. *Therapeutic effectiveness of biosimilar standard interferon versus pegylated interferon for chronic hepatitis C genotypes 2 or 3.* Braz J Infect Dis, 2012. 16(3): p. 232-236.

51. Xu, D.Z., Luo, K.X., Lu, Z.M., Jia, J.D., Wang, Y.M., Zhao, G.Z., Zhang, S.L., and Zhang, D.Z. *A randomized open-label, multi-center study comparing the efficacy and safety of peginterferon alfa-2a (40kDa) (PEGASYS) with conventional interferon alfa-2a (ROFERON -A) in patients with chronic hepatitis C (CHC) in China*. Liver International, 2005. 25, 1308.
52. *Peginterferon-alpha-2a (40kD) plus ribavirin: A new treatment option takes flight in chronic hepatitis C.* Drugs and Therapy Perspectives, 2004. 20(2): p. 1-4.
53. Awad, T., Brok, J., Thorlund, K., Hauser, G., Stimac, D., Mabrouk, M., Gluud, C., and Gluud Lise, L. *Pegylated interferon plus ribavirin versus non-pegylated interferon plus ribavirin for chronic hepatitis C*. Cochrane Database of Systematic Reviews, 2009. DOI: 10.1002/14651858.CD005441.pub2.
54. Chou, R., Hartung, D., Rahman, B., Wasson, N., Cottrell, E.B., and Fu, R. *Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review.* Annals of Internal Medicine, 2013. 158(2): p. 114-23.
55. Condat, B. *Peginterferon alpha-2b plus ribavirine compared with interferon alpha-2 and ribavirine for the treatment of chronic hepatitis C: A randomized trial.* Hepato Gastro, 2002. 9(2): p. 141-142.
56. Fabrizi, F., Dixit, V., Martin, P., and Messa, P. *Combined antiviral therapy of hepatitis C virus in dialysis patients: meta-analysis of clinical trials.* Journal of Viral Hepatitis, 2011. 18(7): p. e263-9.
57. Ford, N., Kirby, C., Singh, K., Mills, E.J., Cooke, G., Kamarulzaman, A., and duCros, P. *Chronic hepatitis C treatment outcomes in low- and middle-income countries: a systematic review and meta-analysis.* Bulletin of the World Health Organization, 2012. 90(7): p. 540-50.
58. Franchini, M., Mengoli, C., Veneri, D., Mazzi, R., Lippi, G., and Cruciani, M. *Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis.* Journal of Antimicrobial Chemotherapy, 2008. 61(6): p. 1191-200.
59. Gordon, C.E., Uhlig, K., Schmid, C.H., Levey, A.S., and Wong, J.B. *Long-term viral negativity after interferon for chronic hepatitis C virus infection in hemodialysis.* Clinical Journal of The American Society of Nephrology: CJASN, 2011. 6(9): p. 2226-34.
60. Goulart, T. *Avaliação da efetividade do tratamento de pacientes co-infectados HCV-HIV com as terapias combinadas interferon + ribavirina e peginterferon + ribavirina*

Evaluation of the effectiveness of treatment of patients co-infected with HCV-HIV combination therapies interferon + ribavirin and peginterferon + ribavirin. 2008: p. 139f-139f.
61. Grieve, R., Roberts, J., Wright, M., Sweeting, M., DeAngelis, D., Rosenberg, W., Bassendine, M., Main, J., and Thomas, H. *Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C.* Gut, 2006. 55(9): p. 1332-8.
62. Hartwell, D. and Shepherd, J. *Pegylated and non-pegylated interferon-alfa and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and meta-analysis.* International Journal of Technology Assessment in Health Care, 2009. 25(1): p. 56-62.
63. Hu, J., Doucette, K., Hartling, L., Tjosvold, L., and Robinson, J. *Treatment of hepatitis C in children: a systematic review.* PLoS ONE [Electronic Resource], 2010. 5(7): p. e11542.
64. Husa, P., Roznovsky, L., Smejkal, P., Husova, L., Penka, M., and Dite, P. *Efficacy and safety of chronic hepatitis C treatment in hemophilic patients.* Hepato-Gastroenterology, 2005. 52(65): p. 1541-4.
65. Iorio, A., Marchesini, E., Awad, T., and Gluud, L.L. *Antiviral treatment for chronic hepatitis C in patients with human immunodeficiency virus.* Cochrane Database of Systematic Reviews, 2010(1): p. CD004888.
66. Jamall, I.S., Yusuf, S., Azhar, M., and Jamal, S. *Is pegylated interferon superior to interferon, with ribavarin, in chronic hepatitis C genotypes 2/3?* World Journal of Gastroenterology, 2008. 14(43): p. 6627-6631.
67. Khuroo, M.S., Khuroo, M.S., and Dahab, S.T. *Meta-analysis: a randomized trial of peginterferon plus ribavirin for the initial treatment of chronic hepatitis C genotype*

4.[Erratum appears in Aliment Pharmacol Ther. 2004 Dec;20(11-2):1388]. Alimentary Pharmacology & Therapeutics, 2004. 20(9): p. 931-8.

68. Kimer, N., Dahl, E.K., Gluud, L.L., and Krag, A. *Antiviral therapy for prevention of hepatocellular carcinoma in chronic hepatitis C: Systematic review and meta-analysis of randomised controlled trials.* BMJ Open, 2012. 2(5).
69. Shepherd, J., Brodin, H., Cave, C., Waugh, N., Price, A., and Gabbay, J. *Pegylated interferon alpha-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.* Health Technology Assessment, 2004. 8(39): p. iii-iv, 1-125.
70. Soriano, V., Maida, I., Nunez, M., Garcia-Samaniego, J., Barreiro, P., Martin-Carbonero, L., and Gonzalez-Lahoz, J. *Long-term follow-up of HIV-infected patients with chronic hepatitis C virus infection treated with interferon-based therapies.* Antiviral Therapy, 2004. 9(6): p. 987-92.
71. Soriano, V., Nunez, M., Sanchez-Conde, M., Barreiro, P., Garcia-Samaniego, J., Martin-Carbonero, L., Romero, M., and Gonzalez-Lahoz, J. *Response to interferon-based therapies in HIV-infected patients with chronic hepatitis C due to genotype 4.* Antiviral Therapy, 2005. 10(1): p. 167-70.
72. Sroczynski, G., Esteban, E., Conrads-Frank, A., Schwarzer, R., Muhlberger, N., Wright, D., Zeuzem, S., and Siebert, U. *Long-term effectiveness and cost-effectiveness of antiviral treatment in hepatitis C.* Journal of Viral Hepatitis, 2010. 17(1): p. 34-50.
73. Zaman, A., Fennerty, M.B., and Keeffe, E.B. *Systematic review: peginterferon vs. standard interferon in the treatment of chronic hepatitis C.* Alimentary Pharmacology & Therapeutics, 2003. 18(7): p. 661-70.
74. Zhang, W., Rao, H., Feng, B., Liu, F., and Wei, L. *Impact of hyperglycaemia levels on the outcome of interferon-alpha antiviral therapy in chronic hepatitis C patients: A systematic review and meta-analysis.* Hepatology, 2011. Conference: p. 62nd Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2011 San Francisco.
75. Zhao, S., Cheng, D., Liu, E., Yu, H., Yang, H., Xue, X., and Chu, Y. *Peginterferon vs. interferon in the treatment of different HCV genotype infections in HIV patients.* European Journal of Clinical Microbiology & Infectious Diseases, 2008. 27(12): p. 1183-92.
76. Zhao, S., Liu, E., Wei, K., Wang, Y., Li, Y., Huang, B., Chen, Y., and Yang, P. *Treatment with peginterferon versus interferon in Chinese patients with chronic hepatitis C*. European Journal of Clinical Microbiology and Infectious Diseases, 2011. 30, 51-57.
77. Zhao, S., Liu, E., Yu, H., Yang, H., Xun, M., Xue, X., Song, J., Xu, K., and Chu, Y. *Comparison of peginterferon and interferon in treating Chinese patients with chronic hepatitis C.* Hepato-Gastroenterology, 2008. 55(84): p. 1047-54.
78. Zhao, S.H., Chu, Y.L., Cheng, D.X., Waqar, A.B., Yu, Q., Yang, P.H., Xue, X., Yang, H.J., and Liu, E.Q. *Treatment with peginterferon plus ribavirin vs. interferon plus ribavirin for 48 weeks in Chinese patients with chronic hepatitis C.* International Journal of Clinical Practice, 2009. 63(9): p. 1334-9.
79. Zhao, S.-H., Liu, E.-Q., Cheng, D.-X., Xue, X., and Chu, Y.-L. *[Meta-analysis on peginterferon plus ribavirin in treatment of hepatitis C virus genotype 1 or 4 infection in HIV patients].* Zhejiang da Xue Xue Bao, 2009. Yi Xue Ban/Journal of Zhejiang University. Medical Sciences. 38(3): p. 315-9.
80. Puoti, M., Babudier, S., Rezza, G., Viale, P., Antonini, M.G., Maida, I., Rossi, S., Zanini, B., Putzolu, V., Fenu, L., Baiguera, C., Sassu, S., Carosi, G., and Mura, M.S. *Use of pegylated interferons is associated with an increased incidence of infections during combination treatment of chronic hepatitis C: A side effect of pegylation?* Antiviral Therapy, 2004. 9(4): p. 627-630.

81. Almeida, P.R., Tovo, C.V., Rigo, J.O., Zanin, P., Alves, A.V., and Mattos, A.A. *Interferon convencional versus interferon peguilado associados à ribavirina no tratamento de pacientes coinfectados pelo vírus da hepatite C (genótipo 1) e da imunodeficiência humana*

Alpha-interferon versus peg-interferon associated to ribavirin in the treatment of genotype 1 hepatitis C virus and human immunodeficiency virus coinfected patients. Arq Gastroenterol, 2009. 46(2): p. 132-137.

82. Cappiello, G., Abbate, I., Lo Iacono, O., Longo, R., Solmone, M., Ferraro, D., Antonucci, G., Di Marco, V., Di Stefano, R., Craxi, A., Ippolito, G., and Capobianchi, M.R. *ISDR pattern and evolution in patients with chronic hepatitis C treated with standard or PEG-IFN plus ribavirin.* Antiviral Therapy, 2003. 8(2): p. 105-10.

83. Gedik , H., Uludag, A., Yahyaoglu, M., Muderrisoglu, C., and Fincanci, M. *The efficacy of conventional interferon or pegylated interferon in combination with ribavirin in treatment of chronic hepatitis C and a comparison study for adverse effects related to treatments.* Nobel Medicus, 2008. 4(2): p. 19-25.

84. Hinrichsen, H., Buggisch, P., Nasser, S., and Foelsch, U.R. *A prospective randomized 24 week trial of peg-interferon alpha2b plus ribavirin versus standard combination therapy in untreated hepatitis C genotype 2 and 3 patients [abstract]*. Hepatology, 2002. 36, 311a.

85. Izumi, N., Asahina, Y., Kurosaki, M., Uchihara, M., Nishimura, Y., Inoue, K., Ueda, K., Tsuchiya, K., Hamano, K., Itakura, J., and Miyake, S. *A comparison of the exponential decay slope between PEG-IFN alfa-2b/ribavirin and IFN alfa-2b/ribavirin combination therapy in patients with chronic hepatitis C genotype 1b infection and a high viral load.* Intervirology, 2004. 47(2): p. 102-7.

86. Kraus, M.-R., Schafer, A., Csef, H., and Scheurlen, M. *Psychiatric side effects of pegylated interferon alfa-2b as compared to conventional interferon alfa-2b in patients with chronic hepatitis C.* World Journal of Gastroenterology, 2005. 11(12): p. 1769-74.

87. Nevens, F., Van Vlierberghe, H., D'Heygere, E., Delwaide, J., Adler, M., Henrion, J., Lenaerts, A., Hendlisz, A., Michielsen, P., Bastens, B., Brenard, R., Laureys, A., and Bernar- Study Group. *A randomized, open-label, multicenter study evaluating the efficacy of peginterferon alfa-2a versus interferon alfa-2a, in combination with ribavirin, in naive and relapsed chronic hepatitis C patients.* Acta Gastroenterologica Belgica, 2010. 73(2): p. 223-8.

88. Pol, S., Carrat, F., Bani-Sadr, F., Rosenthal, E., Lunel, F., Morand, P., Salmon, D., Pialoux, G., Cacoub, P., and Perronne, C. *Final results of ANRS HC02-ribavic: a randomized controlled trial of pegylated-interferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin for naive HCV-HIV co-infected patients*. Journal of Hepatology, 2005. 42, 10-1.