Clinical Infectious Diseases

MAJOR ARTICLE

Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis

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Background. Treatment for hepatitis C virus (HCV) can lead to sustained virological response (SVR) in over 90% of people. Subsequent recurrence of HCV, either from late relapse or reinfection, reverses the beneficial effects of SVR.

Methods. A search identified studies analysing HCV recurrence post-SVR. The recurrence rate for each study was calculated using events/person years of follow-up (PYFU). Results were pooled using a random-effects model and used to calculate 5-year recurrence risk. Three patient groups were analysed: (1) Mono-HCV infected "low-risk" patients; (2) Mono-HCV infected "high-risk" patients (injecting drug users or prisoners); (3) human immunodeficiency virus (HIV)/HCV coinfected patients. Recurrence was defined as confirmed HCV RNA detectability post-SVR.

Results. In the 43 studies of HCV mono-infected "low-risk" patients (n = 7969) the pooled recurrence rate was 1.85/1000 PYFU (95% confidence interval [CI], .71–3.35; $I^2 = 73\%$) leading to a summary 5-year recurrence risk of 0.95% (95% CI, .35%–1.69%). For the 14 studies of HCV monoinfected "high-risk" patients (n = 771) the pooled recurrence rate was 22.32/1000 PYFU (95% CI, 13.07–33.46; $I^2 = 27\%$) leading to a summary 5-year risk of 10.67% (95% CI, 6.38%–15.66%). For the 4 studies of HIV/HCV coinfected patients the pooled recurrence rate was 32.02/1000 PYFU (95% CI, .00–123.49; $I^2 = 96\%$) leading to a summary 5-year risk of 15.02% (95% CI, .00%–48.26%). The higher pooled estimates of recurrence in the high-risk and coinfected cohorts were driven by an increase in reinfection rather than late relapse.

Conclusions. SVR appears durable in the majority of patients at 5 years post-treatment. The large difference in 5 year event rate by risk group is driven mainly by an increased reinfection risk.

Keywords. hepatitis C; sustained virologic response; recurrence; relapse; reinfection.

Infection with the hepatitis C virus (HCV) is a significant public health concern associated with a high burden of morbidity and mortality [1, 2]. Recent estimates suggest that worldwide, of the 185 million individuals infected, over 700 000 people die annually as a result of infection [3, 4].

The attainment of a sustained virological response (SVR), defined as aviremia 12 or 24 weeks after the completion of antiviral therapy (SVR12 or SVR24), is associated with an improved prognosis compared with patients either untreated or failing therapy. These benefits include improved histology, reduced risk of hepatocellular carcinoma, and improved overall survival [5, 6].

Despite these benefits, treatment uptake for chronic HCV has been low due to complexities of treatment and poor success rates. The availability of new highly efficacious regimens provides the foundation for marked treatment scale-up; however, high costs are currently limiting access [7–10].

One challenge to treatment scale-up is the risk of HCV recurrence, either as late relapse post-SVR or reinfection following treatment. HCV recurrence is a particular concern in patients with ongoing high-risk behaviors, such as injecting drug users (IDUs), who are more susceptible to reinfection, and also patients coinfected with human immunodeficiency virus (HIV) who may be at increased risk of relapse due to their immunocompromised status [11–15].

A number of studies have been carried out to examine the durability of treatment-induced SVR in patients with chronic HCV in a variety of patient populations. Our aim was to systematically review the existing evidence and undertake meta-analysis to provide summary estimates of the recurrence rate by risk group. The secondary aim was to evaluate the contribution of late relapse and of reinfection to the recurrence rate. This work fits within the theme one of the PROGRESS framework for prognosis research ("fundamental prognosis research")

Received 30 July 2015; accepted 30 October 2015; published online 19 January 2016.

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Clinical Infectious Diseases® 2016;62(6):683–94

DOI: 10.1093/cid/civ948

and will provide a clearer understanding of HCV recurrence to inform the provision of antiviral therapy [16].

METHODS

Search Strategy and Inclusion Criteria

The MEDLINE database was searched from 1990 until 1 March 2015 for studies analyzing HCV recurrence post-SVR. A sensitive search string was developed using terms including hepatitis C, treatment, SVR, recurrence, relapse, and reinfection (Supplementary Appendix). The reference lists of articles were thoroughly searched to identify additional articles. Lastly, the proceedings of the following conferences were search for additional studies: International Liver Congress (EASL), The Liver Meeting (AASLD), Conference on Retroviruses and Opportunistic Infections, and the International AIDS Conference.

Studies included were to have enrolled adult patients (aged ≥18) who achieved SVR after antiviral treatment for acute or chronic HCV. SVR was defined as undetectable HCV RNA 12 or 24 weeks post-treatment. There was no stipulated method of HCV acquisition or specific antiviral treatment regimen. There were no restrictions on study design however all studies were to have a follow-up longer than 6 months post-SVR. Studies were excluded if they examined rate of recurrence after spontaneous clearance, or if they measured recurrences after the end of treatment, not allowing for the SVR time period to elapse.

Studies were categorized in to 3 groups: (1) Low-risk population, inclusive of studies of mono-HCV infected patients with no recognized risk factors for reinfection; (2) High-risk population, inclusive of studies of mono-HCV infected patients with at least 1 identified risk factor for reinfection; and (3) HIV/HCV coinfection populations, inclusive of all studies of HIV/HCV coinfected persons, regardless of the presence or absence of other risk factors. Risk factors for reinfection were defined as current or former IDU, imprisonment, and men who have sex with men (MSM). Studies of liver transplant recipients were excluded.

Quality Assessment

Articles meeting the inclusion criteria were assessed for methodological quality using the Newcastle–Ottawa Scale (NOS). The assessment was modified to allocate a maximum of 8 stars, for quality of selection, comparability, exposure, and outcome of study participants (Supplementary Appendix). Studies with a NOS rating ≥6 were considered high-quality.

Data Extraction

The following data were extracted for each study: location, design, recruitment, patient characteristics, average follow-up time, number of HCV recurrences, total PYFU, and frequency of HCV RNA assessment. HCV recurrence was defined as confirmed HCV RNA detectability post-SVR. Where possible, recurrence was characterized as either late relapse or as reinfection, with categorization carried out according to the original study definitions and techniques. In all studies using phylogenetic techniques late relapse was defined as detection of HCV RNA of the same virus lineage and reinfection as identification of a different virus. In the majority of studies, this classification was according to the protocol in the original article. In genotyping studies where no criteria for classification were given, the same definitions were applied by the authors of the current meta-analysis. In some studies, categorization was done by the study authors without confirmatory genotyping. In these studies, the decision to classify as late relapse or reinfection was usually made through consultation with patients to assess for the presence or absence of risk behaviors (eg, injecting drug use, unsafe procedures, etc.).

PYFU were accrued from the SVR time-point; in those studies where follow-up originated at the end-of-treatment, PYFU were appropriately adjusted. If total PYFU was not explicitly stated, it was estimated from the average follow-up time; studies in which PYFU was inestimable were excluded. In the case of study duplications, the article providing the most comprehensive account of the study population and longest follow-up period was used.

The literature search, data extraction, and quality assessment were carried out independently by 2 authors (B. S., J. S.), and any differences were resolved by consensus.

Data Synthesis

For each study, the incidence rate of HCV recurrence was calculated as the number of recurrences per 1000 PYFU and was reported with the corresponding 95% Wilson confidence interval (95% CI). Given the rarity of events, estimates were transformed using the Freeman-Tukey double arcsine transformation [17, 18]. A pooled estimate for recurrence was then calculated for each of the three groups separately using a random-effects model [19]. In addition, meta-analyses of the rate of late relapse and of the rate of reinfection were carried out including studies providing this data. The pooled estimates were used to calculate the 5-year event rate for recurrence, late relapse, and reinfection for each population. The summary 5-year risk was calculated using $1 - (1 - \text{pooled incidence rate})^5$ and as such assumed that the pooled rate of recurrence was constant over the follow-up duration. For each calculation, the degree of heterogeneity between studies was quantitatively assessed using I^2 and tau^2, where an $I^2 \geq 50\%$ may indicate substantial heterogeneity and ≥75% is indicative of considerable heterogeneity. The existence of publication bias was evaluated by observational analysis of funnel plots. All analyses were conducted using STATA version 13 (StataCorp LP, Texas).

RESULTS

As shown in Figure 1, a total of 1180 references were identified and screened for eligibility. Of these, results were available from 59 studies reporting on recurrence post-SVR in a total of 9049 patients. Two studies evaluated two distinct subgroups of monoinfected and HIV coinfected patients and as such were included in 2 analysis groups. Of the studies deemed possibly relevant and screened against inclusion criteria, the main reasons

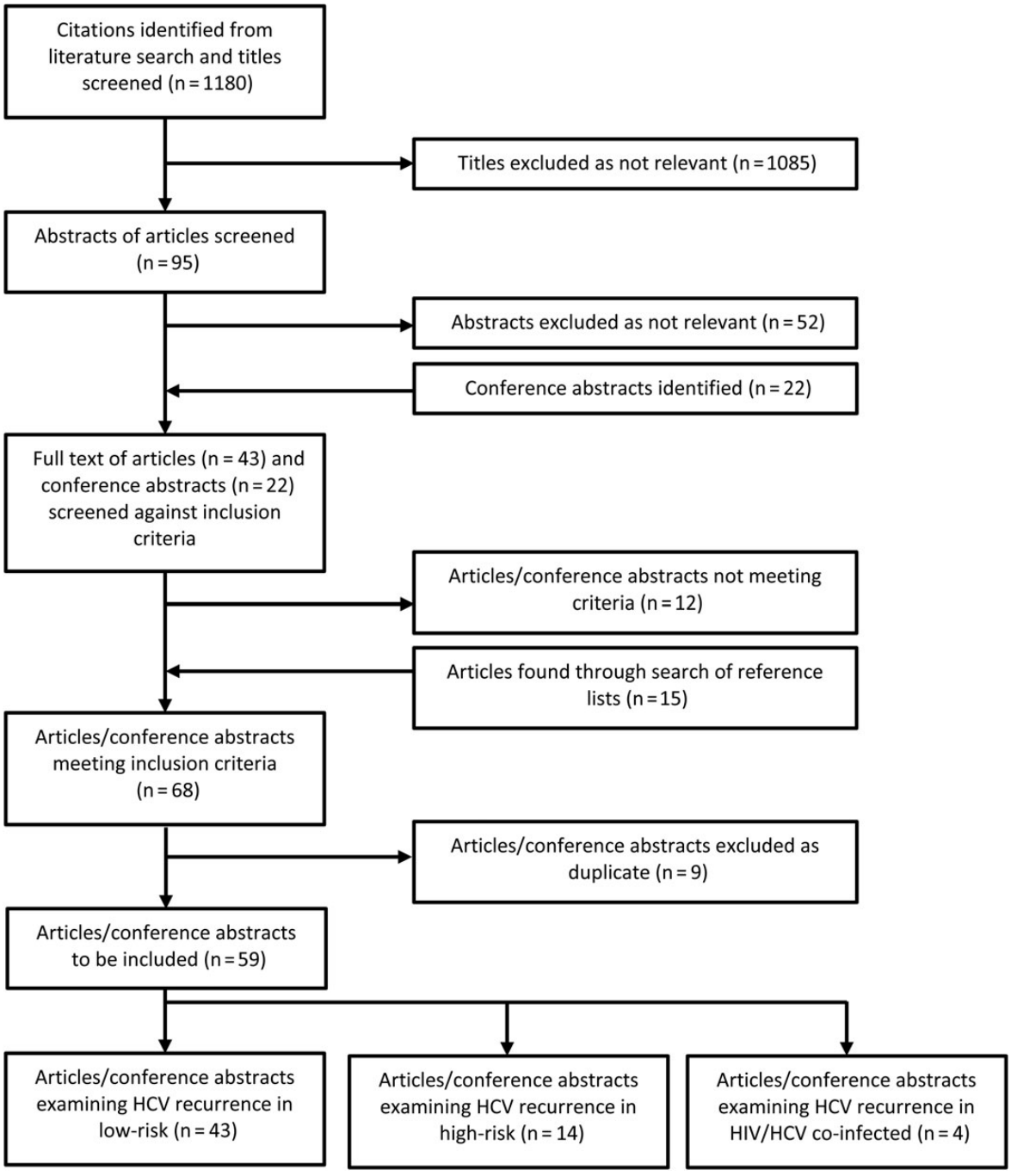

Figure 1. Flow diagram of study selection for systematic review of hepatitis C virus (HCV) recurrence in patients achieving a sustained virologic response after treatment for HCV infection. Low-risk studies include those examining recurrence in general populations and high-risk studies include those studying patients with at least 1 reinfection risk factor (injecting drug use or prison populations). Human immunodeficiency virus (HIV)/HCV coinfected studies include all those of coinfected participants, regardless of risk factors. Total studies in the 3 groups does not equal the total number of studies identified as 2 studies examined 2 populations.

for exclusion were the assessment of recurrence rate after spontaneous clearance and the lack of an SVR time period after the end-of-treatment. The study and cohort characteristics are shown in Table 1. All identified studies evaluated SVR at 24 weeks post-treatment; no studies eligible for inclusion used SVR12 as the endpoint for analysis. Frequency of HCV RNA assessment varied from every 3 months to 1 single assessment during follow-up. For all 3 risk groups, funnel plots appeared symmetrical indicating no evidence of bias. Of all studies, 49/59 (83%) were considered high-quality (NOS score ≥6). The main biases observed were in determining PYFU and in accepting the authors' opinion regarding reinfection vs relapse.

Table 1. Study Characteristics of Included Studies

Study, Year (Ref)	Location and Study Design	Recruitment and Exclusion Criteria	Treatment	Total With SVR	Mean Age	% Male	Frequency of HCV RNA Testing	NOS Rating[a]
Low risk of reinfection								
Howe et al 2015 [20]	Europe, US, and Canada; Long-term FU of RCTs	Genotype-1 with compensated liver disease enrolled in Phase 2/3 BOC studies	BOC + Peg-IFN + RBV	696	NR	NR	Every 3 mo for 6 mo, then 6 mo	7 (1)
Koh et al 2013/Hara et al 2014 [21, 22]	US; Long-term FU of clinical research protocols	Enrolled in clinical research by National Institute of Diabetes and Digestive and Kidney Diseases	Peg-IFN or IFN ± RBV	103	56	56	Regularly (freq. NR)	7 (1)
Manns et al 2013 [23]	International; Long-term FU of RCTs	Enrolled in 2 phase 3 studies; No HBV or HIV coinfection and no active substance abuse	Peg-IFN ± RBV IFN ± RBV	366 636	46 43	62 63	Annually (for 5 y)	6 (0)
Giordanino et al 2013 [24]	Italy; Prospective cohort	Consecutive presentation at hepatology clinics; treatment-naive with no decompensation	Peg-IFN + RBV	115	46	60	Every 6 mo for 3 y, then annually	6 (–)
Hotho et al 2013 [25]	The Netherlands; Long-term FU of RCT	RCT enrolling genotype-1, treatment-naïve and experienced patients	Peg-IFN + RBV + narlaprevir	19	56	74	6 and 18 mo post-SVR	5 (–)
Ignatova et al 2013 [26]	Russia; NR	NR	Antiviral treatment	208	37	52	NR	5 (0)
Papastergiou et al 2013 [27]	Rhodes, Greece; Prospective cohort	Consecutive enrolment of treatment-naïve patients in hepatology unit; No HBV or HIV coinfection	Peg-IFN + RBV	145	47	60	Annually	7 (1)
Rahman et al 2013 [28]	Dhaka, Bangladesh; Prospective cohort	Enrolment from hospital clinic	Peg-IFN + RBV	52	41	78	Annually	5 (0)
Rutter et al 2013 [29]	Vienna, Austria; Long-term FU of clinical research protocols	Enrolment from prospective RCTs and early access programme	Peg-IFN + RBV + DAA	103	48	67	At least annually	6 (1)
Torres Ibarra et al 2013 [30]	Mexico; Retrospective cohort	Consecutive enrolment from medical centre	Peg-IFN or IFN ± RBV	188	43	46	Every 6 mo	7 (0)
Uyanikoglu et al 2013 [31]	Turkey; Retrospective cohort	Consecutive enrolment from hospital clinic	Peg-IFN or IFN ± RBV	196	46	45	Every 6 mo	7 (0)
Li et al 2012 [32]	Chongqing, China; Retrospective cohort	NR	Peg-IFN or IFN ± RBV	146	NR	NR	NR	5 (0)
Maruoka et al 2012 [33]	Chiba, Japan; Retrospective cohort	Consecutive enrolment of patients undergoing liver biopsy at hospital; No HBV or HIV coinfection	IFN therapy	207	48	66	Every 1–3 mo	7 (–)
Choi et al 2011 [34]	Busan, Korea; Retrospective cohort	Consecutive enrolment from hospital clinic	Peg-IFN + RBV	224	48	58	Every 6 mo	7 (–)
Morisco et al 2011 [35]	Italy; Prospective cohort	Consecutive enrolment from hospital clinics	Peg-IFN or IFN ± RBV	150	48	67	Every 6 mo for 3 y, then annually	6 (–)
Puig-del-Castillo et al 2011 [36]	Barcelona, Spain; Retrospective cohort	Consecutive enrolment from hospital clinics	Peg-IFN + RBV	80	41	70	Single assessment after 5 y	7 (1)
Trapero-Marugán et al 2011 [37]	Madrid, Spain; Prospective cohort	Consecutive enrolment from hospital hepatitis clinic; No HIV or HBV coinfection and no alcohol or IDU abuse	Peg-IFN + RBV	153	49	54	Annually (for 5 y)	7 (–)
da Costa Ferreira et al 2010 [38]	São Paulo, Brazil; Retrospective cohort	Enrolment from hospital hepatitis clinic; No HBV or HIV coinfection	Peg-IFN or IFN ± RBV	174	46	73	Annually	7 (0)
De Jesús et al 2010 [39]	Puerto Rico; Retrospective cohort	Enrolment from hospital clinic	Peg-IFN or IFN ± RBV	64	54	98	Single assessment	6 (0)
Giannini et al 2010 [40]	Genoa, Italy; Prospective cohort	Consecutive presentation at hospital hepatitis unit; No HIV coinfection and no IDU or alcohol abuse	Peg-IFN + RBV	231	44	60	Every 6 mo	7 (1)
Kim et al 2010 [41]	Daejeon, Korea; Retrospective cohort	Review of medical records from 1 hospital	Peg-IFN + RBV	37	NR	81	NR	6 (–)
Lee et al 2010 [42]	Seoul, Korea; Prospective cohort	Enrolment from hospital clinic	Peg-IFN + RBV	68	55	62	NR	6 (0)

Table 1 continued.

Study, Year (Ref)	Location and Study Design	Recruitment and Exclusion Criteria	Treatment	Total With SVR	Mean Age	% Male	Frequency of HCV RNA Testing	NOS Rating[a]
Morgan et al 2010 [43]	US; Long-term FU of clinical research protocols	Enrolled in HALT-C trial; patients with advanced disease and treatment-experience	Peg-IFN + RBV	91	49	76	Single assessment	5 (1)
Sood et al 2010 [44]	Ludhiana, India; Prospective cohort	Enrolment from hospital clinic; No HBV or HIV coinfection	Peg-IFN or IFN + RBV	100	41	78	Annually	7 (0)
Swain et al 2010 [45]	Europe, US, and Canada; Long-term FU of RCTs	Enrolled on to multicentre RCTs; No HBV or HIV coinfection and no alcohol or IDU abuse in past year	Peg-IFN + RBV Peg-IFN monotherapy	1077 166	NR NR	63 60	Annually (for 5 y)	6 (0)
George et al 2009 [46]	Madrid, Spain; Prospective cohort	NR; No HBV or HIV coinfection	Peg-IFN or IFN + RBV	147	49	50	Annually	7 (–)
Hofer et al 2009 [47]	Vienna, Austria; Retrospective cohort	Enrolment from hospital clinic	Peg-IFN or IFN ± RBV	251	NR	65	NR	6 (–)
Kim et al 2009 [48]	Incheon, Korea; Retrospective cohort	Enrolment from hospital clinic	Peg-IFN or IFN ± RBV	73	47	36	NR	6 (0)
Maylin et al 2008 [49]	Clichy, France; Retrospective cohort	Enrolment from hospital and follow-up in outpatient clinic	Peg-IFN or IFN ± RBV	344	45	69	Annually	7 (–)
Adamek et al 2007 [50]	Poland; NR	NR; No HBV or HIV coinfection	IFN + RBV	78	43	64	Single assessment	5 (–)
Chavalitdhamrong et al 2006 [51]	Bangkok, Thailand; Retrospective cohort	Enrolment from hospital hepatitis clinic; No HBV or HIV coinfection	IFN therapy	171	48	90	Every 6–12 mo	6 (–)
Ciancio et al 2006 [52]	Turin, Italy; Long-term FU of RCT	Enrolled onto RCT with prior treatment-experience	Peg-IFN + RBV	97	43	72	Every 6 mo	5 (0)
Desmond et al 2006 [53]	Melbourne, Australia; Retrospective cohort	Enrolment from hospital hepatitis clinic	Peg-IFN or IFN ± RBV	147	40	67	Every 6–12 mo	8 (1)
Moreno et al 2006 [54]	Oviedo, Spain; Retrospective cohort	Consecutive enrolment at hospital clinic	Peg-IFN or IFN ± RBV	132	37	64	NR	6 (–)
Yu et al 2005 [55]	Kaohsiung, Taiwan; Prospective cohort	Enrolment from hospital clinic; No HBV coinfection	Peg-IFN or IFN therapy	64	44	47	Annually	7 (0)
Khokhar et al 2004 [56]	Islamabad, Pakistan; Prospective cohort	Enrolment from hospital clinic	IFN + RBV	57	46	NR	Every 6 mo (for 3 y)	8 (0)
Tsuda et al 2004 [57]	Japan; Retrospective cohort	Consecutive enrolment from hospital clinics	IFN therapy	38	51	72	At least every 6 mo	6 (–)
Veldt et al 2004 [58]	Europe; Long-term FU of clinical research protocols	Consecutive enrolment from European centres, all patients participated in protocolled studies	IFN monotherapy	286	41	59	Every 6 mo	6 (0)
Ponsoda Arlettaz et al 2002 [59]	Montpellier, France; NR	NR	IFN ± RBV	125	48	NR	Every 6 mo	5 (–)
Diago et al 2001 [60]	Valencia, Spain; Prospective cohort	NR; Prior treatment experienced	IFN + RBV	19	NR	NR	6 and 18 mo post-SVR	5 (0)
Fontaine et al 2000 [61]	Paris, France; NR	Enrolment from hepatology unit	IFN ± RBV	44	NR	41	Every 6 mo	5 (0)
Marcellin et al 1997 [62]	Clichy, France; Prospective cohort (63% from RCTs)	Consecutive enrolment from clinic; No HBV or HIV coinfection	IFN monotherapy	75	NR	59	Every 6 mo	7 (0)
Reichard et al 1995 [63]	Sweden; Long-term FU of RCT	Multicentre enrolment	IFN monotherapy	14	50	57		6 (0)
High risk of reinfection (IDUs and prisoners)								
Weir et al 2014 [64]	Scotland; Retrospective cohort	IDUs identified using Scottish HCV and clinical laboratory data and records	Antiviral treatment	277	NR	NR	One or two assessments	6 (0)
Ruzic et al 2013 [65]	Vojvodina, Serbia; Retrospective-prospective cohort	IDUs with 1-year abstinence enrolled at infectious disease clinic	Peg-IFN + RBV	20	30	63	Single assessment after 5-years follow-up	6 (–)
Hilsden et al 2013 [66]	Alberta and Vancouver, Canada; Long-term FU of RCT	Recent IDU or crack cocaine use (within 3 mo); enrolled in to community-based RCT to received treatment or delayed treatment; No HBV or HIV coinfection	Peg-IFN + RBV	23	41	91	NR	7 (0)

Table 1 continued.

Study, Year (Ref)	Location and Study Design	Recruitment and Exclusion Criteria	Treatment	Total With SVR	Mean Age	% Male	Frequency of HCV RNA Testing	NOS Rating[a]
Edlin et al 2013 [67]	New York, US; NR	Active IDU enrolled at community based needle exchange program; enrolled both acute and chronic HCV	Peg-IFN + RBV	15	36	74	NR	5 (0)
Conway et al 2013 [68]	Vancouver, Canada; Prospective cohort	IDUs treated within multidisciplinary program; enrolled both acute and chronic HCV	Peg-IFN + RBV or DAA regimen	70	53	96	At least every 6 mo	8 (1)
Deshaies et al 2013 [69]	Quebec City, Canada; Prospective cohort	Active IDU enrolled in community setting (TACTIC project)	Antiviral treatment	20	39	60		5 (0)
Grady et al 2012 [70]	Amsterdam, The Netherlands; Prospective cohort	IDUs enrolled in Amsterdam Cohort Studies of drug users	Peg-IFN + RBV	42	51	74	Every 6–12 mo	7 (0)
Manolakopouos et al 2012 [71]	Athens, Greece; Retrospective cohort	Past and current IDUs enrolled in multidisciplinary supervised program at three liver units	Antiviral treatment	61	38	80	Single assessment (mean 2 y post-SVR)	6 (1)
Grebely et al 2010 [72]	Vancouver, Canada; Prospective cohort	Enrolment at addiction clinics; 54% IDU in previous 6 mo (100% ever IDU); enrolment at community clinics providing addiction services	IFN or Peg-IFN + RBV	35	44	96	Annually	8 (1)
Currie et al 2008 [73]	San Francisco, US; Prospective cohort	IDUs part of a larger study; advertisements for enrolment in hospitals, liver and methadone clinics etc.	Antiviral treatment	9	46	89	Every 6 mo	8 (0)
Backmund et al 2004 [74]	Munich, Germany; Prospective cohort	Opiate-dependent IDUs; enrolled during detoxification treatment	IFN ± RBV	18	32	61	Annually	8 (1)
Dalgard et al 2002 [75]	Oslo, Norway; Prospective long-term FU of RCT	IDU as route of transmission; abstinent for ≥6 mo	IFN ± RBV	27	30	67	NR	6 (1)
Marco et al 2013 [76]	Catalonia, Spain; Retrospective cohort	Prisoners treated in routine clinical practice; 20% with risk factor for reinfection	Peg-IFN + RBV	101	33	97	Annually	8 (1)
Bate et al 2010 [77]	Adelaide, Australia; Retrospective cohort	Incarcerated for entire planned duration of therapy; 55% past/present IDU	IFN or Peg-IFN ± RBV	53	34	95	NR	7 (1)
HIV/HCV coinfected								
Martin et al 2013 [78]	London, UK; Retrospective cohort	HIV-positive MSM enrolled at HIV clinic; patients excluded if primary mode of transmission was via contaminated blood products or IDU; enrolled both acute and chronic HCV	Antiviral treatment (91% on ART)	114	41	100	NR	6 (0)
Marco et al 2013 [76]	Catalonia, Spain; Retrospective cohort	Prisoners treated in routine clinical practice; 20% with risk factor for reinfection	Peg-IFN + RBV (100% on ART)	18	33	98	Annually	7 (1)
Swain et al 2010 [45]	Europe, US, and Canada; Long-term FU of RCTs	HIV-positive enrolled into RCT at different centres	Peg-IFN ± RBV	100	NR	82	Annually (for 5 y)	6 (0)
Soriano et al 2004 [79]	Spain; Retrospective FU of RCTs	HIV-positive enrolled on 4 different RCTs; no HBV coinfection or active drug or alcohol abuse	Peg-IFN + RBV (53% on ART)	77	34	68	Regularly (freq. NR)	7 (–)

Abbreviations: ART, antiretroviral therapy; BOC, boceprevir; DAA, direct acting antiviral; FU, follow-up; HALT-C, hepatitis C antiviral long-term treatment against cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug user; IFN, interferon; MSM, men who have sex with men; NOS, Newcastle-Ottawa Scale; NR, not reported; Peg-IFN, pegylated-interferon; RBV, ribavirin; RCT, randomized controlled trial; SVR, sustained virological response.

[a] NOS score is score out of 8; score in brackets is the score for the quality of categorization of recurrence as either late relapse or reinfection, where 1 indicates distinction was based on genotyping, 0 indicates distinction was by author/clinician discretion or no distinction was made, and – indicates that no recurrences were observed.

Low-risk Population

Forty-three articles were found evaluating the risk of recurrence in 7969 low-risk patients. Of these, 29 were prospective or retrospective cohorts, and 10 follow-up patients enrolled in randomized clinical trials (RCTs) or research protocols; study type was not recorded in 4 studies. All studies were carried out in patients with chronic HCV. In 39 studies, patients were treated with peg-IFN or IFN, either in combination with ribavirin or as monotherapy. In 3 studies, treatment consisted of peg-IFN, ribavirin, and a DAA (boceprevir n = 1, narlaprevir n = 1, unspecified n = 1); treatment regimen was not specified in the final study. The mean of the average follow-up post-SVR was 3.9 years (range, 1.0–8.7 years). Of the 28 studies with at least 1 recurrence, 11 used genotyping or sequencing to determine recurrence type, 5 relied on author judgment/terminology, and 12 did not classify the recurrence.

Overall, 108/7969 experienced HCV recurrence with individual study recurrence rates varying from 0.00/1000 PYFU to 70.18/1000 PYFU (Table 2). Following random effects meta-analysis, the pooled estimate for the recurrence rate was 1.85/1000 PYFU (95% CI, .71–3.35; Table 3); however, a high level of heterogeneity was observed ($I^2 = 73.0\%$). Based on this pooled estimate, the corresponding 5-year recurrence risk was 0.95% (95% CI, .35%–1.69%; Figure 2).

The pooled estimate was 0.82/1000 PYFU (95% CI, .08–2.05) for late relapse, and 0.00/1000 PYFU (95% CI, .00–.00) for reinfection (Table 2). These estimates led to 5-year late relapse and reinfection rates of 0.40% (95% CI, .35%–1.05%) and 0.00% (95% CI, .00%–.00%), respectively (Figure 2).

High-risk Population

In total, 14 articles were found that assessed HCV recurrence in high-risk patients. Of these studies, 12 evaluated the risk in IDUs (n = 617) and 2 in prisoners (n = 154). In sum, 10 of 12 IDU studies were cohorts, and 2 were the long-term follow-up from RCTs. Both studies of prisoners were retrospective cohorts of patients receiving treatment while under detention. Twelve of the studies were conducted in patients with chronic HCV exclusively, and 2 studies enrolled patients with acute and chronic HCV. Patients received peg-IFN or IFN with or without ribavirin in 9 studies and either peg-IFN plus ribavirin or a DAA regimen in 1 study; 4 studies did not specify the antiviral regimen. The average of the mean follow-up post-SVR was 2.8 years (range 1.4–4.9 years). Overall, 9/13 studies with at least 1 recurrence used genotyping to classify the recurrence type.

In total, 42 recurrences were observed in a total of 771 patients. The recurrence rate varied from 0.00/1000 PYFU to 63.09/1000 PYFU in each study (Table 2); the pooled estimate for recurrence was 22.32/1000 PYFU (95% CI, 13.07–33.46) and a low level of heterogeneity was observed ($I^2 = 27.3\%$; Table 3). As shown in Figure 2, this estimate led to a 5-year recurrence rate of 10.67% (95% CI, 6.38%–15.66%) and was driven mainly by reinfection (19.06/1000 PYFU, 95% CI, 11.42–28.16) rather than late relapse.

HIV/HCV Coinfected Population

Of the 4 studies identified assessing recurrence in the HIV/HCV coinfected patients, 1 was carried out exclusively in MSM, 1 enrolled incarcerated patients only, and the remaining 2 recruited a mixed population. Two studies were cohort studies (n = 132) and two (n = 177) were long-term follow-up of RCTs. Three of the studies enrolled patients with chronic HCV, and the remaining study enrolled patients with both acute and chronic disease. Patients received peg-IFN or IFN with or without ribavirin in 3 studies; 1 study did not specify the regimen. In sum, 3 of the 4 studies reported the proportion of patients receiving antiretroviral therapy for HIV infection. In total, 78% of patients were receiving treatment ranging from 53% to 100% in the 3 studies. Of the 4 studies, 2 excluded patients with active IDU, and 2 enrolled patients with either a history of IDU or drug use during or after treatment. The average of the mean follow-up post-SVR was 3.3 years (1.6–4.3 years). One of the 3 studies reporting at least 1 recurrence used genotyping techniques to classify the recurrence.

Overall, 31/309 patients experienced a recurrence for a pooled recurrence rate of 32.02/1000 PYFU (95% CI, .00–123.49; Table 3); however, a substantial level of heterogeneity was observed and individual study recurrence rates varied from 0.00 to 133.93/1000 PYFU. The pooled rate led to a 5-year recurrence rate of 15.02% (95% CI, .00%–48.26%; Figure 2).

By recurrence type, the pooled estimate for late relapse was 0.00/1000 PYFU (95% CI, .00–.03) and for reinfection it was 32.02/1000 PYFU (95% CI, .00–123.49), leading to a 5-year risk of 0.0% (95% CI, .0%–.01%) and 15.02% (95% CI, .00%–48.26%), respectively. The uncertainties of the reinfection estimate are reflected by the wide 95% CI and the high level of heterogeneity observed.

To attempt to understand the heterogeneity, an analysis of RCTs compared with unselected patient cohorts was conducted. The pooled estimate of recurrence was significantly lower for patients followed-up after RCTs, leading to a significantly lower 5-year recurrence rate compared to the unselected cohorts (0.46% [95% CI, .00–2.65] vs 45.86% [95% CI, 32.86–58.27]). These data however should be interpreted with caution given the small number of studies available for evaluation (2 studies in each group) and the substantial between study heterogeneity observed ($I^2 = 98.7\%$).

DISCUSSION

Achieving SVR substantially reduces the risk of hepatocellular carcinoma, cirrhosis, and mortality, however these benefits are lost following recurrent infection [80]. In this meta-analysis, the risk of HCV recurrence after treatment-induced SVR was found to be 1.85/1000 PYFU in the low-risk group and rose to

Table 2. Hepatitis C Virus Recurrences and Rate of Recurrence in Included Studies

Study		Number With SVR	Avg. Follow-up Post-SVR (Total PYFU Post-SVR)	Method	Recurrences			Recurrence Rate per 1000 PYFU (95% CI)
					Late Relapse (Confirmed)[a]	Reinfection (Confirmed)[b]	Total[c]	
Low-risk studies								
Howe et al 2015		696	3.4 (2227.2)	Sequencing	3 (0)	1 (1)	4	1.80 (.70–4.61)
Koh et al 2014		103	7.5 (772.5)	Genotyping	3 (3)	0	3	3.88 (1.32–11.36)
Manns et al 2013	Peg-IFN ± RBV	366	4.1 (1517.1)	Genotyping	3 (0)	2 (2)	5	3.30 (1.41–7.69)
	IFN ± RBV	636	4.94 (3141.8)		6 (0)	0	6	1.91 (.88–4.16)
Giordanino et al 2013		115	8.7 (1000.5)	–	0	0	0	0.00 (.00–3.82)
Hotho et al 2013		19	1.8 (34.2)	–	0	0	0	0.00 (.00–100.98)
Ignatova et al 2013		208	4.7 (972.4)	None	–	–	3	3.09 (1.05–9.03)
Papastergiou et al 2013		145	5.7 (820.0)	Genotyping and risk factors	1 (0)	1 (1)	2	2.44 (.67–8.85)
Rahman et al 2013		52	4.2 (216.0)	Terminology	4 (0)	0	4	18.52 (7.22–46.64)
Rutter et al 2013		103	1.8 (180.3)	Genotyping and sequencing	2 (2)	0	2	11.09 (3.05–39.54)
Torres Ibarra et al 2013		188	5.8 (1081.0)	None	–	–	3	2.78 (.94–8.13)
Uyanikoglu et al 2013		196	2.8 (547.2)	Terminology	2 (0)	0	2	3.65 (1.00–13.23)
Li et al 2012		146	1.5 (219.0)	None	–	–	7	31.96 (15.57–64.50)
Maruoka et al 2012		207	7.5 (1552.5)	–	0	0	0	0.00 (.00–2.47)
Choi et al 2011		224	1.5 (336.0)	–	0	0	0	0.00 (.00–11.30)
Morisco et al 2011		150	8.6 (1290.0)	–	0	0	0	0.00 (.00–2.97)
Puig-del-Castillo et al 2011		80	5.0 (400.0)	Genotyping	1 (0)	0	1	2.50 (.44–14.02)
Trapero-Marugán et al 2011		153	6.3 (969.0)	Genotyping	0	0	0	0.00 (.00–3.95)
da Costa Ferreira et al 2010		174	3.9 (681.5)	None	–	–	1	1.47 (.26–8.26)
De Jesús et al 2010		64	2.6 (164.8)	Risk factors	1 (0)	0	1	6.07 (1.07–33.57)
Giannini et al 2010		231	3.1 (725.7)	Genotyping and risk factors	2 (2)	0	2	2.76 (.76–9.99)
Kim et al 2010		37	1.0 (37.0)	–	0	0	0	0.00 (.00–94.06)
Lee et al 2010		68	1.6 (108.8)	None	–	–	5	45.96 (19.79–103.09)
Morgan et al 2010		91	6.6 (596.1)	Genotyping	1 (0)	0	1	1.68 (.30–9.44)
Sood et al 2010		100	3.0 (301.0)	None	–	–	8	26.58 (13.53–51.56)
Swain et al 2010	Peg-IFN + RBV	1077	3.8 (4079.1)	None	–	–	9	2.21 (1.16–4.19)
	Peg-IFN mono	166	4.6 (760.5)		–	–	2	2.63 (.72–9.54)
George et al 2009		147	4.6 (673.3)	–	0	0	0	0.00 (.00–5.67)
Hofer et al 2009		251	4.2 (1054.2)	–	0	0	0	0.00 (.00–3.63)
Kim et al 2009		73	1.4 (103.1)	None	–	–	1	9.70 (1.71–52.91)
Maylin et al 2008		344	3.3 (1258.5)	–	0	0	0	0.00 (.00–3.04)
Adamek et al 2007		78	1.8 (142.4)	–	0	0	0	0.00 (.00–26.27)
Chavalitdhamrong et al 2006		171	2.4 (418.6)	–	0	0	0	0.00 (.00–9.09)
Ciancio et al 2006		97	7.2 (695.2)	Terminology	11 (0)	0	11	15.82 (8.86–28.11)
Desmond et al 2006		147	2.3 (338.1)	Genotyping and risk factors	1 (0)	0	1	2.96 (.52–16.56)
Moreno et al 2006		132	3.0 (396.0)	–	0	0	0	0.00 (.00–9.61)
Yu et al 2005		64	6.8 (435.8)	Genotyping	–	–	1	2.29 (.41–12.88)
Khokhar et al 2004		57	3.0 (171.0)	None	–	–	5	29.24 (12.55–66.61)
Tsuda et al 2004		38	5.7 (216.6)	Genotyping	0	0	0	0.00 (.00–17.43)
Veldt et al 2004		286	4.4 (1225.5)	Terminology	12 (0)	0	12	9.79 (5.61–17.04)
Ponsoda Arlettaz et al 2002		125	1.2 (145.8)	–	0	0	0	0.00 (.00–25.67)
Diago et al 2001		19	1.5 (28.5)	None	–	–	2	70.18 (19.46–223.00)
Fontaine et al 2000		44	1.2 (53.9)	None	–	–	1	18.55 (3.28–97.88)
Marcellin et al 1997		75	3.5 (250.1)	None	–	–	1	4.00 (.71–22.30)
Reichard et al 1999		26	4.9 (127.4)	Genotyping	2 (0)	0	2	15.70 (4.32–55.43)
High-risk studies								
Weir et al 2014		277	4.5 (410.0)	Terminology	0	7 (0)	7	17.07 (8.29–34.82)
Ruzic et al 2013		20	5 (100.0)	–	0	0	0	0.00 (.00–36.99)
Hilsden et al 2013		23	1.8 (35.5)	Risk factors	0	1 (0)	1	28.17 (4.99–143.49)
Edlin et al 2013		15	NR (45.1)	Terminology	0	1 (0)	1	22.17 (3.92–115.43)
Conway et al 2013		70	2.0 (138.6)	Genotyping	0	4 (4)	4	28.86 (11.28–71.85)

Table 2 continued.

Study	Number With SVR	Avg. Follow-up Post-SVR (Total PYFU Post-SVR)	Method	Recurrences			Recurrence Rate per 1000 PYFU (95% CI)
				Late Relapse (Confirmed)[a]	Reinfection (Confirmed)[b]	Total[c]	
Deshaies et al 2013	20	1.6 (31.7)	Genotyping	0	2 (1)	2	63.09 (17.48–203.15)
Grady et al 2012	42	2.0 (110.6)	Sequencing	0	1 (0)	1	9.04 (1.60–49.45)
Manolakopouos et al 2012	61	2.0 (122.0)	Genotyping	0	5 (4)	5	40.98 (17.63–92.36)
Grebely et al 2010	35	2.0 (62.5)	Genotyping and risk factors	0	2 (1)	2	32.00 (8.82–109.38)
Currie et al 2008	9	3.6 (38.0)	Terminology	0	1 (0)	1	26.32 (4.66–134.95)
Backmund et al 2004	18	2.8 (48.8)	Genotyping	0	1 (1)	2	40.98 (11.31–137.65)
Dalgard et al 2002	27	4.9 (118.0)	Genotyping	0	1 (1)	1	8.47 (1.50–46.45)
Marco et al 2013	101	1.4 (148.5)	Genotyping and risk factors	0	6 (5)	6	40.40 (18.65–85.34)
Bate et al 2010	53	3.4 (180.4)	Genotyping	5 (5)	4 (4)	9	49.89 (26.47–92.08)
HIV/HCV coinfected							
Martin et al 2013	114	1.6 (224.3)	Terminology	0	27 (0)	27	120.37 (84.06–169.47)
Marco et al 2013	18	NR (22.4)	Genotyping and risk factors	0	3 (2)	3	133.93 (46.62–328.41)
Swain et al 2010	100	4.0 (398.3)	Risk factors	0	1	1	2.51 (.44–14.08)
Soriano et al 2004	77	4.3 (333.7)	–	0	0	0	0.00 (.00–11.38)

Entries marked with a dash gave no indication whether the recurrence was a late relapse or a reinfection.

Number of late relapses plus number of reinfections does not always equal the total number of cases if the description of certain cases was not provided.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NR, not reported; Peg-IFN, pegylated-interferon; PYFU, person-years of follow-up; RBV, ribavirin; SVR, sustained virologic response.

[a] Number of suspected late relapses (no. confirmed by genotyping or sequencing).

[b] Number of suspected reinfections (no. confirmed by genotyping or sequencing).

[c] Total number of late relapses and reinfections.

22.32 and 32.02/1000 PYFU in the high-risk and HIV/HCV coinfection populations, respectively. These incidence rates led to estimated 5-year recurrence rates of 0.95%, 10.67%, and 15.02% in the low-risk, high-risk, and coinfection groups, respectively. Thus, despite higher recurrence rates in those with identified ongoing risk behaviors and/or HIV infection, SVR is durable, and the great majority of patients have SVR at 5 years post-treatment.

The current analysis suggests that the greater recurrence risk in the high-risk and HIV coinfected populations is driven by an increased likelihood of reinfection, highlighting the need for prevention campaigns targeted at individuals who continue to place themselves at high-risk of HCV re-exposure. According to the inclusion criteria, the meta-analysis evaluated the risk of recurrence post-treatment. Consequently, studies evaluating spontaneous cleared were excluded [81–86]. The data from these studies support the notion that the risk of recurrence is driven by reinfection in those with high-risk behaviors [87, 88].

Included studies reported contradictory results about the risk of HCV recurrence among patients with HIV. There remains a question as to whether higher recurrence rates in HIV patients are a consequence of HIV and related immune suppression or to the presence of risk behaviors associated with HCV acquisition. Given that RCTs tend to have more restricted inclusion criteria than open cohorts, we compared recurrence between the 2 types of study. Although the number of studies was low, evidence from RCTs suggested a significantly lower recurrence rate than data from open cohorts, supporting the notion that reinfection in these patient groups, rather than an increased propensity to relapse, is the main driver to recurrence [45, 76, 78, 79].

It is important to highlight that the majority of studies included analyzed recurrence after treatment with interferon-based therapies. The use of such regimens is decreasing in favor of interferon-free regimens, and although there is no evidence to support the notion that recurrence rates may differ with new treatments, it is possible that this will be the case, particularly if the consequences of reinfection are perceived to be low. Thus, collecting prospective data on recurrence rates after treatment with newer therapies is important.

There are a number of limitations to the present study. First, it is likely that a number of spontaneously clearing recurrent infections were missed, leading to an underestimate of recurrence. Evidence indicates that the probability of spontaneously clearing recurrent infection is high, and the duration of spontaneously clearing infection is about one month [89]. Thus, HCV RNA assessment at intervals of 6–12 months, as was the case in the majority of studies, is unlikely to capture all recurrences. Second, the analysis was limited by the detection and sequencing methods utilized in the original studies. Evidence from more sensitive detection methods indicates that long-term persistence of low levels of HCV RNA is possible [90, 91]. While the clinical significance is unclear, it suggests that some patients thought to have achieved SVR may still harbor the HCV.

Table 3. Meta-analysis of Recurrence

Studies	Subgroup	No. of Studies	Pooled Estimate of Recurrence/1000 PYFU (95% CI)	Heterogeneity (I^2, *P* Value)
Low-risk				
All studies	All	43 (45)[a]	1.85 (.71–3.35)	73.0%; .0039
Sensitivity analysis	High-quality (NOS ≥6)	33 (35)[a]	1.54 (.56–2.85)	69.3%; .0028
Meta-analysis subgroups	Late relapse	31 (32)[b]	0.82 (.08–2.05)	67.3%; .0028
	Reinfection	31 (32)[b]	0.00 (.00–.00)	0.0%; .0000
High-risk				
All studies	All	14	22.32 (13.07–33.46)	27.3%; .0035
Sensitivity analysis	High-quality (NOS ≥6)	12	22.03 (12.50–33.65)	32.0%; .0039
Meta-analysis subgroups	Late relapse	14	0.00 (.00–1.72)	0.0%; .0000
	Reinfection	14	19.06 (11.42–28.16)	10.5%; .0011
	All IDU studies	12	16.99 (8.61–27.41)	13.8%; .0017
	All prisoner studies	2	45.48 (24.95–71.32)	92.2%; –
HIV/HCV coinfected				
All studies	All	4	32.02 (.00–123.49)	96.0%; .1095
Sensitivity analysis	High-quality (NOS ≥6)	4	32.02 (.00–123.49)	96.0%; .1095
Meta-analysis subgroups	Recurrence in cohorts	2	115.47 (76.58–160.38)	98.7%; –
	Recurrence in RCTs	2	0.91 (.005.35)	98.7%; –
	Late relapse	4	0.00 (.00–.03)	0.0%; .0000
	Reinfection	4	32.02 (.00–123.49)	96.0%; .1095

Forest Plots of recurrence rates can be found in the Supplementary Appendix.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug user; NOS, Newcastle–Ottawa Scale; PYFU, person-years of follow-up; RCT, followed-up from randomized controlled trial.

[a] Two studies included 2 different treatment groups.

[b] One study included 2 different treatment groups.

The use of insensitive sequencing methods has particular implications for the late relapse/reinfection subanalysis. Recent evidence with more sensitive deep sequencing techniques suggests that a number of reinfections may be wrongly classified and are actually the emergence of preexisting resistant minority variants rather than reinfection [92]. Despite this, previous evidence

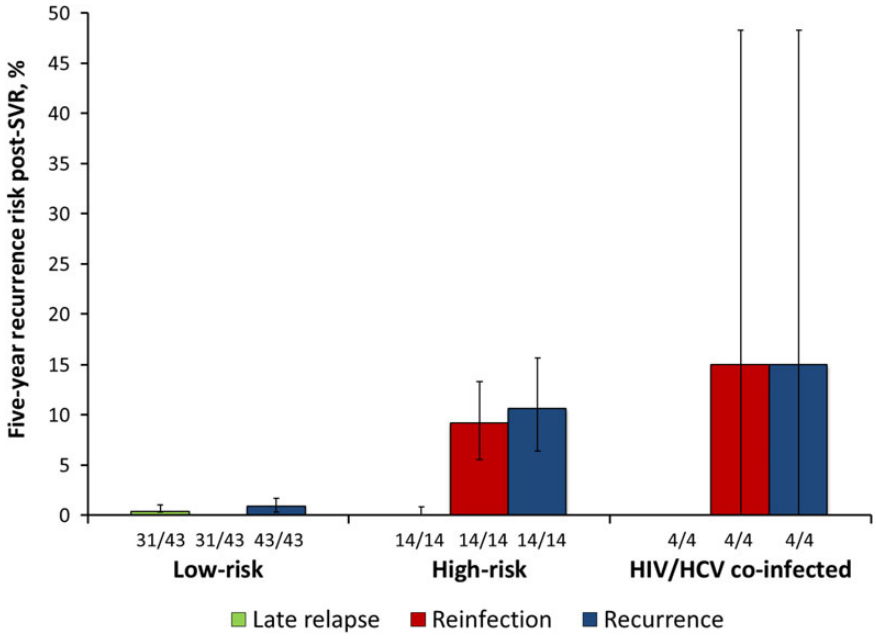

Figure 2. Summary 5-year risk (95% confidence interval) of recurrence post-sustained virological response (SVR), by risk group. Presented are the pooled estimates for the 5-year risk of recurrence after achieving an SVR. Also shown are the number of studies that were included to derive each estimate. Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

corroborates this analysis showing that late relapse following SVR is rare, occurring in <1% of mono- and coinfected individuals [45]. Furthermore, many recurrent cases have good outcomes, in terms of high spontaneous and treatment-induced clearance rates, supporting the mechanism of reinfection with novel susceptible virus, rather than the emergence of resistant low-level variants [93]. The distinction between late relapse and reinfection is particularly important when the epidemiological differences between risk groups are considered. In some populations, epidemics are concentrated, limiting genetic diversity such that reinfection will likely be with a highly similar strain, and thus will require better techniques to distinguish late relapse from reinfection [94].

In those studies not utilizing genotyping methods, bias may have been introduced by the tendency of study authors to classify recurrent infection as late relapse vs reinfection. Indeed, the late relapse rate was highest in the low risk group, suggesting recurrences were more likely attributed to late relapse over reinfection, possibly overestimating the relapse rate in this population. Similarly, in high-risk groups, relapse may have been underestimated by the tendency to classify recurrence as reinfection when uncertain. Finally, the estimates of late relapse and reinfection may have been biased by the availability of studies for inclusion in these analyses. Studies not classifying recurrence were excluded meaning that zero event studies were overrepresented in calculations, possibly leading to an underestimate of the true relapse and reinfection rates.

Despite the limitations, the results of the analysis will be helpful to inform treatment scale-up and modeling of strategies, which prioritize different groups for therapy with the ultimate goal of disease eradication. Although the probability of late relapse is low, reinfection in high-risk groups such as IDUs, prisoners, and HIV-positive MSM present both a challenge and an opportunity for epidemic control. As such, strategies to minimize the risk of reinfection in high-risk groups need to be intensified in parallel to introduction of interferon-free regimens in order to curtail onward transmission. The current analysis highlights the notion that estimates from RCTs may underestimate recurrence and emphasizes the need for real-life analyses and an updated analysis once the results of long-term interferon-free studies are available.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Acknowledgments. We thank Emma Thomson for her advice and helpful comments.

Financial support. This work was funded in part by UNITAID. G. S. C. is funded in part by the Biomedical Research Centre of Imperial College National Health Service trust and supported by the Medical Research Council (MRC) STOP hepatitis C virus (HCV) consortium.

Potential conflicts of interest. A. H. has received consultancy payments from Janssen, not connected with this project. G. S. C. has received consultancy payments and funding for HCV clinical trials from pharmaceutical companies not connected with this project. R. D. R. reports no conflicts but has received funding from the MRC for HCV treatment and outcomes and prognosis research work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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61–94. These references are available in the Supplementary Appendix.