Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis

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Objectives: To estimate stage-specific transition probabilities in individuals coinfected with HIV and hepatitis C virus (HCV), to examine the effect of covariates on these rates, and to investigate the effect of HIV on HCV-related cirrhosis in the era of highly active antiretroviral therapy (HAART).

Design: Systematic review of natural history studies among HCV-infected individuals.

Methods: Markov maximum likelihood estimation method was used to estimate stage-specific transition probabilities. A meta-analysis was performed to obtain pooled transition probabilities, and a meta-regression to investigate the impact of covariates on these rates. Risk of cirrhosis between individuals monoinfected with HCV and coinfected with HIV/HCV were compared by HAART status.

Results: The estimated mean (95% confidence intervals) annual transition probabilities of 3567 individuals coinfected with HIV/HCV ($n = 17$ studies) were as follows: fibrosis stage (F) F0 → F1 0.122 (0.098–0.153); F1 → F2 0.115 (0.095–0.140); F2 → F3 0.124 (0.097–0.159); and F3 → F4 0.115 (0.098–0.135) units/year. The prevalence of cirrhosis after 20 and 30 years of HCV infection was 21% (16–28%) and 49% (40–59%), respectively. Longer duration of HCV infection was significantly associated with slower rate of fibrosis progression. The overall rate ratio of cirrhosis between individuals coinfected with HIV/HCV and monoinfected with HCV ($n = 27$ studies) was 2.1 (1.5–3.0), 2.5 (1.8–3.4) in the non-HAART group, and 1.7 (1.1–2.8) in the HAART group.

Conclusion: The rate of fibrosis progression among individuals coinfected with HIV/HCV appears constant. Our results confirm that chronic hepatitis C outcomes are worse among coinfected individuals. Over the period studied, HAART did not appear to fully correct the adverse effect of HIV infection on HCV prognosis.

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Keywords: cirrhosis, fibrosis, hepatitis C virus, HIV/hepatitis C virus coinfection, meta-regression, risk factors, systematic review

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Introduction

Coinfection with HIV and hepatitis C virus (HCV) is common among injecting drug users and patients with hemophilia who received contaminated blood or blood products prior to serologic screening of donated blood for HCV [1–3]. Low rates of liver fibrosis progression have been reported in medium-term to long-term follow-up of HCV-infected injecting drug users. The prevalence of cirrhosis has been reported to be less than 5% after 10–25 years of infection [4–6]. On the contrary, several natural history studies among individuals infected with HCV and hemophilia and mixed populations have demonstrated that HIV accelerates the progression of liver disease [7–18], with increased risk of cirrhosis and hepatocellular carcinoma, and shorter survival following hepatic decompensation [19–21]. The underlying mechanism of this accelerated rate of liver fibrosis progression is unclear, but may be linked to immunosuppression [12,16,22]. As highly active antiretroviral therapy (HAART) became widely accessible in developed countries after 1996 [23], the survival of individuals with HIV/HCV coinfection has considerably improved and HCV-related end-stage liver disease has emerged as a significant burden of disease in this population [24–27].

In both HCV-monoinfected and individuals coinfected with HIV/HCV, the rate of liver fibrosis progression varies [12,19,28–32] due to factors that are not well understood. Previous estimates have been undermined by the assumption of a linear progression of liver fibrosis over time and inadequate adjustment for potential covariates, including study design factors, clinical factors, and the effect of HAART.

A systematic review [33] of eight studies in the pre-HAART era reported a three-fold increase in the risk of cirrhosis in individuals coinfected with HIV/HCV compared with HCV-monoinfected individuals. Although recent data suggest that HAART is associated with a reduction in liver-related mortality [34,35], its effects on liver fibrosis progression remain unclear. Cross-sectional or retrospective studies have shown that an effective HAART can attenuate the rate of liver fibrosis progression in individuals coinfected with HIV/HCV [14,31,36–39]. Other studies [12,16,22,40], however, have not demonstrated a beneficial effect of HAART.

The objectives of our systematic review and meta-analysis were: to obtain more precise rates of fibrosis progression by estimating stage-specific transition probabilities in individuals coinfected with HIV/HCV; to examine the effect of covariates on these rates; and to investigate the effect of HIV on HCV disease progression by comparing the rate of progression to cirrhosis between individuals with HCV monoinfection and HIV/HCV coinfection in the era of HAART.

Methods

Search strategy and selection criteria

Human studies that examined liver fibrosis progression in individuals with HCV monoinfection and HIV/HCV coinfection were searched by the MEDLINE, EMBASE, and PubMed databases of publications in any language covering the period from January 1990 to September 2007 (up to December 2006 for non-English articles), with combinations of 'HCV', 'hepatitis non-A', 'HIV', 'AIDS', 'fibrosis', 'cirrhosis', 'cohort studies', 'case–control studies', 'prognosis', 'disease-free survival', 'medical: futil', 'treatment outcome', 'treatment failure', 'disease progression', 'morbidity', 'mortality', 'fatal outcome', 'hospital mortality', 'survival analysis', and 'natural history'. Citations were crosschecked through review of bibliographies of relevant published papers (Fig. 1).

For the estimation of stage-specific transition probabilities, studies were included if they satisfied the following criteria: full-length and peer-reviewed original articles; chronic HCV infection defined as the presence of anti-HCV antibody detected by second or third generation enzyme-linked immunosorbent assay and at least one of HCV RNA as detected by polymerase chain reaction, recombinant immunoblot assay positivity, an elevated alanine aminotransferase (ALT) level without an alternative cause of chronic liver disease, or liver biopsy consistent with chronic hepatitis C; HIV infection determined by the positivity of both enzyme-linked immunosorbent assay and western blot assays; and no HCV treatment prior to the first liver biopsy or between subsequent biopsies.

To compare the rate of progression to cirrhosis between individuals monoinfected with HCV and coinfected with HIV/HCV, studies were included if they satisfied the above criteria, and wherever the infected groups were directly compared.

Studies were excluded if they included fewer than 20 patients or if fibrosis progression rates could not be calculated (e.g. duration of HCV infection not reported). If duplicate publications presented several updates of the data, the most recent data or studies with more complete information were included.

Data abstraction

Data were collected using data abstraction forms that included relevant items identified in previous studies such as study-related factors; host-related factors – age, sex, estimated duration of HIV and HCV infection, mode of HCV acquisition, alcohol consumption, hepatitis B virus infection, and presence of hepatic steatosis; virus-related factors – HCV genotype, HCV RNA positivity, HIV and HCV viral load, and history of antiretroviral therapy; immunologic factors – CD4+ T-cell count and CDC clinical category [41]; and liver-related factors – ALT

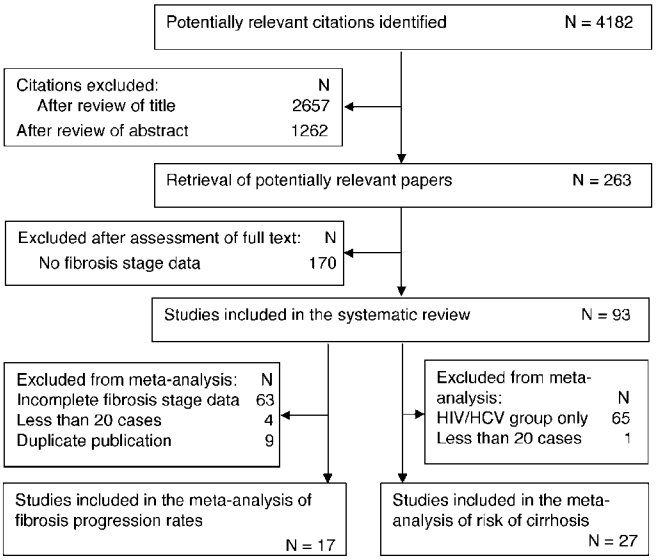

Fig. 1. Identification of relevant literature of the natural history of hepatitis C. HCV, hepatitis C virus.

level, fibrosis stage on the basis of established histopathologic criteria [42–46], clinical or histological diagnosis of cirrhosis, and histological activity index. Cirrhosis was defined on the basis of well established histopathologic criteria [42–46]. In those studies that also used nonhistopathologic criteria, cirrhosis was defined on the basis of clinical or ultrasound evidence consistent with cirrhosis [47,48].

The mean age at HCV acquisition was calculated by taking the difference between the mean age at assessment for liver disease and the mean duration of HCV infection when this information was not directly available. Studies reporting Ishak [44] fibrosis stages (S0–S6) were converted to the well validated METAVIR scoring system [42], in which the stage of fibrosis is assessed on a five-point scale: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with rare septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis (i.e. S0 = F0; S1 = F1; S2 = F2; S3–S4 = F3; S5–S6 = F4). For the Knodell scoring system (F0–F4 without F2 stage), F3 was distributed 50 : 50 to F2 and F3. Stage distribution was not performed if three or more stages were reported collectively (e.g. F0–F2, F2–F4).

Statistical analysis

Estimation of fibrosis progression rates

We used two methods to estimate fibrosis progression rates: the Markov maximum likelihood estimation (MMLE) method developed and validated by Yi *et al.* [49] to estimate annual stage-specific transition probabilities (e.g. F0 → F1, ..., F3 → F4); and the indirect (stage-constant) method that assumes that fibrosis progression rates are constant [50]. For each study, the mean observation time and distribution of fibrosis stages at the latest follow-up point in longitudinal studies (if available) and at time of recruitment in cross-sectional/retrospective studies were used to calculate the most likely set of transition probabilities characterizing the rate of movement between stages.

In the stage-constant method [50], the METAVIR stage was divided by the estimated duration of HCV infection (person-years).

A meta-analysis was performed to estimate the pooled transition probabilities derived using the MMLE and the stage-constant methods. Both fixed and random effects model estimates were obtained from the individual study transition probabilities and their standard errors (SEs); inverse variance weighting $w = 1/SE^2$ was used for pooling of transition probabilities [51], which gives a mean estimate and 95% confidence intervals (CIs). The effect of individual studies on the pooled transition probabilities was assessed by re-estimating the overall effect after omitting each study. We examined study-specific data graphically with funnel plots for apparent heterogeneity across studies and potential publication bias, and tested for significance with Egger's test for asymmetry [52]. The cumulative probability of cirrhosis (mean, 95% CIs) up to 30 years after HCV exposure was estimated using the estimated progression rates and their lower and upper bounds.

The impact of potentially important covariates on stage-specific transition probabilities was examined by a univariate regression analysis and a meta-regression. For the meta-regression, we used a linear mixed model –

maximum likelihood method, adjusting for covariates. Missing data were replaced using the multiple imputation method [53]. The meta-regression models included sex, age at HCV infection, duration of infection, injecting drug use, HCV acquisition via blood transfusion, excess alcohol consumption, genotype, CD4+ T-cell count at liver disease assessment, and HAART as explanatory factors and natural log of stage-specific transition probabilities and single pooled transition probabilities as dependent variables. The regression was weighted by a multiplicative variance adjustment factor, taking into account both within-study variances of transition probabilities and the residual between-study heterogeneity [54].

Risk ratios of cirrhosis

We extracted adjusted relative risks or risk ratios (RRs) and 95% CIs of cirrhosis among individuals monoinfected with HCV and coinfected with HIV/HCV from studies when available [7–11,18,21,33,55]. For other studies, RRs and 95% CIs were estimated using the number of individuals with cirrhosis in each infection group and the corresponding estimated duration of HCV infection. RRs were reported as adjusted values in which HCV groups were matched for specific covariates. For two studies in which there were no reports of cirrhosis in the group monoinfected with HCV [10] or the group coinfected with HIV/HCV [56], an event in each group was attributed to facilitate the calculation of RRs.

A meta-analysis and meta-regression of RRs for cirrhosis was performed using the method described above. The meta-regression model included CD4+ T-cell count and proportion receiving HAART as explanatory factors and natural log of the RR as dependent variable.

A two-sided significance level of 0.05 was used in all statistical procedures. Statistical analysis was performed with SAS Inc. (Cary, North Carolina, USA) version 9.1 and Proc Mixed ML [57] was used for meta-regression.

Results

Estimated fibrosis progression rates in studies of HIV/hepatitis C virus coinfection

Seventeen reports of natural history studies, involving 3567 individuals coinfected with HIV/HCV were included in the meta-analysis (Tables 1 and 2 [12–14, 16,22,29,30,32,38–40,58–72]). All studies had a cross-sectional/retrospective design, and were performed in tertiary care settings such as HIV, infectious diseases, or liver clinics. The studies primarily included men (75%), individuals reporting injecting drug use as the mode of HCV acquisition (82%), HCV RNA positive individuals (98%), those with elevated ALT levels (83%), and those receiving antiretroviral therapy (79%). Two-thirds (67%) of the patients were receiving HAART, including 41% of individuals who were on a protease inhibitor-based regimen. The proportion of patients with genotype 1 was 50%. The mean (range) age at liver disease assessment was 40 (34–50) years. The estimated duration of HCV infection was 17 (10–24) years. The mean (range) CD4+ T-cell count at liver disease assessment was 460 (320 629) cells/μl. Seven studies included individuals with CD4+ T-cell count less than 200 cells/μl (mean, 14%) and five studies included individuals with Centres for Disease Control and Prevention (CDC) category C or AIDS (mean, 25%). Most patients had a liver biopsy (99%). There were 515 patients of F0, 1005 F1, 863 F2, 683 F3, and 501 patients of cirrhosis with 58 363 person-years of follow-up. Excess alcohol consumption was defined as more than 20 g/day in one, more than 40 g/day in two and more than 50 g/day in eight studies.

The pooled annual stage-specific transition probabilities are reported in Table 3. Due to the presence of significant heterogeneity in the transition probabilities between most studies (Supplementary Table 1), the results for the fixed effects model should be interpreted with caution, though they are not substantially different from the random effects model estimates. Based on the random effects model, the estimated weighted mean (95% CI) stage-specific transition probabilities were: F0 → F1 0.122 (0.098–0.153); F1 → F2 0.115 (0.095–0.140); F2 → F3 0.124 (0.097–0.159); and F3 → F4 0.115 (0.098–0.135) units/year. The estimated weighted proportions of individuals with cirrhosis at 20 and 30 years after HCV infection were 21% (95% CI, 16–28%) and 49% (40–59%), respectively (Table 3). The adjusted transition probabilities did not appear to be different from the unadjusted estimates. The corresponding median (IQR) estimates were 0.124 (0.107–0.167); 0.123 (0.089–0.153); 0.147 (0.090–0.172); and 0.119 (0.079–0.143). The 20-year and 30-year cirrhosis rates using the median progression rates were 25% (15 31%) and 54% (38 63%), respectively.

Visual examination of the funnel plots of the log stage-specific transition probabilities against the study size of all studies included in the meta-analysis revealed symmetry of the individual studies to the pooled mean estimates. Sensitivity analyses showed that the pooled estimates were in general robust to the exclusion of any one study.

Based on the random effects model, the estimated weighted mean (95% CI) fibrosis progression rates using the stage-constant method were 0.115 (0.101–0.129) units/year. This corresponds to a cirrhosis prevalence of 19% (16–22%) at 20 years and 46% (40–51%) at 30 years.

In the univariate regression analysis, genotype 1 was significantly associated with fibrosis progression from F0 → F1 (coefficient = −1.028, SE = 0.460, $P = 0.044$) and duration of HCV infection was significantly associated

Table 1. Study and clinical characteristics of individuals with HIV/hepatitis C virus coinfection.

Reference	Study period	Country	Sample	Liver biopsy, *N*	Mean age (years)	Mean age at HCV (years)	Mean duration of HCV (years)	Histological classification	F0[a], *n*	F1[a], *n*	F2[a], *n*	F3[a], *n*	F4[a], *n*	Person-years[b]
[13,14,58,59]	1995–2000	France	182	182	36.8	21.9	14.9	METAVIR	15	62	45	34	26	2719.1
[60]	1998–2004	USA	154	154	50.3	30.3	20.0	Scheuer	28	30	29	29	38	3080.0
[61]	2000–2002	USA	89	89	45.0	23.8	21.2	Scheuer	6	14	39	19	11	1886.8
[29,30,32,39,62–64]	1991–2005	Spain	683	683	38.0	23.0	14.0	Scheuer	121	169	174	122	97	9562.0
[22]	1992–2002	Europe	914	914	37.0	20.0	16.0	METAVIR	98	299	197	198	122	14624.0
[16]	1996–	Spain	41	41	35.8	20.5	15.3	Scheuer/Desmet	8	15	4	5	9	627.3
[40]	2001–2002	USA	210	210	44.5	21.0	23.5	METAVIR/Ishak	69	57	29	19	36	4935.0
[12]	1994–2002	UK	55	55	37.6	21.0	16.0	METAVIR/Ishak	2	14	11	12	16	880.0
[65]	1997–2004	USA	92	92	47.0	25.0	22.0	Batts-Ludwig	30	16	27	13	6	2024.0
[66]	1997–2002	Spain	112	112	38.0	19.0	18.0	Knodell	6	41	21	27	17	2016.0
[67]	1995–1998	France	75	71	34.1	20.1	14.0	METAVIR/Knodell	13	24	20	8	6	994.0
[68]	2000–2005	Spain	256	256	38.9	18.3	20.6	Batts-Ludwig	1	96	81	47	31	5273.6
[69]	NA	France	37	37	37.9	23.6	14.3	METAVIR	2	8	21	5	1	529.1
[38]	NA	Spain	180	180	36.6	20.5	10.1	Knodell	58	39	37	37	9	1818.0
[70]	1997–2003	Italy	326	326	40.5	26.5	14.0	Ishak	31	81	81	79	54	4564.0
[71]	1987–	Spain	116	116	38.0	22.0	16.0	Scheuer	19	19	36	23	19	1856.0
[72]		France	51	49	42.0	24.0	18.0	METAVIR/Knodell	8	21	11	6	3	882.0

HCV, hepatitis C virus infection.

[a]Hepatic fibrosis stage based on METAVIR fibrosis scoring system: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = portal fibrosis with numerous septa without cirrhosis, F4 = cirrhosis.

[b]Person-years were calculated by multiplying the mean duration of infection by the meta-analysis sample size. For example, in a study reporting a stage distribution of 15 F0, 62 F1, 45 F2, 34 F3, and 26 F4 with an estimated mean duration of infection of 15 years, the fibrosis progression is calculated as follows: $[(15 \times 0) + (62 \times 1) + (45 \times 2) + (34 \times 3) + (26 \times 4)]/[(15+62+45+34+26) \times 15] = 0.131$ fibrosis units per year.

Table 2. Clinical characteristics of individuals with HIV/HCV coinfection.

Reference	Men %	ALT Mean IU/l	Excess alcohol >20 g/day %	IDU %	BT %	Sporadic %	HCV RNA+ %	HCV load log_{10} copies/ml	Genotype 1 %	Genotype non1 %	HIV load log_{10} copies/ml	CD4 cells/μl Mean	CD4 <200 cells/μl %	AIDS %	Total ART %	HAART %
[13,14,58,59]	63	ND	28	91	9	0	100	ND	23	11	4.3	360	ND	ND	78	35
[60]	95	82	0	92	8	0	100	6.6	80	20	ND	429	20	ND	84	84
[61]	67	82	ND	56	1	43	100	ND	87	13	ND	437	14	ND	72	72
[29,30,32,39,62 64]	83	78	17	90	ND	10	100	6.0	54	46	ND	504	ND	ND	83	75
[22]	75	ND	23	83	5	12	100	ND	45	35	ND	480	9	ND	69	54
[16]	71	94	12	85	3	12	100	6.8	51	49	ND	577	32	ND	100	100
[40]	67	47	40	77	ND	23	100	6.6	ND	ND	2.4	366	ND	ND	64	54
[12]	73	73	7	78	22	0	100	ND	16	15	ND	320	ND	ND	71	64
[65]	92	ND	ND	76	1	23	100	ND	80	20	3.8	492	ND	ND	72	72
[66]	76	95	ND	87	1	12	100	6.0	59	41	1.7	484	ND	21	100	100
[67]	71	ND	23	100	0	0	100	ND	39	33	3.9	400	ND	ND	17	17
[68]	76	ND	40	85	0	15	100	ND	58	40	ND	484	0	ND	100	100
[69]	62	106	ND	78	14	8	100	ND	43	57	ND	629	0	ND	95	38
[38]	78	76	54	82	0	18	78	ND	34	44	1.9	531	21	21	91	58
[70]	72	ND	0	56	0	44	83	6.3	33	50	ND	500	ND	ND	64	40.2
[71]	85	62	28	94	ND	6	100	5.9	47	53	4.6	500	ND	24	100	91
[72]	65	ND	ND	80	ND	20	100	5.9	ND	ND	2.0	329	ND	ND	86	86

HAART is defined as a three-drug regimen that included one or two nucleoside analogues and a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor; patients who received ART consisting of a protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor. ALT, alanine aminotransferase; ART, antiretroviral therapy; BT, blood/blood product transfusion; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug use; IU/l, international units per liter; ND, no data; RNA, ribonucleic acid.

Table 3. Annual stage-specific transition probabilities and predicted cumulative probability of cirrhosis in individuals with HIV/HCV coinfection – Markov maximum likelihood estimation.

	Fixed effects model unadjusted probability Mean (95% CI)	Random effects model unadjusted probability Mean (95% CI)	Random effects model adjusted probability[a] Mean (95% CI)
Fibrosis stage			
F0 → F1	0.119 (0.114–0.125)	0.122 (0.098–0.153)	0.123 (0.104–0.145)
F1 → F2	0.114 (0.108–0.120)	0.115 (0.095–0.140)	0.113 (0.094–0.135)
F2 → F3	0.139 (0.129–0.149)	0.124 (0.097–0.159)	0.124 (0.102–0.150)
F3 → F4	0.115 (0.104–0.127)	0.115 (0.098–0.135)	0.116 (0.101–0.133)
Predicted cumulative probability of cirrhosis after HCV infection			
5 years	0.1 (0.08–0.11)	0.1 (0.06–0.15)	0.09 (0.06–0.13)
10 years	2.5 (2.2–2.8)	2.3 (1.6–3.5)	2.3 (1.7–3.2)
15 years	9.9 (8.8–11.0)	9.3 (6.9–13.2)	9.3 (7.2–12.2)
20 years	21.8 (19.8–23.8)	20.8 (16.0, 27.6)	20.8 (16.6–25.9)
25 years	35.9 (33.1–38.7)	34.6 (27.7–43.7)	34.6 (28.6–41.5)
30 years	50.0 (46.8–53.1)	48.5 (40.3–58.5)	48.5 (41.4–56.2)

CI, confidence intervals; HCV, hepatitis C virus. Hepatic fibrosis stage based on METAVIR fibrosis scoring system: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = portal fibrosis with numerous septa without cirrhosis, F4 = cirrhosis.
[a]Adjusted for mean proportions/values of covariates: male gender (74.8%), age at HCV infection (22.4 years), duration of HCV infection (16.9 years), injecting drug use (81.8%), blood/blood product transfusion (4.8%), excess alcohol consumption (22.6%), CD4 cell count (460/μl), HAART (67.1%) (Tables 2 and 4).

with fibrosis progression from F1 › F2 (coefficient = −0.057, SE = 0.024, $P = 0.033$). In the meta-regression analysis (stage-specific models), duration of HCV infection was the only factor significantly associated with progression from F1→F2 (coefficient = −0.068, SE = 0.024, $P = 0.040$) (Table 4). Similarly, in the single pooled model, duration of HCV infection was significantly associated with fibrosis progression (coefficient = 0.082, SE = 0.023, $P = 0.027$. The effects of other covariates, including CD4+ T-cell count and HAARTon transition rates, did not reach statistical significance.

Risk ratios of cirrhosis

A total of 27 reports of natural history studies, involving 7666 individuals with HCV monoinfection ($n = 4970$) and HIV/HCV coinfection ($n = 2636$) were included in the meta-analysis (Supplementary Tables 2 and 3). There were 74 and 80% men ($P = 0.10$), 54 and 72% of individuals reporting injecting drug use as mode of HCV acquisition ($P = 0.07$), 36 and 20% reporting receipt of blood or blood product ($P = 0.03$), 20 and 22% reporting excess alcohol consumption ($P = 0.77$), 89 and 83% with HCV RNA positivity ($P = 0.76$), and 51 and 45% with genotype 1 ($P = 0.42$), respectively, in each group. The mean age of individuals monoinfected with HCV was 39.5 years compared with 36.9 years in the individuals coinfected with HIV/HCV ($P = 0.25$), and the duration of HCV infection was 16.5 years and 15.5 years ($P = 0.52$), respectively. Among individuals coinfected with HIV/HCV, CD4+ T-cell count at liver disease assessment was reported in 17 studies. The mean CD4+ T-cell count was 429 cells/μl. There were no reports of HAART in 13 studies. In studies reporting HAART ($n = 13$), 74% of the individuals were receiving

Table 4. Meta-regression[a] of covariates associated with hepatic fibrosis progression in individuals with HIV/HCV coinfection.

	F0 → F1[b]			F1 → F2[b]			F2 → F3[b]			F3 → F4[b]		
Covariates	β	SE	*P*	β	SE	*P*	β	SE	*P*	β	SE	*P*
Intercept	1.065	1.728	0.568	−2.340	1.151	0.099	−1.461	1.586	0.399	−3.234	2.038	0.182
Men[d]	−0.965	1.507	0.552	1.639	0.952	0.142	1.794	1.459	0.278	−0.435	1.559	0.791
Age at HCV infection	−0.054	0.050	0.328	0.031	0.030	0.338	0.042	0.044	0.390	0.032	0.037	0.433
Duration of infection	−0.069	0.038	0.138	−0.068	0.024	0.040	−0.071	0.035	0.098	0.016	0.037	0.689
Injecting drug use	−0.493	0.833	0.577	−0.638	0.550	0.294	−0.855	0.785	0.322	1.742	0.843	0.090
Blood transfusion[d]	1.772	1.754	0.364	−0.470	1.128	0.694	0.270	1.648	0.877	−1.811	2.001	0.423
Excess alcohol use[d]	−0.389	0.775	0.640	0.012	0.480	0.982	0.890	0.731	0.284	−1.312	0.700	0.121
Genotype 1[d]	0.387	0.823	0.668	0.107	0.509	0.843	−1.070	0.679	0.178	−1.551	0.684	0.078
CD4 cell count[c]	−0.020	0.151	0.899	0.018	0.106	0.873	−0.229	0.158	0.206	−0.061	0.260	0.827
HAART[d]	0.415	0.459	0.407	−0.314	0.320	0.369	0.564	0.506	0.322	0.547	0.434	0.262

β, coefficient; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; RR, relative risk; SE, standard error.
[a]Linear mixed model maximum likelihood method.
[b]Log stage-specific transition probabilities.
[c]CD4 cell count expressed as per 100 per μl.
[d]Proportion.

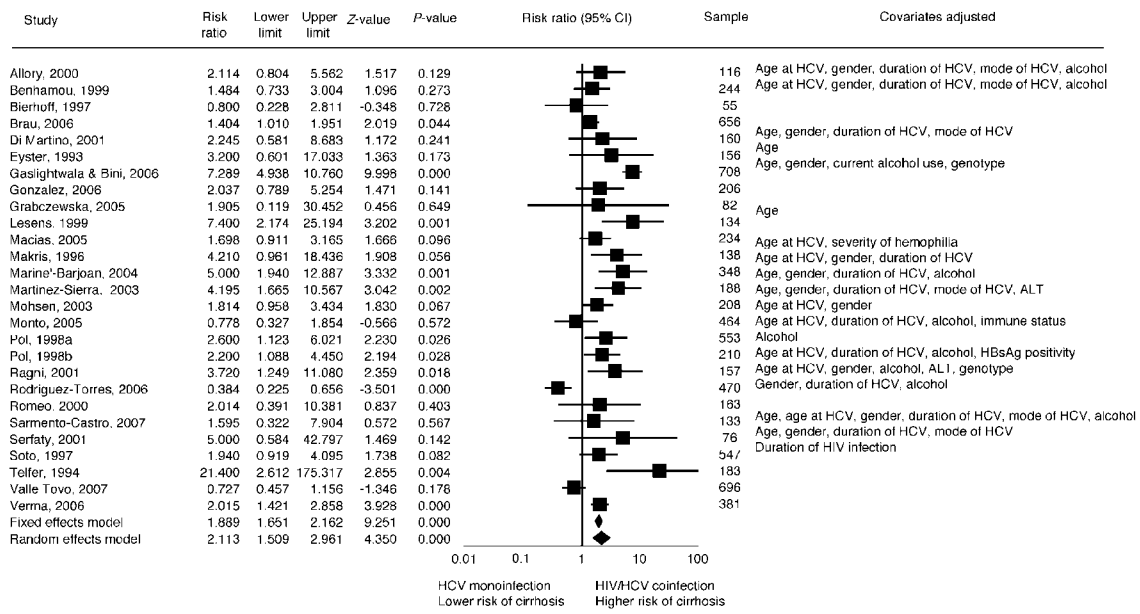

Fig. 2. Risk ratios of cirrhosis between individuals monoinfected with hepatitis C virus and individuals coinfected with HIV/HCV – meta-analysis. Risk ratios were calculated from available data. Adjusted relative risks were obtained directly from [7–11,18,21,55]. ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

HAART for at least 1 year at the time of liver disease assessment.

The estimated weighted pooled RRs of cirrhosis for the 27 studies are shown in Figs 2 and 3 ([73–77]). There was significant heterogeneity in the RRs between studies ($P < 0.0001$). On the basis of the random effects model, the overall RR of cirrhosis among patients coinfected with HIV/HCV, relative to HCV monoinfected patients was 2.11 (95% CI, 1.51–2.96); 1.40 (1.01–1.93) for studies unadjusted for covariates ($n = 8$); and 2.61 (1.62–4.22) for studies adjusted for covariates ($n = 19$). For the non-HAART group, the RR was 2.49 (95% CI, 1.81–3.42). The RR of cirrhosis in the HAART group was 1.72 (95% CI, 1.06–2.80) (Fig. 3).

In the meta-regression analysis, there was no significant association between HAART and risk of cirrhosis ($n = 26$ studies; $P = 0.25$). Similarly, there was no significant association between CD4+ T-cell count and risk of cirrhosis ($n = 17$ studies, $P = 0.59$). The associations between HAART and CD4+ T-cell count and risk of cirrhosis remained insignificant when adjusted for both HAART ($P = 0.26$) and CD4+ T-cell count ($P = 0.43$).

Discussion

Our systematic review of the natural history of hepatitis C, involving 3567 individuals coinfected with HIV/HCV, has demonstrated that liver fibrosis progression in this group appears to be constant across all stages of fibrosis, and that disease progression is significantly influenced by duration of HCV infection. The predicted cumulative probability of cirrhosis at 20 years after HCV infection was 21% (95% CI, 17–26%) and 49% (40–59%) at 30 years. The cumulative cirrhosis rate was modestly lower in the stage-constant method compared with the MMLE method.

Our 20-year-predicted estimate of 21% cirrhosis differs from estimates among patients with hemophilia: 11% in a study by Telfer *et al.* [11]; and 42% in a study by Eyster *et al.* [10]. Our sample consists mainly of injecting drug users. Our 20-year-predicted cirrhosis rates among individuals coinfected with HIV/HCV are comparable to published estimates among patients monoinfected with HCV in liver clinic series (22%, 95% CI, 18–26%) and posttransfusion cohorts (24%, 11–37%), but much higher than those of blood donor series (4%, 1–7%) or community-based cohorts (7%, 4–10%) [78].

Several factors such as male gender, older age at HCV infection, longer duration of HCV infection, excess alcohol consumption, and immunosuppression have been associated with increased risk of fibrosis progression in individuals coinfected with HIV/HCV [9,12,14,16, 18,22,79]. Our results found that longer duration of HCV infection was significantly associated with slower rate of fibrosis progression. The reasons are unclear, but may include diminishing transition rates over time; recall

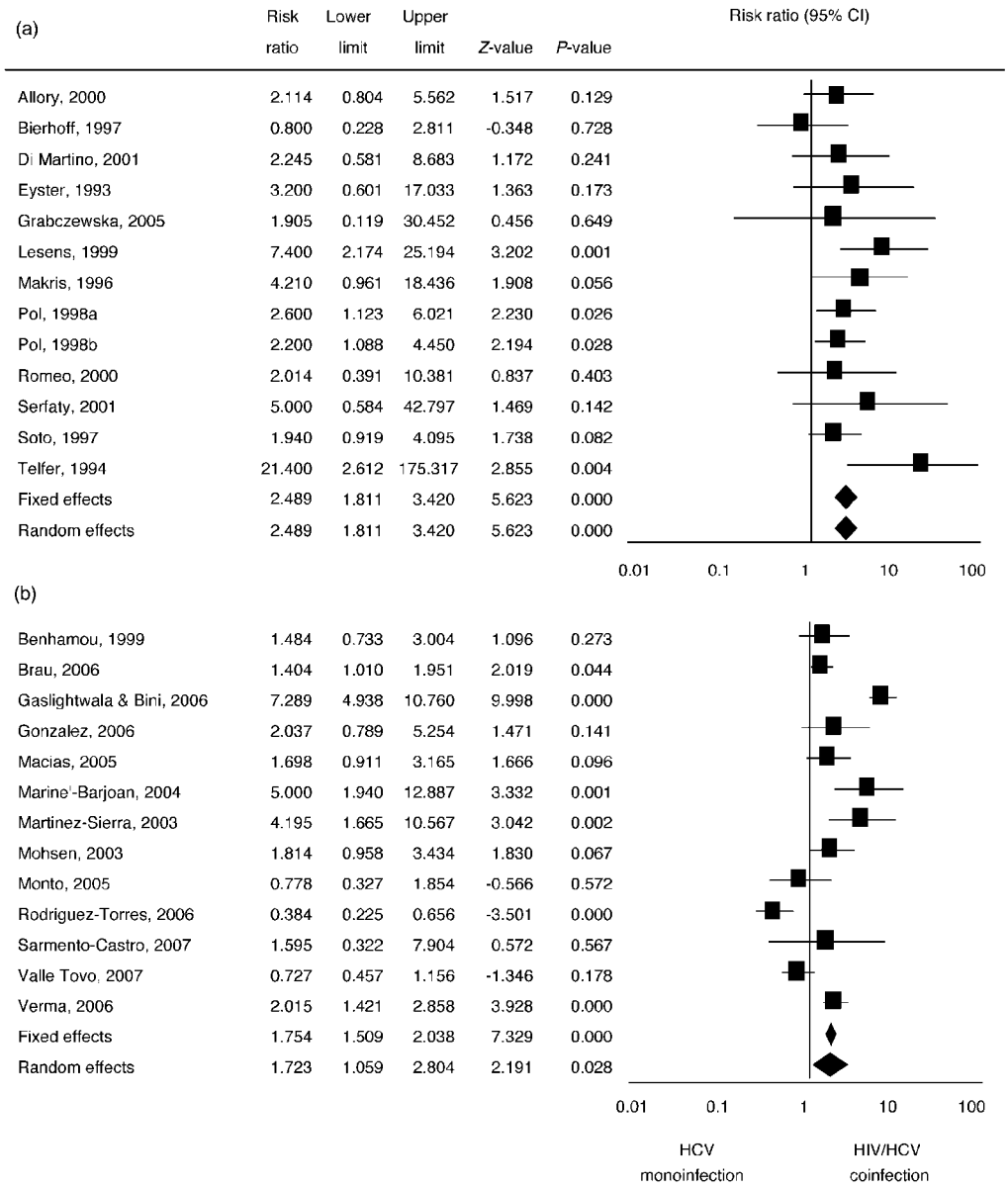

Fig. 3. Risk ratios of cirrhosis between individuals monoinfected with hepatitis C virus monoinfected and individuals coinfected with HIV/HCV. (a) Non-HAART group; and (b)* HAART group. *74% of individuals were receiving HAART. HAART, highly active antiretroviral therapy; HCV, hepatitis C virus.

bias for those with remote date of infection; and referral or survival bias, such that individuals surviving longer and who were infected earlier may have an overall lower risk of progression. Progression of fibrosis was not related to other factors, including the proportion of patients on HAART or the mean CD4+ T-cell count.

We found that liver fibrosis progression appears constant across all stages of fibrosis. We did not have particular hypotheses about how transition probabilities vary across stages as a function of study population. We believe that referral bias is a potential problem in cohort studies, and that, when present, may affect the pattern of transition probabilities across stages.

The methodology of our analysis has some potential limitations. First, the concept of dynamic fibrosis progression restricts the analyses to individuals with a known or estimated duration of HCV infection and studies that reported intermediate stages of fibrosis F0–F4.

Exclusion of studies that do not report duration of infection means that our estimates may not be generalizable to the approximately 14% of the whole population without known risk factors. Second, though the MMLE method has the advantage of estimating stage-specific transition rates from a single biopsy, these estimates are sensitive to the completeness of fibrosis stage data and the accuracy of stage classification [49]. In addition, the requirement of individual patient data from the primary papers may introduce bias, as some covariates were not available for a number of studies. Nevertheless, in the absence of individual patient data, meta-regression offers the best method to explain heterogeneity among study results [80].

Third, exclusion of the 'gray literature' and small studies (<20 cases) may mask potential publication bias. However, publication bias is more of a concern in experimental studies, in which negative trials are more likely to be suppressed. Here, we reviewed prognostic studies. We could not identify a particular incentive for favorable or unfavorable prognostic studies to be selectively suppressed. Thus, though we cannot exclude the possibility that exclusion of the 'gray literature' may be a source of bias, we think it unlikely. Fourth, the prevalence of cirrhosis in our study may be underestimated due to selection bias. Patients who attended clinical visits were adherent to antiretroviral therapy, were abstinent from alcohol, had stable HIV infection, and may have been more likely to undergo liver biopsy. Thus, there is a possible bias towards patients with less advanced HIV infection. Finally, our meta-regression model may be underpowered and may miss some predictors of fibrosis progression.

Our results in a relatively homogeneous population suggest that chronic hepatitis C outcomes are significantly worse in individuals coinfected with HIV/HCV than in individuals monoinfected with HCV. The estimated risk of cirrhosis for the 27 studies was two-fold higher in individuals with HIV/HCV coinfection compared with those with HCV monoinfection: 2.5 (95% CI, 1.8–3.4) in the non-HAART group; and 1.7 (1.1–2.8) in the HAART group. Overall, the risk of cirrhosis in our study in the HAART era is slightly lower compared with the pre-HAART meta-analysis [33] (RR: 2.11, 95% CI, 1.51–2.96 vs. 2.92, 1.70–5.01).

Over the period studied, HAART did not appear to fully correct the adverse effect of HIV infection on HCV prognosis. This may be explained by a number of factors. Approximately three-quarters (74%) of coinfected patients were receiving HAART in the HAART group. HAART patients had a short duration of exposure and some had a suboptimal response. In addition, HAART may have dual effects [81,82], producing slower fibrosis progression as a result of immune reconstitution, but also inducing liver toxicity [83], which may lead to an enhancement of fibrogenesis. Finally, there may be some other factors attributing to worse HCV prognosis than the coinfection *per se*.

In our analysis of risk of cirrhosis, exclusion of patients with decompensated liver disease in some studies may underestimate the difference in the rates of cirrhosis between individuals coinfected with HIV/HCV and monoinfected with HCV. Complete case analysis for the effect of CD4+ T-cell count and HAART on the risk of cirrhosis may also reduce precision of the results [84]. However, the lack of an effect of HAART on the risk of cirrhosis persisted even without complete case analysis.

Our study also has significant strengths, thereby improving on previous studies such as it is more comprehensive, including non-English language studies; it uses MMLE method to estimate prognosis, which does not require the assumption of constant progression rates for each stage; it allows estimation of the effects of clinical factors and HAART on liver fibrosis progression; and it compares the risk of cirrhosis between individuals receiving HAART and those not receiving HAART.

Our estimates are generalizable to the injecting drug user population with HIV/HCV coinfection. These estimates should provide more accurate information for the prediction of HCV disease burden, economic evaluation of antiviral therapies and preventive strategies, and healthcare policy decision-making among the injecting drug user population. Our findings have implications for the early evaluation of HCV treatment in individuals coinfected with HIV/HCV.

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There are no conflicts of interest.

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2–6th November, 2007, Boston; and the 4th Annual Canadian Association for the Study of Liver Diseases Winter Meeting 1–3rd March, 2008, Montreal.

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