HIV/AIDS

# Meta-Analysis: Increased Mortality Associated with Hepatitis C in HIV-Infected Persons Is Unrelated to HIV Disease Progression

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**Background.** It is unclear whether coinfection with hepatitis C virus (HCV) increases mortality in patients with human immunodeficiency virus (HIV) infection during the era of highly active antiretroviral therapy (HAART). With use of a meta-analysis, we estimated the effect of HCV infection on HIV disease progression and overall mortality in the pre-HAART and HAART eras.

**Method.** The PubMed and EMBASE databases were searched for studies published through 30 April 2008. Additional studies were identified from cited references. Studies reporting disease progression or mortality among HCV-HIV coinfected patients were selected. Cross-sectional studies, studies without HCV-negative control subjects, and studies involving children and/or patients who had undergone liver transplantation were excluded. Two authors reviewed articles and extracted data on the demographic characteristics of study populations and risk estimates. Meta-regression was used to explore heterogeneity.

**Results.** Ten studies from the pre-HAART era and 27 studies from the HAART era were selected. In the pre-HAART era, the risk ratio for overall mortality among patients with HCV-HIV coinfection, compared with that among patients with HIV infection alone, was 0.68 (95% confidence interval [CI], 0.53–0.87). In the HAART era, the risk ratio was 1.12 (95% CI, 0.82–1.51) for AIDS-defining events and 1.35 (95% CI, 1.11–1.63) for overall mortality among patients with HIV monoinfection.

**Conclusions.** HCV coinfection did not increase mortality among patients with HIV infection before the introduction of HAART. In contrast, in the HAART era, HCV coinfection, compared with HIV infection alone, increases the risk of mortality, but not the risk of AIDS-defining events. Future studies should determine whether successful treatment of HCV infection could reduce this excess risk of mortality in coinfected patients.

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) share routes of transmission, and thus, the prevalence of HCV infection is 15%–30% among HIV-infected patients. Because of the enhanced transmissibility of HCV by percutaneous injection, compared with that of HIV, the prevalence of HCV infection can exceed 85% among HIV-infected injection drug users [1, 2]. Before the introduction of highly active antiretroviral therapy (HAART), mortality related to HIV overwhelmed that related to HCV. By

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© 2009 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2009/4910-0024\$15.00 DOI: 10.1086/644771 contrast, although patients with HIV infection live longer in the HAART era than they did in the pre-HAART era, chronic diseases, such as viral hepatitis, have emerged as important causes of morbidity and mortality [3, 4]. It has been strongly suggested that HIV infection accelerates HCV-related disease progression and mortality [5–7], but the reciprocal effect of HCV on the rate of HIV disease progression remains muddled because of the heterogeneity of study results. Understanding whether coinfection with HCV affects progression and mortality related to HIV may elucidate challenging issues for health care providers who treat patients with HIV-HCV coinfection and give insight into the complex interactions between these 2 persistent viruses.

Some studies have reported a strong association between HCV-HIV coinfection and increased risk of HIV disease progression [8, 9], whereas other studies have

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not confirmed this result after the widespread use of HAART [10, 11]. This systematic review estimates the effect of HCV infection on both mortality and HIV disease progression in HCV-HIV coinfected patients during the HAART era. We compared studies from the pre-HAART and HAART eras, focusing on the latter, because they are more likely than the former to inform future practice.

### METHODS

**Data sources.** A literature search was conducted to identify publications that reported HIV disease progression or survival among cohorts of patients with HIV-HCV coinfection using the PubMed and EMBASE databases without language restriction through 30 April 2008. Titles and/or abstracts were screened to determine the relevance of studies. Full texts of selected studies were reviewed. Additional studies were identified from cited references.

*Study selection.* Publications that reported data on disease progression, mortality, and/or survival of HIV infection among cohorts of adults with HIV infection and adults with HIV-HCV coinfection were selected for inclusion, whereas studies involving nonadolescent children were excluded. Studies were classified as taking place in the pre-HAART era if they occurred entirely during the period before January 1996, and they were classified as occurring in the HAART era if at least one-half of the study period was after January 1996, unless the study was specifically divided into 2 categories by the author. Publications regarding liver disease–related mortality were not included unless overall mortality was also reported because of the potential for misclassification. Cross-sectional studies, studies on survival after undergoing liver transplantation, and studies without HIV-monoinfected control groups were excluded.

**Data extraction.** One author (T-Y.C.) completed the search and extracted data from the studies on 2 occasions. Study design, period, and population; number of subjects; median or mean duration of follow-up; treatments for HIV and HCV infection; outcome measures; percentage of patients with injection drug use (IDU); and adjustments for potential confounders were extracted by 2 authors (T-Y.-C. and A.Y.K.). For studies reporting only incidence rates or cumulative incidence rates of death or AIDS-defining events, risk ratio and 95% confidence intervals (CIs) were calculated from the available data provided. If studies presented several risk estimates, the final adjusted risk estimate was recorded.

**Study quality assessment.** Study quality was assessed for studies in the HAART era with primary outcomes of overall mortality and/or AIDS-defining diseases. The quality of these studies was evaluated according to (1) study design (prospective studies were considered to have higher quality than retrospective studies) and (2) duration of follow-up (studies with a longer median or mean duration of follow-up were considered to have higher quality and provide the studies with a longer median or mean duration of follow-up were considered to have higher quality that here the studies with a longer median or mean duration of follow-up were considered to here the studies of the studies with a longer median or mean duration of follow-up were considered to here the studies of the studies were considered to here the studies were the studies were considered to here there the studies were consta

to be more likely to reflect the true effect of HCV infection on HIV-related disease progression).

Statistical analysis. Quantitative analyses were conducted for overall mortality in the pre-HAART era and for 3 different outcome measures: overall mortality, AIDS-defining events and the combination of AIDS-defining events and mortality in the HAART era. Conventional random effect models were used to estimate summary risks ratios and 95% CIs, given the variability inherent among observational studies [12]. Heterogeneity across studies was evaluated by I<sup>2</sup> test [13]. I<sup>2</sup> statistic >20% suggests heterogeneity, and an I<sup>2</sup> statistic >50% indicates substantial heterogeneity. Publication bias was assessed with funnel plots and Begg's and Egger's tests [14, 15]. Sensitivity analysis was conducted by omitting 1 study at a time to examine the influence of individual studies on overall mortality. Univariate random-effect meta-regressions with use of aggregate-level data, including percentage of patients receiving HAART, percentage of IDUs in the study population, study duration, and sex were performed for overall mortality in the HAART era to assess potential effect modification [16]. The effect of study quality was assessed by subgroup analysis. Stata software, version 9, was used for all analysis.

## RESULTS

Study selection. Figure 1 summarizes the study selection process. The electronic search yielded 537 citations in PubMed and 623 in the EMBASE database. Among the total of 1160 titles and abstracts screened, 52 articles were selected for in-depth review. Seven articles provided data from both the pre-HAART and HAART eras [11, 17-22]. For pre-HAART analysis, 10 studies were excluded for  $\geq 1$  of the following reasons: (1) AIDS and overall mortality were combined as a single end point [17, 23, 24], (2) lack of an HCV-negative control group [21, 25, 26]; or (3) data were not able to be pooled [22, 27-29]. As a result, data were extracted for 10 studies [11, 18-20, 30-35]. For analysis of studies conducted in the HAART era, 12 studies were excluded for  $\geq 1$  of the following reasons: (1) lack of an HCV-negative control group [5, 21, 36-39], (2) use of a crosssectional design [40-42], (3) having data that were not extractable [22], or (4) having a cohort that was duplicated [43, 44]. Thus, data were extracted from a total of 33 studies, with 10 studies contributing data from the pre-HAART era and 27 studies contributing data from the HAART era (4 studies contributed data from both eras).

*Study characteristics.* Ten studies, involving a total of 4413 HCV-HIV coinfected patients and 10,213 HIV-monoinfected patients, were included for the pre-HAART era; 27 studies, involving 25,319 HCV-HIV coinfected patients and 61,697 HIV-monoinfected patients, were included for the HAART era (Table 1). For the pre-HAART era, study sample sizes ranged from 95 patients [11] to 10,896 patients [18]. In the HAART



\*7 studies contribute to both branches with 4 studies selected for final analysis.

Figure 1. Selection process for study inclusion in the meta-analysis of hepatitis C virus (HCV) on overall mortality and/or human immunodeficiency virus–related progression. HAART, highly active antiretroviral therapy.

era, study sample sizes ranged from 330 patients [10] to 23,441 patients [4]. Study outcomes included overall mortality in 20 studies [4, 10, 11, 18-20, 45-58], AIDS-defining events in 7 studies [11, 19, 54-57, 59], and combined AIDS-defining events and mortality in 7 studies [8, 9, 17, 54, 60-62]. One study reported all 3 outcome measures, and 5 studies reported both mortality and AIDS-defining events. HAART use was defined as a regimen that included at least 3 antiretroviral agents. Nine studies recruited only patients who were receiving HAART [8, 9, 46, 48-50, 58, 60, 61], and 2 studies did not report the percentage of patients who were receiving HAART [18, 20]. The percentage of patients who were receiving HAART in the remaining studies ranged from 35% to 89%. Most studies either did not report treatment of HCV infection or reported only a small percentage of coinfected patients who were receiving treatment (range, 0%-7%). The percentage of IDUs in study populations ranged from 0% to 64%. The study without IDUs was selected for a subgroup analysis of non-IDU patients [20]. Mean or median duration of follow-up ranged from 1.1 to 5.9 years for studies conducted entirely during the HAART era.

*Study quality.* Of 27 HAART-era studies, 4 reported overall mortality or AIDS-defining diseases as secondary outcomes and were excluded from quality assessment [4, 49, 50, 61]. Of 23 studies with a primary outcome of interest, 5 were retrospective designs [18, 45, 51, 53, 56], and 1 collected data both retrospectively and prospectively [19]. There are 8 studies with mean or median duration of follow-up of 1–3 years [8, 11, 19, 47, 53, 55–57], and 10 studies have mean or median durations of

follow-up >3 years [9, 10, 17, 18, 46, 48, 54, 58–60]. Five studies did not report mean or median duration of follow-up [20, 45, 51, 52, 62].

**Measured outcomes.** In the pre-HAART era, the risk ratio for overall mortality among HCV-HIV coinfected patients, compared with HIV-monoinfected patients, was 0.69 (95% CI, 0.54–0.88; Figure 2). The  $\chi^2$  test for heterogeneity was not statistically significant (P = .67), with an I<sup>2</sup> statistic of 0 (95% CI, 0–62). Sensitivity tests on the influence of individual studies showed pooled risk ratios ranged from 0.66 to 0.87. The study by El-Serag et al [18] showed a dominant influence on the pooled risk ratio: when removed, the protective effect of HCV coinfection became statistically insignificant, with a risk ratio of 0.87 (95% CI, 0.62–1.23). Only 1 of 9 studies from this era included the use of antiretroviral therapy as a covariate, precluding analysis on the impact of treatment [34].

In the HAART era, the pooled risk ratio for overall mortality among HCV-HIV coinfected patients, compared with patients with HIV-monoinfection, was 1.35 (95% CI, 1.11–1.63; Figure 3*A*). Results of the  $\chi^2$  test for heterogeneity were not statistically significant (P = .13), with an I<sup>2</sup> statistic of 26 (95% CI, 0–58). A sensitivity test on the influence of individual studies showed pooled risk ratios ranging from 1.30 to 1.43, all of which were statistically significant. Evaluation of publication bias by funnel plot showed a symmetric distribution of studies (data not shown). Neither Begg's test (P = .72) nor Egger's test (P = .95) suggested publication bias.

Potential sources of between-studies heterogeneity were ex-

Study (year)	Country	Study design	Study years	Outcome measure(s)	Study population
	,				
Diamondstone et al [35] (1995)	United States	RS	1984-1993	М	Hemophilia
El-Serag et al [18] (2005)	United States	RS	1991-1996	M	Hospitalized veterans
Havdon et al [33] (1998)	United Kingdom	PC and BS	1985-1996	M	
Hung et al $[11]$ (2005)	Taiwan	PC	1994-1997	M	Adults
Klein et al [19] (2003)	Canada	PC and BS	1989-1996	M	Adults
Macias et al [22] (1998)	Spain	RS	1989–1996	M	Adults
Ockenga et al [32] (1997)	Germany	PC	1993–1996	M	Adults
Staples et al [34] (1999)	United States	RS	1992-1997	M	Veterans
Voirin et al [20] (2004)	France	PC	1992-1996	M	Adults
Wright et al [30] (1994)	United States	RS	1984–1989	M	Adults
HAART era					
Anderson et al [45] (2004)	United States	RS	1997–2001	Μ	Veterans
Backus et al [46] (2005)	United States	PC	1997–2003	Μ	Veterans
Bonacini et al [47] (2004)	United States	PC	1993–2001	Μ	Adults
Braitstein et al [48] (2005)	Canada	PC	1996–2003	Μ	Adults
Crane et al [49] (2007)	United States	RS	1995–2005	Μ	Adults
De Luca et al [9] (2002)	Italy	PC	1997–2001	С	Adults
Dorrucci et al [17] (2004)	Italy	PC	1996–2001	С	Adults
El-Serag et al [18] (2005)	United States	RS	1996–2001	Μ	Hospitalized veterans
Greub et al [8] (2000)	Switzerland	PC	1996–2000	С	Age ≥16 years
Hung et al [11] (2005)	Taiwan	PC	1997–2002	M, A	Adults
Jaen et al [61] (2008)	Spain	PC and RS	1998–2004	С	Age ≥16 years
Jaggy et al [50] (2003) <sup>d</sup>	Switzerland	PC	1997–2001	Μ	Adults
Klein et al [19] (2003)	Canada	PC and RS	1996–1999	M, A	Adults
Lincoln et al [62] (2003)	Australia	PC	1999–2002	С	Adults
Marins et al [51] (2005)	Brazil	RS	1995–2002	Μ	Adults
Mayor et al [52] (2006)	Puerto Rico	PC	1998–2003	Μ	Adults
Monga et al [53] (2001)	United States	RS	1994–1998	Μ	Veterans
Riley et al [10] (2005)	United States	PC	1996–2002	Μ	Homeless
Rockstroh et al [54] (2005)	Europe	PC	1994–2004	M, A, C	Adults
Stebbing et al [59] (2005)	United Kingdom	PC	1996–NR	A	Adults
Sulkowski et al [55] (2002)	United States	PC	1995–2001	M, A	Adults
Sullivan et al [56] (2006)	United States	RS	1998–2004	M, A	Age ≥13 years
Tedaldi et al [57] (2003)	United States	PC	1996–2001	M, A	Adults
Torti et al [60] (2007)	Italy	PC	1996–2002	С	Adults
Voirin et al [20] (2004)	France	PC	1996–2002	Μ	Adults
Weber et al [4] (2006)	International	PC	1999–2004	Μ	Adults
Weis et al [58] (2006)	Denmark	PC	1995–2004	Μ	Age ≥15 years

# Table 1. Studies Included in Meta-Analysis of Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) Coinfection

NOTE. A, AIDS; C, combination of AIDS and mortality; HAART, highly-active antiretroviral therapy; IDU, injection drug use; M, overall mortality; NR, not reported; PC, prospective cohort; RS, retrospective.

<sup>a</sup> Calculated according to the proportion reported in HCV positive and negative groups if not reported directly.

<sup>b</sup> Age at HIV seroconversion.

<sup>c</sup> Hard drug use.

<sup>d</sup> Demographic data derived from Greub et al [8].

<sup>e</sup> Assumption made according to the study population.

Male sex, %	Age, mean or median years	No. of HCV-positive patients/no. of HCV-negative patients	Receipt of HAART, % of patients	Receipt of HCV therapy	IDU <sup>a</sup> , % of patients
100	25	565/16			NR
98	45	3048/7848			NR
68	23 <sup>b</sup>	202/38			100
92	36	11/84			3
86	36	42/620			5
77	34	214/106			61
78	38	56/154			28
99	38	115/235			20
81	34	121/980			0
98	NR	39/132			40
99	42	306/664	73	NR	22
98	46	4668/7548	100	3% receiving therapy	37°
84	41	256/126	52	NR	21
85	37	606/580	100	NR	27
87	37	144/550	100	NR	NR
75	33	600/720	100	No therapy	39
66	27 <sup>b</sup>	458/337	35	NR	56
98	45	2272/4913	NR	NR	NR
71	36	1157/1954	100	NR	36
92	36	42/303	85	No therapy	3
75	36	642/1135	100	NR	33
71	36	1645/2318	100	NR	36
77	38	83/456	58	NR	17
94	NR	223/1481	61	NR	8
72	30	279/554	50	NR	34
70	38	193/163	45	NR	58
99°	46	166/263	42	NR	30
84	40	212/118	75	NR	64
75	36	1960/3997	51	2% receiving therapy	28
87	34	85/1382	<49	NR	NR
70	37	873/1082	61	<2% on therapy	45
72	35	2024/8457	70	NR	21
NR	37	267/556	84	7% receiving therapy	26
78	38	334/417	100	NR	41
79	35	107/1273	NR	NR	0
76	39	5274 /18167	89	NR	NR

# Table 1. (Continued.)

75

39

443/2183

100

<1% receiving therapy

10



Figure 2. Forest plots of overall mortality during the pre-highly active antiretroviral therapy era.

plored by meta-regression stratified analyses and subgroup analyses. Stratified results are summarized in Table 2. Although stratification for sex, age, follow-up duration, and treatment did not reveal statistically significant effect modifications, the results suggested that adverse effects of HCV infection on overall mortality may be stronger among older patients and among patients receiving HAART. The adverse effect of HCV-HIV coinfection was also more apparent with longer follow-up. Subgroup analyses according to the quality of the studies yielded pooled estimates of 1.22 (95% CI, 0.82–1.81) for 6 retrospective studies [18, 19, 45, 51, 53, 56] and 1.30 (95% CI, 1.02–1.66) for 11 prospective studies [10, 11, 20, 46–48, 52, 54, 55, 57, 58].

Seven studies reported data on the risk of developing AIDSdefining events among patients with HIV infection with and without HCV coinfection (Table 1) [11, 19, 54–57, 59]. The pooled risk ratio was 1.12 (95% CI, 0.82–1.51; Figure 3*B*), indicating a similar risk of developing AIDS-defining events for HIV-infected patients with and without HCV coinfection. The  $\chi^2$  test for heterogeneity was not statistically significant (*P* = .88). The funnel plot did not show asymmetry, and neither the results of Begg's test (*P* = .13) nor of Egger's test (*P* = .11) supported publication bias.

Seven other post-HAART studies reported on the effect of HCV infection on HIV disease progression, defined as either the development of an AIDS-defining disease or overall mortality (Table 1) [8, 9, 17, 54, 60–62], with a pooled risk ratio of 1.49 (95% CI, 1.08–2.05; Figure 3*C*). No publication bias was observed.

### DISCUSSION

Our meta-analysis summarized 10 studies with 14,626 patients in the pre-HAART era and 20 studies with 113,073 patients in the HAART era. The study demonstrated a 32% reduction in overall mortality risk among HCV-HIV coinfected patient in the pre-HAART era and a 35% increase in overall mortality risk in the HAART era.

The potentially protective role of HCV infection with respect to mortality during the pre-HAART era is dominantly influenced by El-Serag's study, which included many patients but was also unique in its methodology, including restriction to an inpatient population and a retrospective design [19, 20, 34]. Recruiting patients through hospitalization is prone to survival bias. If a patient died of AIDS-related events before a diagnosis of HCV infection was made, the study would not identify them as being HIV-HCV coinfected, especially considering that HCV infection was not routinely screened for during the pre-HAART era. Excluding this study, the remaining selected studies did not show a protective effect, either individually or in aggregate.

By contrast, our meta-analysis demonstrates that HIV-HCV coinfection is associated with increased mortality during the HAART era. Subgroup analyses showed that (1) a longer duration of follow-up is needed to observe a statistically significant difference in mortality between HCV-HIV coinfected patients and HIV-monoinfected patients, and (2) the adverse effect of coinfection was more apparent among patients who were receiving HAART than it was among those not receiving HAART. The latter finding parallels the observation that HIV-related mortality dominated the pre-HAART era [63]. Patients who were not receiving HAART were likely to die of AIDS-related complications, regardless of HCV infection status, and increased risk of mortality attributable to HCV coinfection is less likely to be observed.

The meta-analysis showed no statistically significant increased risk of developing AIDS-defining events among patients with HIV-HCV coinfection in the HAART era, despite studies that suggested this possibility [25, 59]. There might be some effect of HCV infection on HIV disease progression that



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Figure 3. Forest plots of studies from the highly active antiretroviral therapy era showing data on overall mortality (A) AIDS-defining events (B), and AIDS plus mortality (C).

is masked, because death from hepatic complications is a competing risk of AIDS-defining events. However, considering the prolonged time period required to develop HCV-related complications and the fact that death due to HIV-related complications remains the leading cause of mortality among HIVinfected individuals [4, 64], competing risk and insufficient end point events are unlikely to confound our results. When examining the few studies with combined AIDS-defining events and mortality as their outcome, we found an increased (~50% higher) risk among HCV-HIV coinfected patients; however, determining the relative contribution of each outcome was not possible. Therefore, potential mechanisms by which HCV infection may accelerate progression to AIDS (eg, a blunted immunologic response to HAART) may not have significant clinical impact [65].

Given the lack of an association between progression to AIDS and HCV coinfection, the major contributor to mortality among coinfected subjects during the HAART era is likely to be liver disease, based on an expanding body of supporting data [39, 66, 67]. Generally, AIDS-related mortality would be heralded by Table 2. Stratified Analysis of Hepatitis C Virus (HCV) Coinfection and Total Mortality among Human Immunodeficiency Virus(HIV)-Positive Patients in the Era of Highly Active AntiretroviralTherapy (HAART)

Variable	Risk ratio (95% confidence interval)	P
$Sex^{a} (n = 19)$		
Women	2.49 (0.57-11.00)	.420
Men	1.19 (0.81–1.75)	
Age (n = 20)		
<38 years	1.28 (0.97-1.69)	.611
≥38 years	1.42 (1.07-1.89)	
Follow-up duration ( $n = 17$ )		
<3 years	1.11 (0.79–1.55)	.120
≥3 years	1.54 (1.20–1.98)	
$IDU^{a} (n = 17)$		
Non-IDU	1.57 (0.98–2.51)	.533
IDU	1.00 (0.37–2.73)	
Concurrent treatment <sup>b</sup> ( $n = 18$ )		
Not receiving HAART	0.81 (0.42-1.56)	.074
Receiving HAART	1.70 (1.33–2.17)	

NOTE. IDU, injection drug use.

<sup>a</sup> Sex-specific and IDU-specific results estimated from meta-regression of the proportion of each sex and the proportion of IDUs in each study.

<sup>b</sup> HAART-specific results estimated from meta-regression of proportion of patients ever on HAART in each study.

AIDS-related events. Because AIDS-related events were not affected by coinfection status, excess mortality during the HAART era among coinfected patients, compared with that among HIVmonoinfected patients, was unmasked, coincident with the acceleration of liver disease, which was present almost exclusively in the coinfected group. Unfortunately we did not observe that greater duration of HAART availability positively impacts coinfected patients; rather, we observed the opposite effect-a trend towards a greater effect of HCV infection on mortality with greater length of study. Although HAART may have benefits for liver disease progression and related mortality [36, 68], it does not reverse it, which implies that broader application of more effective anti-HCV therapies is needed to reduce this excess mortality. Moreover, if HCV infection is the major direct contributor to increased mortality, death rates among coinfected patients with HCV viremia should differ from death rates among those patients with spontaneous clearance (and reduced risk of liver-disease progression). Unfortunately, this parameter was not controlled for in past studies, because ascertainment of HCV infection status was largely determined by antibody level.

Independent of HCV pathogenesis, HCV-HIV coinfected patients may have increased mortality if they are less likely to be prescribed HAART and/or have poorer adherence to their treatment regimens. Several studies within this meta-analysis observed a shorter duration of exposure to HAART for patients with HIV-HCV coinfection, compared with that for patients with HIV monoinfection [17, 45, 46, 55, 57, 58]. In one study, coinfected patients were statistically significantly less likely to initiate HAART than were HIV-monoinfected patients, even after adjusting for IDU [58]. Moreover, HIV-HCV coinfection is also independently associated with decreased adherence to therapy [69].

Because HCV infection is highly correlated with IDU, the increased risk of mortality associated with coinfection might arguably be confounded by IDUs who have less access to HAART [70]. Despite an expectation that IDU would be an effect modifier, coinfection with HCV increased risk of death in both non-IDU and IDU patients in our subgroup analysis. The studies by Weis et al [19] and Klein et al [58] demonstrated increased risk of mortality after excluding or stratifying patients with IDU in their studies, which suggests that the negative effect of HCV infection on mortality is independent of IDU. The nonsignificant interaction could be partially explained by lack of power, attributable to the small number of coinfected patients without IDU (the reported number of such patients ranged from 29 [15% of the coinfected patients] [52] to 1774 [38% of the coinfected patients] [46]), as well as to the misclassification of IDU patients as non-IDU patients. Our findings are nevertheless consistent with those of a recent study that did not find a statistically significant association between IDU and increased HIV-related mortality among those patients who initiated HAART [71]. Mortality attributable to IDU is further confounded by the timing of the introduction of HIV infection into various populations and whether patients are former or current IDUs. HIV infection may have been acquired later in IDU populations than in MSM populations [72], and thus HIV-related mortality may have been relatively delayed, resulting in a form of lead-time bias. Current IDU is associated with additional risks from complications, such as infection, drug overdose, and homicide; however, these covariates were not reported in most studies. Finally, active IDU, which is associated with the highest mortality rates, may not be fully represented in these cohorts because of poor access to care and/or to follow-up.

Our study has potential limitations. Although tests for publication bias had negative results, studies presented solely in conferences or in local journals may have been overlooked. In addition, each outcome analyses during the HAART era may not be entirely comparable, because studies differed with respect to the data provided. Nevertheless, all analyses included >15,000 patients with HIV infection, and sensitivity analysis revealed no statistically significant change when subtracting any single HAART-era study, which suggests that these limitations are unlikely to weaken the validity of our results. The observational nature of selected studies limits our ability to overcome residual confounding from individual studies, especially time from seroconversion to the initiation of HAART, alcohol consumption, and GB virus C coinfection, factors that were analyzed only in either a small minority or none of the studies. However, 20 of 27 studies adjusted for important factors, such as CD4<sup>+</sup> cell counts and HIV therapy. Finally, we could not examine the role of interferon-based treatments, but the lack of their widespread application among coinfected individuals suggests that HCV treatment would not be a major confounder during the era studied [55, 58, 73].

To conclude, this study synthesizes >30 studies that included a total of >100,000 patients and indicates increased risk of overall mortality among patients with HIV-HCV coinfection in the HAART era. The meta-analysis did not demonstrate increased risk of developing AIDS-defining events among coinfected patients. Future studies that examine mortality among coinfected subjects should attempt to determine the relative contributions of (1) HCV viremia as a surrogate for liver disease risk, (2) whether IDU is current or active, and (3) whether broader application of HCV treatment positively impacts mortality of coinfected individuals.

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