Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Tsiara CG. et al. (2013) Effect of hepatitis C virus on immunological and virological responses in HIV-infected patients initiating highly active antiretroviral therapy: a meta-analysis. *Journal of Viral Hepatitis*, 20(10):715-724
Date of Review:	March 24, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☒ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **HCV/HIV co-infected patients** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Greece** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; to assess the impact of HCV on HIV disease progression by evaluating the effect of HCV on immunological and virological response in HIV patients receiving highly active antiretroviral therapy (HAART)or combined antiretroviral treatment
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Data and information for this study has not been used for decision-making.

Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	Findings can be extended to patients worldwide.
The research study/tool/data dictionary is easily accessed/available electronically	☐	☒	☐	Purchase required for view at http://onlinelibrary.wiley.com/
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☒	☐	No funding stated
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- HCV/HIV co-infected affects early immune response in HIV+ patients who start antiretroviral therapy - Comparable virological response to HAART in HIV patients regardless of HCV status
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☐	☒	☐	Search of published literature up to February 2012
Are these data regularly collected at and/or below a national level?	☐	☒	☐	

Are these data collected manually or electronically?	☐	☐	☐	Electronically: Medline, Scopus and ISI Web of Science database
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	*Journal of Viral Hepatitis*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Existing data: 21 studies included

JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2013, **20**, 715–725 doi:10.1111/jvh.12101

Effect of hepatitis C virus on immunological and virological responses in HIV-infected patients initiating highly active antiretroviral therapy: a meta-analysis

C. G. Tsiara,[1] G. K. Nikolopoulos,[1,2] N. L. Dimou,[3] P. G. Bagos,[3] G. Saroglou,[4] E. Velonakis[5] and A. Hatzakis[6] [1]*Hellenic Centre for Disease Control and Prevention, Athens, Greece;* [2]*National Development and Research Institutes (IAS/NIDA Post-Doctoral Research Fellow), New York, NY, USA;* [3]*Department of Computer Science and Biomedical Informatics, University of Central Greece, Lamia, Greece;* [4]*Department of Internal Medicine, Faculty of Nursing, University of Athens, Athens, Greece;* [5]*Department of Public Health, Laboratory of Prevention, Faculty of Nursing, University of Athens, Athens, Greece; and* [6]*Department of Hygiene, Epidemiology and Medical Statistics, Medical School, University of Athens, Athens, Greece*

Received December 2012; accepted for publication February 2013

SUMMARY. Co-infection of human immunodeficiency virus (HIV) with hepatitis C virus (HCV) is rather common. In the era of highly active antiretroviral therapy (HAART), viral hepatitis could result in adverse outcomes in HIV+ patients. The current meta-analysis aims to evaluate the impact of HCV on immunological and virological responses after HAART initiation in HIV/HCV co-infected individuals by synthesizing the existing scientific evidence. A comprehensive search of electronic databases was performed. Eligible studies were analysed using univariate and multivariate meta-analytic methods. Totally, 21 studies involving 22533 individuals were eligible. The estimated summary difference in CD4 cell counts increase between HIV and HIV/HCV co-infected subjects after 3–12 months on HAART was 34.86 cells/mm^3 [95% confidence interval (CI): 16.82–52.89]. The difference was more prominent in patients with baseline CD4 counts below 350 cells/mm^3 (38.97, 95% CI: 20.00–57.93) and attenuated 2 years later (13.43, 95% CI: 0.83–26.04). The analysis of ratio measures yielded similar findings. The virological control remained unaffected by the presence of HCV (adjusted Hazard Ratio for co-infected patients vs those with HIV alone: 0.99, 95% CI: 0.91–1.07). The bivariate meta-analytic method confirmed the results of the univariate approaches. This meta-analysis supports the adverse effect of HCV on immune recovery of HIV+ patients initiating HAART, especially of those with initially impaired immunologic status. Although this effect diminishes over time, early administration of HAART in the setting of co-infection seems to be justified.

Keywords: antiretroviral treatment, HCV, HIV, immunological response, virological response.

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) led to an impressive decrease in morbidity and mortality of people infected by human immunodeficiency virus (HIV) [1,2], but their prolonged survival allowed the emergence of co-morbidities, including infection with hepatitis C virus (HCV).

Double infection by HIV and HCV is common due to similar modes of transmission. Globally, nearly, 20 per cent of individuals with HIV have chronic hepatitis C [3]. Among HIV+ injecting drug users (IDUs), the prevalence of HCV infection ranges between 82 and 93 per cent [4–7]. HCV incidence has also increased in HIV+ male homosexuals during the last decade [8].

Primary studies assessing the impact of HCV on HIV disease progression have yielded conflicting results [9–12]. A recent meta-analysis showed that HIV/HCV co-infection did not affect the incidence of acquired immune deficiency syndrome (AIDS) but increased overall mortality in the HAART era [13]. In terms of early HAART effectiveness, a quantitative synthesis in 2005 showed a less robust immune reconstitution in co-infected patients who initiated antiretroviral treatment [14].

Abbreviations: AIDS, Acquired Immune Deficiency Syndrome; ART, Antiretroviral Treatment; c-ART, combined Antiretroviral Treatment; CI, Confidence Interval; HAART, Highly Active Antiretroviral Therapy; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; HR, Hazard Ratio; I^2, I-squared index; IDUs, Injecting Drug Users; IR, Immunologic Response; NA, Not Available; OR, Odds Ratio; RCTs, Randomized Clinical Trials; RR, Relative Risk; UVL, Undetected Viral Load; VL, Viral Load; VR, Virologic Response.

Correspondence: Angelos Hatzakis, Professor of Epidemiology and Preventive Medicine, Director, Department of Hygiene, Epidemiology and Medical Statistics, Head, National Retrovirus Reference Center, Medical School, University of Athens M. Asias 75, GR-11527, Athens, Greece. E-mail: ahatzak@med.uoa.gr

In the meantime, more relevant studies have been undertaken. The new pieces of information and the lack of a summary appraisal of virological response to HAART in the HIV/HCV setting warranted the conduct of an updated systematic review. The aim of the current meta-analysis was to combine and evaluate the accumulated scientific evidence concerning the effect of HCV on immunological and virological response in HIV-infected patients receiving HAART or combined antiretroviral treatment (c-ART) including at least 3 drugs.

MATERIALS AND METHODS

Eligibility criteria, data sources and search strategy

This meta-analysis was performed according to the MOOSE guidelines [15] and the PRISMA statement [16]. Studies of HIV+ patients were included in the analysis if: (i) they had examined the effect of HIV/HCV co-infection on immunological and/or virological response of persons receiving HAART or c-ART, (ii) they had included HAART-naive patients at baseline and (iii) they had provided a value for CD4 T-cell counts or HIV-RNA levels difference from baseline to 3–24 months after ART initiation, or an estimate of Relative Risk (RR) for immunological and/or virological response, or sufficient data to calculate these measures. No language restrictions were imposed.

Pertinent studies were identified in Medline, Scopus and ISI Web of Science using a combination of the following terms: 'HIV', 'HCV', 'HAART', 'antiretroviral treatment', 'CD4 T', 'HIV-RNA' and 'viral load' (last search: February 2012). Titles and abstracts were screened to exclude irrelevant records. Full-text versions of the remaining articles were evaluated for eligibility. References of relevant publications and conference abstracts were also appraised to identify further studies for inclusion.

Data extraction

Data were extracted by C.T. and G.N., and discrepancies were resolved by consensus. For each eligible study, the following information, if available, was retrieved: (i) first author's name, year of publication, geographic setting and study design, (ii) diagnostic method for HCV infection, (iii) number of participants and length of follow up, (iv) patients' baseline characteristics and laboratory data, (v) mean differences (with their standard deviations) in CD4 T-cell counts and HIV-RNA levels between measurements at the time of HAART or c-ART initiation and those 3–24 months later and (vi) RRs of achieving a CD4 T-cell increase and/or a HIV-RNA reduction with the corresponding 95% confidence intervals (CIs).

Statistical analysis

Unstandardized mean differences and their 95% CIs were analysed using fixed- and random-effects models [17]. Combined RRs were derived from the univariate random-effects method [18]. Hazard Ratios (HRs) in individual studies, if not directly provided, were computed as suggested by Perneger *et al.* [19]. Heterogeneity tests included the Cochran's Q statistic [17] and the I-squared (I^2) index [20]. The presence of publication bias was investigated by Begg's [21] and Egger's [22] tests. Potential time trends were detected in cumulative analyses [23]. Sensitivity analyses were performed through subgroup investigations or by excluding studies one at a time. A bivariate approach was also implemented to account for the potential correlation of RRs for immunological and virological response [24].

All analyses were conducted in Stata 12 (Stata Corporation, College Station, Texas, USA). Except for heterogeneity statistics (significance was declared if $P < 0.10$), the results were considered significant if the corresponding P value was less than 0.05. All P values were two tailed.

Unless stated differently, only random-effects estimates are presented.

RESULTS

Description of eligible studies

The literature search yielded 31 relevant studies. Ten of them were excluded because they provided insufficient data or were part of multiple publications (Fig. 1). Finally, 21 studies involving 5278 HIV/HCV co-infected patients and 17255 individuals infected by HIV alone were eligible. Among them, 10 included information on immunologic response [9,12,25–32] and 11 about both outcomes [33–43] (Table 1). Immunological response was measured either as CD4 T-cell count change from baseline to 3–24 months after ART initiation [9,12,25,26,28,29,31,32,35–37,40–43] and/or as a CD4 T-cell count increase of at least 50, 75, 100, or 200 cells/mm^3 [9,12,26,27,29,30,32–35,38,39]. Virological response was mostly defined as decreasing plasma HIV-RNA levels below 50, 400, or 500 copies/mL or under the limit of detection [33–42]. In 7 studies, the diagnosis of HCV was made on the basis of a positive anti-HCV test and of HCV-RNA detection in plasma [25,27,29,32,36,42,43]. The majority of eligible studies were prospective cohorts [9,12,25,27,30,32–35,37,39,42].

Immunological and virological response

Immunological response

There was no difference between the baseline CD4 T-cell counts of the two patient groups ($P > 0.05$). As presented in Table 2 and in Fig. 2, the summary difference

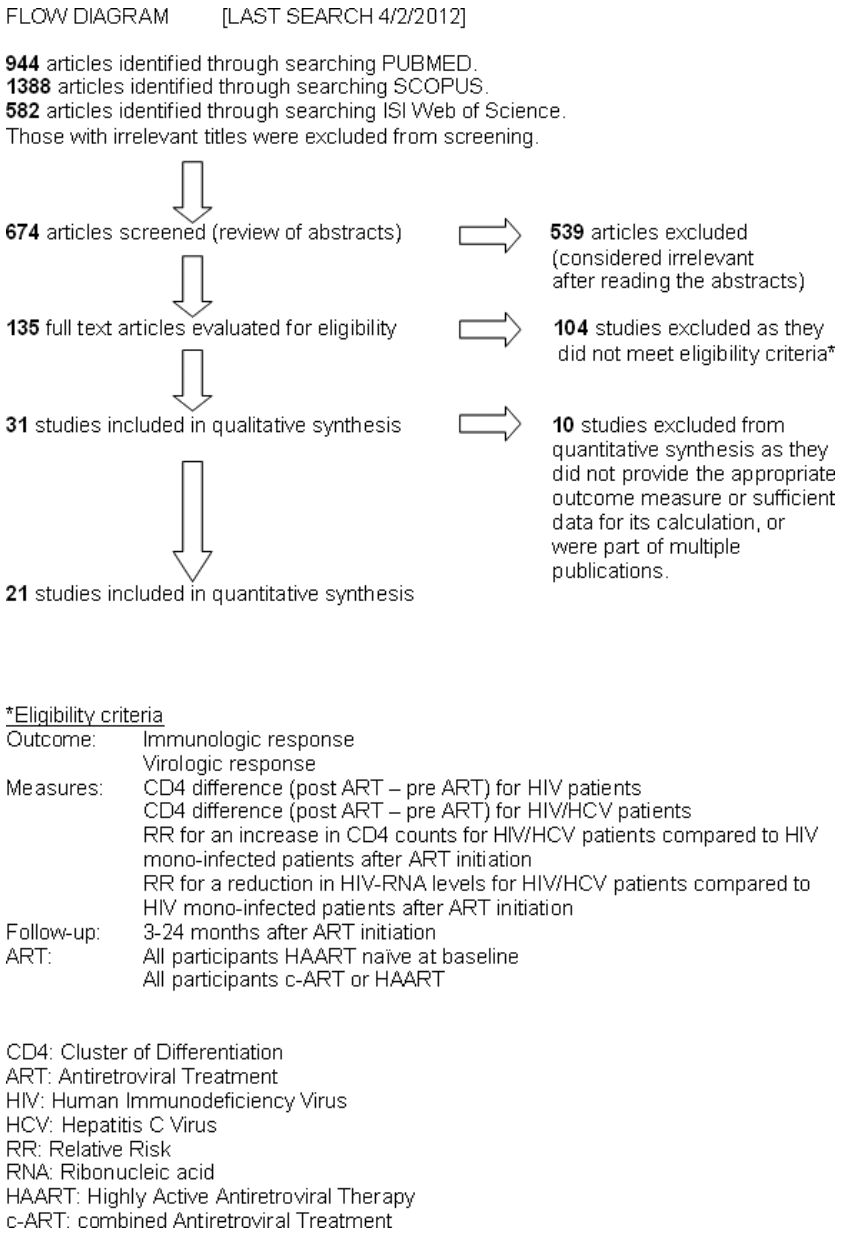

Fig. 1 Identification process of eligible studies.

in CD4 T-cell counts increase between HIV+ and HIV/HCV co-infected subjects in 12 studies after 3–12 months on HAART or c-ART was 34.86 cells/mm^3 (95% CI: 16.82–52.89, I^2 = 92.3%). This difference became bigger when the baseline CD4 T-cell counts were below 350 cells/mm^3 (38.97, 95% CI: 20.00–57.93) (Table 2). The results were nonsignificant (27.26, 95% CI: −2.21 to 56.72) (Table 2) in the analysis of studies with dual (serologic and molecular) diagnosis of HCV. The between groups difference attenuated 2 years after ART initiation (13.43, 95% CI: 0.83–26.04, I^2 = 0.0%) (Table 2). The results of all subgroup analyses are presented in Table 2.

The quantitative synthesis of HRs for increased CD4 T-cell counts (50 or 75 or 100 cells/mm^3) in co-infected versus mono-infected patients after the commencement of ART yielded also significant estimates (summary adjusted HR of 8 studies: 0.82, 95% CI: 0.75–0.91) (Table 2).

Virological response

The difference in virological response was examined in 10 studies involving 13394 patients. The summary adjusted HRs for achieving undetectable viral load or HIV-RNA levels less than 50, 400 or 500 copies/mL after HAART or c-ART initiation for HIV/HCV patients compared with HIV

Table 1 Description of primary studies

Study	Type	*N*		ART-naïve (%)		ART regimen	Endpoint	Outcome measure
		HIV	HIV/HCV	HIV	HIV/HCV			
Santin *et al.* [25]	Prospective cohort	24	15	100	100	Combined ART, at least 3 drugs	48 weeks after ART initiation	CD4 difference
Macias *et al.* [32]	Prospective cohort	58	60	100	100	HAART	12 months after HAART initiation	CD4 difference*, HR of CD4 recovery of 50† and 200 cells/mm^3
Braitstein *et al.* [26]	Nested cohort	580	606	100	100	HAART	48 weeks after HAART initiation, time to IR	CD4 difference, HR of CD4 recovery of $\geq$75 cells/mm^3
Sulkowski *et al.* [12]	Prospective cohort	122	65	NA	NA	HAART	$\geq$1 year $\geq$2 years $\geq$3 years after HAART initiation	CD4 difference, HR of CD4 recovery of $\geq$50 cells/mm^3†, HR of CD4 recovery of $\geq$100 cells/mm^3†
Filippini *et al.* [42]	Prospective cohort	8	8	NA	NA	HAART	1, 3, 6 months after HAART initiation	CD4 difference†, VL pre and after, HR of achieving UVL†
Antonucci *et al.* [27]	Prospective cohort	1219	284	100	100	HAART	Time to IR	HR of CD4 recovery of $\geq$100 cells/mm^3
Castagna *et al* [28]	Retrospective multicohort	1053	435	NA	NA	HAART	12, 24 weeks after HAART initiation	CD4 difference
Seminari *et al.* [29]	Retrospective cohort	673	171	47	35	HAART	At time of UVL (<12 months), 12 months after suppressive HAART (12 < ..<24 months)	CD4 difference, OR of CD4 recovery of $\geq$100 cells/mm^3
De Luca *et al.* [34]	Prospective cohort	674	556	100	100	Combined ART, at least 3 drugs	Time to IR and VR	HR of CD4 recovery of $\geq$100 cells/mm^3 or of achievement of 500 cells/mm^3, HR of achieving VL<500 copies/mL
Rockstroh *et al.* [33]	Prospective cohort	1492	768	NA	NA	HAART	Time to IR and VR	HR of CD4 recovery of $\geq$50 cells/mm^3, HR of achieving VL<500 copies/mL

(continued)

Table 1 *(continued)*

Study	Type	*N*		ART-naïve (%)		ART regimen	Endpoint	Outcome measure
		HIV	HIV/HCV	HIV	HIV/HCV			
Klein *et al.* [35]	Prospective cohort	263	52	NA	NA	HAART	24 months after HAART initiation, time to IR and VR	CD4 difference, HR of CD4 recovery of ≥ 50 cells/mm^3, HR of achieving VL<500 copies/mL
Chung *et al.* [36]	Retrospective cohort	129	40	NA	NA	HAART	16, 48 weeks after HAART initiation	CD4 difference, HR of achieving VL<500 copies/mL†
Zhou *et al.* [37]	Prospective cohort	371	43	NA	NA	HAART	180 days after HAART initiation	CD4 difference, HR of achieving VL<400 copies/mL†
Carmo *et al.* [38]	Retrospective cohort	748	76	56	34	HAART	Time to IR and VR	HR of CD4 recovery of ≥ 50 cells/mm^3, HR of achieving VL<400 copies/mL
Turner *et al.* [39]	Prospective cohort	5500	396	100	100	HAART	Time to IR and VR	HR of CD4 recovery of >50 cells/mm^3, HR of achieving VL<50 copies/mL
Stapleton *et al.* [40]	Longitudinal cohort	1238	148	100	100	Combined ART (at least 3 drugs) and HAART	48 weeks after ART initiation	CD4 difference, HR of achieving VL<50 copies/mL†
Lincoln *et al.* [41]	Retrospective cohort	772	112	NA	NA	HAART	12, 24 months after HAART initiation	CD4 difference, HR of achieving UVL†
Zhao *et al.* [43]	Retrospective cohort	178	168	100	100	HAART	1 year after HAART initiation	CD4 difference†, VL pre and after
Isa *et al.* [30]	Prospective cohort	149	68	100	100	HAART	3, 6 months after HAART initiation	HR of CD4 recovery of ≥ 50 cells/mm^3†
Emokpae *et al.* [31]	Retrospective cohort	50	50	100	100	HAART	6 months after HAART initiation	CD4 difference†
Greub *et al.* [9]	Prospective cohort	1954	1157	52	59	HAART	12 months after HAART initiation	CD4 difference*, HR of CD4 recovery of ≥ 50 cells/mm^3

*Data provided by the meta-analysis of Miller *et al.* [14]

†Calculated by provided data.

N, number of subjects; HIV, Human immunodeficiency virus; HCV, Hepatitis C virus; ART, Antiretroviral treatment; CD4, Cluster of differentiation; HAART, Highly active antiretroviral therapy; HR, Hazard ratio; IR, Immunological response; NA, Not available; VL, Viral load; UVL, Undetected VL; OR, Odds ratio; VR, Virological response.

Table 2 Results of meta-analyses of studies evaluating the difference in immunological and virological responses between HIV and HIV/HCV patients receiving antiretroviral treatment

Outcome	Outcome measure	Endpoint	Number of HIV - HIV/HCV patients	Number of studies	Summary Estimate	95% Confidence interval	I^2 (%)
Immunological response	CD4 difference (cells/mm^3)	3–12 months	5834, 2604	12	34.86	16.82–52.89	92.3
Subgroup analysis							
HCV diagnosis based only on positive HCV serology			4764, 2142	6	38.91	15.51–62.30	95.5
HCV diagnosis based on positive HCV serology and detection of HCV-RNA			1070, 462	6	27.26	−2.21–56.72	73.4
ART-naïve at baseline			2127, 1047	6	51.87	21.66–82.08	95.4
ART experienced (HAART-naïve) at baseline			3707, 1557	6	21.77	9.19–34.36	53.1
Baseline CD4 < 350			5288, 2497	9	38.97	20.00–57.93	91.7
Baseline CD4 ≥ 350			175, 64	3	1.61	−88.68–91.89	89.8
Immunological response	CD4 difference (cells/mm^3)	13–24 months	1830, 396	4	13.43	0.83–26.04	0.0
Immunological response	Adjusted HR for HIV/HCV vs HIV	Time to IR	12402, 3492	8	0.82	0.75–0.91	53.9
Immunological response	Unadjusted HR for HIV/HCV vs HIV	Time to IR	5523, 2550	8	0.72	0.64–0.81	57.6
Virological response	Adjusted HR for HIV/HCV vs HIV	Time to VR	8677, 1848	5	0.99	0.91–1.07	0.0
Virological response	Unadjusted HR for HIV/HCV vs HIV	Time to VR	4949, 1244	8	0.89	0.76–1.04	50.5

HIV, Human immunodeficiency virus; HCV, Hepatitis C virus; CD4, Cluster of differentiation; RNA, Ribonucleic acid; ART, Antiretroviral treatment; HAART, Highly active antiretroviral therapy; HR, Hazard ratio; IR, Immunological response; VR, Virological response.

mono-infected individuals was 0.99 (95% CI: 0.91–1.07, I^2: 0.0%) (Table 2, Fig. 3).

Bivariate meta-analysis

The bivariate synthesis produced similar findings. The adjusted HRs for immunological and virological responses in the HIV/HCV group compared with those patients infected with HIV alone were 0.82 (95% CI: 0.74–0.91) and 0.96 (95% CI: 0.89–1.04), respectively.

Publication bias

In all analyses, the statistical tests of Begg and Egger supported the absence of publication bias.

DISCUSSION

This meta-analysis of 21 studies demonstrated that HCV co-infection adversely affects early immune responses in HIV+ patients who start HAART or c-ART, especially those with baseline CD4 T-cell counts below 350 cells/mm^3. This impact was less pronounced 2 years after ART initiation. The virological suppression in persons receiving potent antiretroviral therapy seems to remain unaffected by the simultaneous existence of HCV.

HIV/HCV co-infection hastens HCV-associated hepatic disease in the HAART era [44–47]. The reciprocal effect of HCV on the natural history of HIV disease is not clarified. Our meta-analysis showed the negative impact of HCV on early CD4 T-cell counts recovery in HIV+ subjects. This phenomenon has biological basis. CD4 T-cells can be infected by HCV and interactions of HIV and HCV at the cellular level could affect the immune efficacy of HAART [48]. Moreover, chronic HCV infection, in the presence of HIV, increases T-cell immune activation, which is known to limit CD4 T-cell gains [47,49–51]. Finally, HCV has also been found to enhance CD4 T-cell apoptosis [52]. As a matter of fact, if apoptosis is partly implicated in the poorer CD4 T-cell recovery of co-infected patients, the restoration of their CD4 T-cells over time that was found in this meta-analysis dovetails with the observation that HIV replication control by HAART gradually attenuates the CD4 T-cell apoptosis rates in HIV+ patients with concomitant HCV infection [52].

This meta-analysis showed that there was a comparable virological response to HAART in HIV+ persons regardless of HCV status. By contrast, a recent analysis of randomized clinical trials (RCTs) reported that HCV carriage was associated with altered HIV-RNA suppression in co-infected individuals [53]. This report, however, considered studies that were not designed to assess the impact of co-infection as the primary outcome of their analysis, recruited HAART-experienced patients and lacked clear description of meta-analytic techniques. Because most of the results of these trials were presented as abstracts, a new analysis of

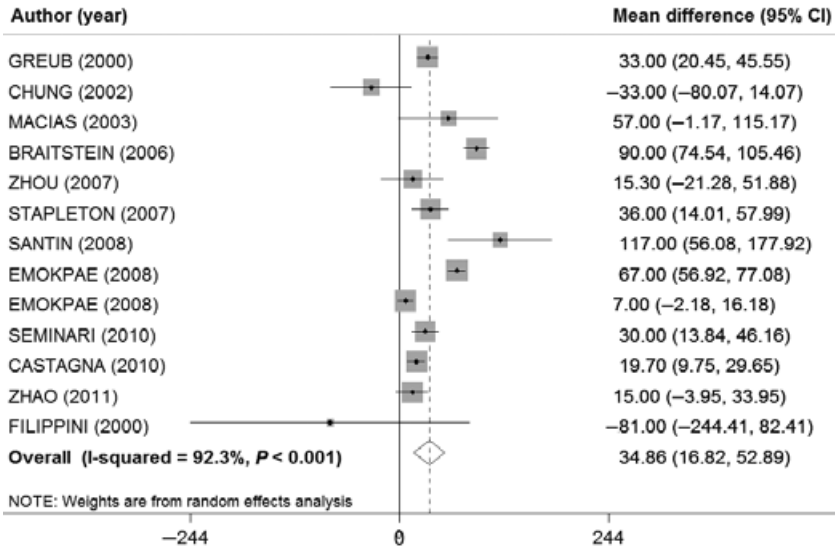

Fig. 2 Univariate random-effects meta-analysis concerning the difference in CD4 T-cell increase between HIV and HIV/HCV subjects after initiation of antiretroviral treatment. *Note*: CI: Confidence interval.

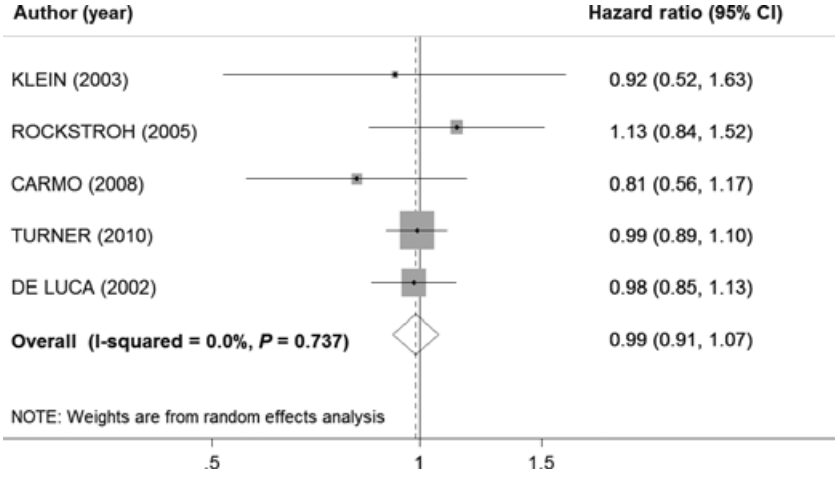

Fig. 3 Univariate random-effects meta-analysis of adjusted Hazard Ratios for virological response in the HIV/HCV group compared with the HIV mono-infection group after initiation of antiretroviral treatment. *Note*: CI: Confidence interval.

forthcoming full-text publications or of individual data would help clarify potential discrepancies between RCTs and observational research.

The meta-analysis of CD4 T-cell count change was characterized by substantial between-studies heterogeneity that predicated the conduct of subgroup analyses to explore its sources and potential impact. Previous receipt of antiretrovirals could result in heterogeneous effect estimates. Although it would be ideal to consider not only HAART- (as we did) but also ART-naïve individuals in this meta-analysis, some of the eligible studies had recruited patients with ART experience. Previous ART therapy could compromise HAART adherence, HIV load control and immunological response [54]. However, as shown in Table 2, in spite of unexpected differences in magnitude, the effect estimates were statistically significant in both cases indicating a diminished CD4 T-cell response in HIV/HCV individuals irrespective of prior ART exposure.

It is important to diagnose HCV infection based on HCV-RNA detection to avoid misclassification of HCV antibody positive patients who are HCV aviremic [55]. To explore the effect of potential misclassification, the meta-analysis of CD4 T-cell increase was performed separately by method of HCV diagnosis. The subanalyses showed that the results ceased being statistically significant in studies that adopted both serological and molecular testing. Although this could be a chance finding, it certainly calls for more accurate and consistent across studies definition of HCV infection.

The negative effect of co-infection on immunological response to HAART was observed only in patients with baseline CD4 T-cell counts below 350 cells/mm^3. This finding supports the current European Guidelines for Antiretroviral Treatment [56], which recommend immediate ART administration in HIV/HCV co-infected patients when CD4 T-cell counts drop below 500 cells/mm^3. It should be noted, however, that this meta-analysis included a limited number of studies that had involved patients with initial CD4 counts above 350 cells/mm^3. Future research needs to address this stratifying always immunological response by baseline CD4 T-cell counts.

The differences in CD4 T-cell recovery could be attributed to unmeasured confounding effects. For instance, the rates of HCV infection are extremely high among IDUs and previous research has shown that CD4 T-cell recovery is compromised in drug injectors compared with other groups [57], although this finding was not corroborated in other studies [58,59]. It seems, however, that the immunological response of IDUs to ART could be influenced by many factors that result in poor adherence to the prescribed regimen including their potential incarceration, their participation in substitution programmes, their current injection status, the presence of psychiatric conditions or the provision of psychological support [60–63]. The optimal way to elucidate the confounding effect of HIV risk groups in CD4 T-cell increase is to compare HIV mono-infected and HIV/HCV co-infected individuals by HIV risk group. Unfortunately, many of the eligible studies in this meta-analysis lacked the necessary information to perform this type of subgroup investigations.

The current work updates a previous synthesis [14] using thirteen more reports, performing many subgroup analyses, and implementing some new meta-analytic methods. It indicates a delayed immunological response in HIV/HCV co-infected patients receiving potent combinations of antiretrovirals, especially among those with CD4 T-cell counts below 350 cells/mm^3. The delayed recovery of CD4 T-cells during the first year of HAART could increase the risk of toxicities or non-AIDS events. However, the clinical significance of the blunted CD4 T-cell response in the first months of HAART therapy is not fully elucidated yet and future prospective studies should explore its short-term and long-term consequences.

AUTHORS' CONTRIBUTION

Chrissa G. Tsiara: Acquisition, analysis and interpretation of data; drafting the manuscript; approval of the final version. Georgios K. Nikolopoulos: Analysis and interpretation of data; drafting the manuscript; approval of the final version. Niki L. Dimou: Analysis and interpretation of data; critical revision of the manuscript; approval of the final version. Pantelis G. Bagos: Analysis and interpretation of data; critical revision of the manuscript; approval of the final version. Georgios Saroglou: Conception and design; critical revision of the manuscript; approval of the final version. Emmanuel Velonakis: Conception and design; critical revision of the manuscript; approval of the final version. Angelos Hatzakis: Conception and design; critical revision of the manuscript; approval of the final version.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

None were declared.

REFERENCES

1 UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. Available at: http://www.unaids.org/globalreport/global_report.htm (accessed 3 September 2012).
2 Puhan MA, Van Natta ML, Palella FJ, Addessi A, Meinert C, Ocular Complications of AIDS Research Group. Excess mortality in patients with AIDS in the era of highly active antiretroviral therapy: temporal changes and risk factors. *Clin Infect Dis* 2010; 51: 947–956.
3 Soriano V, Vispo E, Labarga P, Medrano J, Barreiro P. Viral hepatitis and HIV co-infection. *Antiviral Res* 2010; 85: 303–315.
4 Nelson PK, Mathers BM, Cowie B *et al.* Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011; 378: 571–583.
5 Larsen C, Pialoux G, Salmon D *et al.* Prevalence of hepatitis C and hepatitis B infection in the HIV-infected population of France, 2004. *Euro Surveill* 2008; 13: 1–4.pii=18888. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18888 (accessed 3 September 2012).
6 Mohsen AH, Murad S, Easterbrook PJ. Prevalence of hepatitis C in an ethnically diverse HIV-1-infected cohort in south London. *HIV Med* 2005; 6: 206–215.
7 Solomon SS, Srikrishnan AK, Mehta SH *et al.* High prevalence of HIV, HIV/hepatitis C virus co-infection, and risk behaviors among injection drug users in Chennai, India: a cause for concern. *J Acquir Immune Defic Syndr* 2008; 49: 327–332.
8 Danta M, Rodger AJ. Transmission of HCV in HIV-positive populations. *Curr Opin HIV AIDS* 2011; 6: 451–458.
9 Greub G, Ledergerber B, Battegay M *et al.* Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus co-infec-

tion: the Swiss HIV Cohort Study. *Lancet* 2000; 356: 1800–1805.
10 Anderson KB, Guest JL, Rimland D. Hepatitis C virus co-infection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: data from the HIV Atlanta VA Cohort Study. *Clin Infect Dis* 2004; 39: 1507–1513.
11 Macías J, Pineda JA, Leal M *et al.* Influence of hepatitis C virus infection on the mortality of antiretroviral-treated patients with HIV disease. *Eur J Clin Microbiol Infect Dis* 1998; 17: 167–170.
12 Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. *JAMA* 2002; 288: 199–206.
13 Chen TY, Ding EL, Seage GR III, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clin Infect Dis* 2009; 49: 1605–1615.
14 Miller MF, Haley C, Koziel MJ, Rowley CF. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. *Clin Infect Dis* 2005; 41: 713–720.
15 Stroup DF, Berlin JA, Morton SC *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–2012.
16 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; 8: 336–341.
17 Petitti DB. Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis, 2nd ed. New York: Oxford University Press, 2000.
18 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
19 Perneger T. Estimating the relative hazard by the ratio of logarithms of event-free proportions. *Contemp Clin Trials* 2008; 29: 762–766.
20 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
21 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
22 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
23 Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992; 327: 248–254.
24 Riley RD, Thompson JR, Abrams KR. An alternative model for bivariate random-effects meta-analysis when the within-study correlations are unknown. *Biostatistics* 2008; 9: 172–186.
25 Santin M, Mestre M, Shaw E *et al.* Impact of hepatitis C virus co-infection on immune restoration during successful antiretroviral therapy in chronic human immunodeficiency virus type 1 disease. *Eur J Clin Microbiol Infect Dis* 2008; 27: 65–73.
26 Braitstein P, Zala C, Yip B *et al.* Immunologic response to antiretroviral therapy in hepatitis C virus-co-infected adults in a population-based HIV/AIDS treatment program. *J Infect Dis* 2006; 193: 259–268.
27 Antonucci G, Girardi E, Cozzi-Lepri A *et al.* HepaI.Co.N.A. Study Group, Italian Cohort Naive for Antiretrovirals Study Group. Role of hepatitis C virus (HCV) viremia and HCV genotype in the immune recovery from highly active antiretroviral therapy in a cohort of antiretroviral-naïve HIV-infected individuals. *Clin Infect Dis* 2005; 40: e101–e109.
28 Castagna A, Galli L, Torti C *et al.* Predicting the magnitude of short-term CD4 (+) T-cell recovery in HIV-infected patients during first-line highly active antiretroviral therapy. *Antivir Ther* 2010; 15: 165–175.
29 Seminari E, Tinelli C, Ravasi G *et al.* MASTER Cohort. Hepatitis C infection on immune recovery in HIV-positive patients on successful HAART: the role of genotype 3. *Curr HIV Res* 2010; 8: 186–193.
30 lsa SE, Gwamzhi LN, Akolo C, Giyan J. A prospective cohort study of immunologic and virologic outcomes in patients with HIV/AIDS and hepatitis virus co-infection in Jos, Nigeria. *Niger J Med* 2010; 19: 279–285.
31 Emokpae MA, Nwokedi EE, Jegede EE. Impact of hepatitis C co-infection on CD4 T cell count in HIV infected subjects. *OJHAS* 2008; 7: 1–4.
32 Macías J, Pineda JA, Lozano F *et al.* Impaired recovery of CD4 + cell counts following highly active antiretroviral therapy in drug-naïve patients coinfected with human immunodeficiency virus and hepatitis C virus. *Eur J Clin Microbiol Infect Dis* 2003; 22: 675–680.
33 Rockstroh JK, Mocroft A, Soriano V. *et al.* EuroSIDA Study Group. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis* 2005; 192: 992–1002.
34 De Luca A, Bugarini R, Lepri AC *et al.* Italian Cohort Naive Antiretrovirals Study Group. Co-infection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. *Arch Intern Med* 2002; 162: 2125–2132.
35 Klein MB, Lalonde RG, Suissa S. The impact of hepatitis C virus co-infection on HIV progression before and after highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2003; 33: 365–372.
36 Chung RT, Evans SR, Yang Y *et al.* AIDS Clinical Trials Group 383 Study Team. Immune recovery is associated with persistent rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects. *AIDS* 2002; 16: 1915–1923.
37 Zhou J, Dore GJ, Zhang F, Lim PL, Chen YM, TREAT Asia HIV Observational Database. Hepatitis B and C virus co-infection in The TREAT Asia HIV Observational Database. *J Gastroenterol Hepatol* 2007; 22: 1510–1518.

38 Carmo RA, Guimarães MD, Moura AS *et al.* The influence of HCV co-infection on clinical, immunological and virological responses to HAART in HIV-patients. *Braz J Infect Dis* 2008; 12: 173–179.
39 Turner J, Bansi L, Gilson R *et al.* UK Collaborative HIV Cohort (UK CHIC) Study. The prevalence of hepatitis C virus (HCV) infection in HIV-positive individuals in the UK - trends in HCV testing and the impact of HCV on HIV treatment outcomes. *J Viral Hepat* 2010; 17: 569–577.
40 Stapleton JT, Bennett K, Bosch RJ, Polgreen PM, Swindells S. Effect of antiretroviral therapy and hepatitis C co-infection on changes in lipid levels in HIV-Infected patients 48 weeks after initiation of therapy. *HIV Clin Trials* 2007; 8: 429–436.
41 Lincoln D, Petoumenos K, Dore GJ, Australian HIV Observational Database. HIV/HBV and HIV/HCV co-infection, and outcomes following highly active antiretroviral therapy. *HIV Med* 2003; 4: 241–249.
42 Filippini P, Coppola N, Scolastico C *et al.* Can HCV affect the efficacy of anti-HIV treatment? *Arch Virol* 2000; 145: 937–944.
43 Zhao J, Yu ZJ, Kan QC, Li XF, Li ZQ, Liang HX. A retrospective study: the influence of human immunodeficiency virus co-infection with hepatitis C virus or hepatitis B virus on the efficacy with HAART in China AIDS area. *Life Science J* 2011; 8: 27–31.
44 Thein HH, Yi Q, Dore GJ, Krahn MD. 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. *AIDS* 2008; 22: 1979–1991.
45 Martin-Carbonero L, de Ledinghen V, Moreno A *et al.* Liver fibrosis in patients with chronic hepatitis C and persistently normal liver enzymes: influence of HIV infection. *J Viral Hepat* 2009; 16: 790–795.
46 Smit C, van den Berg C, Geskus R, Berkhout B, Coutinho R, Prins M. Risk of hepatitis-related mortality increased among hepatitis C virus/HIV-co-infected drug users compared with drug users infected only with hepatitis C virus: a 20-year prospective study. *J Acquir Immune Defic Syndr* 2008; 47: 221–225.
47 Operskalski EA, Kovacs A. HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. *Curr HIV/AIDS Rep* 2011; 8: 12–22.
48 Laskus T, Radkowski M, Jablonska J *et al.* Human immunodeficiency virus facilitates infection/replication of hepatitis C virus in native human macrophages. *Blood* 2004; 103: 3854–3859.
49 Hunt PW, Martin JN, Sinclair E *et al.* T cell activation is associated with lower CD4 T+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis* 2003; 187: 1534–1543.
50 Sandberg JK, Falconer K, Gonzalez VD. Chronic immune activation in the T cell compartment of HCV/HIV-1 co-infected patients. *Virulence* 2010; 1: 177–179.
51 Gonzalez VD, Falconer K, Blom KG *et al.* High levels of chronic immune activation in the T-cell compartments of patients coinfected with hepatitis C virus and human immunodeficiency virus type 1 and on highly active antiretroviral therapy are reverted by alpha interferon and ribavirin treatment. *J Virol* 2009; 83: 11407–11411.
52 Korner C, Kramer B, Schulte D *et al.* Effects of HCV co-infection on apoptosis of CD4 T-cells in HIV positive patients. *Clin Sci* 2009; 116: 861–870.
53 Pulido F, Hill A, van Delft Y, Moecklinghoff C. Impact of hepatitis C co-infection on response to antiretroviral treatment. *AIDS Rev* 2012; 14: 124–131.
54 Horberg M, Silverberg M, Hurley L, Delorenze G, Quesenberry C. Influence of prior antiretroviral experience on adherence and responses to new highly active antiretroviral therapy regimens. *AIDS Patient Care STDS* 2008; 22: 301–312.
55 Thomas DL, Astemborski J, Rai RM *et al.* The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000; 284: 450–456.
56 European AIDS Clinical Society. European Guidelines for treatment of HIV infected adults in Europe - Version 6. Available at: http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EACSGuidelines-v6.0-English.pdf (accessed 3 September 2012).
57 Collazos J, Asensi V, Carton JA, Grupo Español para el Estudio Multifactorial de la Adherencia (GEEMA). Association of HIV transmission categories with sociodemographic, viroimmunological and clinical parameters of HIV-infected patients. *Epidemiol Infect* 2010; 138: 1016–1024.
58 Mocroft A, Madge S, Johnson AM *et al.* A comparison of exposure groups in the EuroSIDA study: starting highly active antiretroviral therapy (HAART), response to HAART, and survival. *J Acquir Immune Defic Syndr* 1999; 22: 369–378.
59 Wisaksana R, Indrati AK, Fibriani A *et al.* Response to first-line antiretroviral treatment among human immunodeficiency virus-infected patients with and without a history of injecting drug use in Indonesia. *Addiction* 2010; 105: 1055–1061.
60 Mehta SH, Lucas G, Astemborski J, Kirk GD, Vlahov D, Galai N. Early immunologic and virologic responses to highly active antiretroviral therapy and subsequent disease progression among HIV-infected injection drug users. *AIDS Care* 2007; 19: 637–645.
61 Giordano TP, Hartman C, Gifford AL, Backus LI, Morgan RO. Predictors of retention in HIV care among a national cohort of US veterans. *HIV Clin Trials* 2009; 10: 299–305.
62 Ortego C, Huedo-Medina TB, Llorca J *et al.* Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. *AIDS Behav* 2011; 15: 1381–1396.
63 Malta M, Strathdee SA, Magnanini MM, Bastos FI. Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review. *Addiction* 2008; 103: 1242–1257.