### Best Practice/Intervention:


| 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
- Level: Group
- Target Population: HCV/HIV co-infected patients
- Setting: Health care setting/Clinic
- Country of Origin: Greece
- Language: English

#### Part B

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<td>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</td>
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<td>- HCV/HIV co-infected affects early immune response in HIV+ patients who start antiretroviral therapy</td>
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<td>- Comparable virological response to HAART in HIV patients regardless of HCV status</td>
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<td>☐</td>
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<td>Journal of Viral Hepatitis</td>
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<td>☐</td>
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<td>Existing data: 21 studies included</td>
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</table>
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, G. K. Nikolopoulos, N. L. Dimou, P. G. Bagos, G. Saroglou, E. Velonakis and A. Hatzakis

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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/mm³ [95% confidence interval (CI): 16.82–52.89]. The difference was more prominent in patients with baseline CD4 counts below 350 cells/mm³ (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, 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].

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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 (I²) 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/mm³ [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
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>
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<tr>
<th>Study</th>
<th>Type</th>
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<td>CD4 difference</td>
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<td>60</td>
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<td>HAART</td>
<td>12 months after HAART initiation</td>
<td>CD4 difference*, HR of CD4 recovery of 50 and 200 cells/mm³</td>
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<td>Braitstein et al. [26]</td>
<td>Nested cohort</td>
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<td>606</td>
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<td>HAART</td>
<td>48 weeks after HAART initiation, time to IR ≥ 1 year ≥ 2 years ≥ 3 years after HAART initiation</td>
<td>CD4 difference, HR of CD4 recovery of ≥ 50 cells/mm³, HR of CD4 recovery of ≥ 100 cells/mm³</td>
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<td>Sulkowski et al. [12]</td>
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<td>CD4 difference, HR of CD4 recovery of ≥ 50 cells/mm³, HR of CD4 recovery of ≥ 100 cells/mm³</td>
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<td>Filippini et al. [42]</td>
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<td>HAART</td>
<td>1, 3, 6 months after HAART initiation</td>
<td>CD4 difference*, VL pre and after, HR of achieving UVL†</td>
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<td>Antonucci et al. [27]</td>
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<td>Castagna et al. [28]</td>
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<td>12, 24 weeks after HAART initiation At time of UVL (&lt;12 months), 12 months after suppressive HAART (12 &lt; .. &lt; 24 months)</td>
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<td>171</td>
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<td>HAART</td>
<td>Time to IR and VR HR of CD4 recovery of ≥ 100 cells/mm³ or of achievement of 500 cells/mm³, HR of achieving VL &lt; 500 copies/mL</td>
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<td>Rockstroh et al. [33]</td>
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<td>52</td>
<td>59</td>
<td>HAART 12 months after HAART initiation</td>
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*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.
mono-infected individuals was 0.99 (95% CI: 0.91–1.07, I²: 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/mm³. 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...
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.

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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.
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/mm³. 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/mm³. 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/mm³. 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/mm³. 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.

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