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

| | |
|---|---|
| **Best Practice/Intervention:** | Hua L. et al. (2013) Hepatitis C virus/HIV coinfection and responses to initial antiretroviral treatment. *AIDS*, 27(17):2725-2734 |
| **Date of Review:** | March 15, 2015 |
| **Reviewer(s):** | Christine Hu |

**Part A**

| | |
|---|---|
| ***Category:*** | **Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐<br>**Social Science** ☐ **Programmatic Review** ☒ |
| ***Best Practice/Intervention:*** | **Focus:** **Hepatitis C** ☐ **Hepatitis C/HIV** ☒ **Other:** _____<br>**Level:** **Group** ☒ **Individual** ☐ **Other:** _____<br>**Target Population:** **HIV/HCV co-infected patients**<br>**Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** **ACTG A5073, A5095, A5142 and A5202 randomized studies**<br>**Country of Origin:** **USA**<br>**Language:** **English** ☒ **French** ☐ **Other:** _____ |

**Part B**

| | YES | NO | N/A | COMMENTS |
|---|---|---|---|---|
| *Is the best practice/intervention a meta-analysis or primary research?* | ☒ | ☐ | ☐ | Cross-study analysis; use data from four randomized studies of initial antiretroviral regimens in HIV-1 treatment-naïve patients to explore the relationship between HCV/HIV coinfection and responses to initial antiretroviral treatment (ART) |
| *Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?* | ☐ | ☒ | ☐ | The International Antiviral Society-USA Panel and the Department of Health and Human Services' HIV treatment guidelines suggest HCV infection might influence the decisions to when ART should be started. |

| | | | | |
|---|---|---|---|---|
| | | | | Finding from this study demonstrates HCV/HIV coinfection is associated with increased risk of clinical progression and attenuated CD4 cell response to antiretroviral treatment, which supports the guideline recommendations for earlier initiation of therapy. |
| *Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?* | ☐ | ☒ | ☐ | - Only data from patients with HCV infection status assessed between 1 year prior to and within 4 weeks after randomization at study entry were included<br>- Exclusion of patients with significant transaminase elevation or hyperbilirubinemia<br>- Due to small sample sizes, patients with race/ethnicity other than white non-Hispanic, black non-Hispanic, or Hispanic were excluded from analyses |
| *Are the best practices/methodology/results described applicable in developed countries?* | ☐ | ☐ | ☒ | The four studies included in the analysis was all conducted in the United States by the AIDS Clinical Trial Group |
| | **YES** | **NO** | **N/A** | **COMMENTS** |
| *Are the best practices/methodology/results described applicable in developing countries?* | ☐ | ☐ | ☒ | |
| *The research study/tool/data dictionary is easily accessed/available electronically* | ☐ | ☒ | ☐ | Journal subscription required for download from http://journals.lww.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*** | ☒ | ☐ | ☐ | The study was supported by National Institute of Allergy and Infectious Disease (NIAID) at the National Institutes of Health funding to the AIDS Clinical Trial Group. |
| *Is the best practice/intervention dependent on external funds?* | ☒ | ☐ | ☐ | The four studies included in the analysis was all conducted by the AIDS Clinical Trial Group |
| *Other relevant criteria:* _____ | ☐ | ☐ | ☐ | |
| **WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW** | | | | |
| *Are these data regularly collected?* | ☐ | ☐ | ☒ | Unclear |
| *Are these data regularly collected at and/or below a national level?* | ☐ | ☐ | ☒ | Unclear |
| *Are these data collected manually or electronically?* | ☐ | ☐ | ☐ | Manually |
| **RESEARCH REPORTS** | | | | |
| *Has this research been published in a juried journal?* | ☒ | ☐ | ☐ | *AIDS* |
| *Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?* | ☐ | ☐ | ☐ | Existing data |

# Hepatitis C virus/HIV coinfection and responses to initial antiretroviral treatment

Lei Hua[a], Janet W. Andersen[a], Eric S. Daar[b], Marshall J. Glesby[c], Kimberly Hollabaugh[a] and Camlin Tierney[a]

**Objective:** To explore the relationship between hepatitis C virus (HCV)/HIV coinfection and responses to initial antiretroviral treatment (ART).

**Methods:** Four AIDS Clinical Trials Group HIV treatment studies' data were combined to compare initial ART responses between HCV/HIV-coinfected and HIV-monoinfected patients as evaluated by virologic failure, $CD4^+$ cell measures, occurrence of AIDS/death and grade 3/4 safety events, using Kaplan–Meier estimates and proportional hazard, regression and mixed effects models, adjusting for baseline covariates.

**Results:** Of the 3041 included participants, 81% were men, 19% had prior history of AIDS, the median (25th, 75th percentile) baseline HIV RNA was 4.72 (4.38–5.18) $\log_{10}$ copies/ml, and the median (25th, 75th percentile) baseline $CD4^+$ cell count was 216.0 (76.5–327.0) cells/μl. The 279 HCV/HIV-coinfected individuals were older (44 vs. 37 years), more likely to be black non-Hispanic (47 vs. 36%), and previous/current intravenous drug user (52 vs. 5%) than the 2762 HIV-monoinfected patients (all $P$ values $<0.001$). HCV/HIV coinfection was associated with earlier virologic failure, hazard ratio (95% confidence interval): 1.43 (1.07–1.91); smaller mean $CD4^+$ cell increase and $CD4^+$% increase [−33.8 (−52.2 to −15.4) cells/μl and −1.16% (−1.43 to −0.89%), respectively] over a median of 132 weeks of follow-up; earlier occurrence of grade 3/4 safety event, hazard ratio 1.51 (1.26–1.81); and increased AIDS/mortality, hazard ratio 2.10 (1.31–3.37). Treatment effects comparing antiretroviral regimens were not significantly different by HCV/HIV coinfection status.

**Conclusion:** HCV/HIV coinfection is associated with attenuated response to ART. Results support earlier initiation of HIV therapy and increased monitoring of those initiating ART with HCV/HIV coinfection.



*AIDS* 2013, **27**:2725–2734

**Keywords: antiretroviral treatment, $CD4^+$ cell responses, early virologic failure, hepatitis C virus/HIV coinfection, treatment naive**

## Introduction

Approximately 30% of HIV-1-infected individuals in the United States are coinfected with hepatitis C virus (HCV) [1,2]. HCV/HIV is also causing health burden worldwide [3,4]. Despite extensive research and subsequently better understanding of the negative effects of HIV infection on HCV replication, persistence, and liver fibrogenesis [5–8], whether HCV is associated with HIV progression continues to be debated. Natural history studies show that, prior to antiretroviral treatment (ART) initiation, HCV/HIV-coinfected patients have similar HIV disease progression compared with HIV-monoinfected patients [2,9,10]. However, inconsistent results have been reported for $CD4^+$ cell and HIV virologic responses to ART as well as HIV progression and mortality. Whereas some studies have shown that HCV coinfection is associated with either smaller $CD4^+$ cell increases after initiation of ART [11–16] or a delayed $CD4^+$ cell response [17], other studies report early detected differences in

[a]Harvard School of Public Health, Boston, Massachusetts, [b]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, and [c]Weill Cornell Medical College, New York, New York, USA.

Correspondence to Lei Hua, PhD, Harvard School of Public Health, 651 Huntington Avenue, Boston, MA 02115, USA.

Tel: +1 617 432 2526; fax: +1 617 432 3163; e-mail: lhua@sdac.harvard.edu

Received: 27 March 2013; revised: 15 June 2013; accepted: 24 June 2013.

DOI:10.1097/01.aids.0000432470.46379.dd

$CD4^+$ cell response wane over time [4,18]. Many studies have not found such an association [3,19–25]. Most of the aforementioned studies did not report on or find any association between HCV/HIV coinfection and patients' HIV-1 virologic responses [12,13,26]. In a recent meta-analysis, HCV/HIV coinfection was not found to be related to AIDS-defining endpoints [15], consistent with some previous studies [27,28], although other studies have shown the opposite [29]. These inconsistent results may be explained by relatively small sample sizes of some cohort studies, the heterogeneous populations studied, the limited baseline information collected, and the different ART regimens studied, including many regimens that are no longer in use.

This article reports on analyses combining data from four randomized studies of initial antiretroviral regimens in HIV-1-infected treatment-naive individuals that were conducted in the United States by the AIDS Clinical Trial Group (ACTG). The aims of this cross-study analysis were to evaluate the association of HCV/HIV coinfection with patients' responses to ART initiation from different perspectives, including virologic responses, immunologic responses, safety concerns and clinical outcomes, and to assess whether HCV/HIV coinfection modifies ART treatment effect when comparing specific regimens.

## Methods

### Study design

Randomized treatment arms, sample sizes, and extent of follow-up of the four included studies, ACTG A5073 [30,31], A5095 [32], A5142 [33], and A5202 [34–36], are detailed in cited published papers and summarized in Table 1. These studies were approved by site institutional review boards; participants provided written informed consent.

In the analyses, data from two treatment arms were excluded because of their limited applicability: in A5073, one arm received directly observed therapy; in A5095, the triple nucleoside reverse transcriptase inhibitor (NRTI) arm was terminated early because of its inferiority to efavirenz (EFV)-containing arms [32]. Participants were followed by study-specified schedules, typically at 12-week intervals, which were independent of whether the participants were on their initially assigned regimen. Analyses were restricted to participants with at least one follow-up HIV-1 RNA measurement. Race/ethnicity is a potential confounder for the association between HCV/HIV coinfection and participants' responses to ART. Because of small sample sizes, participants with race/ethnicity other than white non-Hispanic, black non-Hispanic, or Hispanic were excluded from analyses.

### Liver-related measurements

All four studies required HCV serology as well as hepatitis B virus (HBV) test results within 1 year prior to study entry, except for participants enrolled into A5095 under protocol version 1.0. As HCV RNA was not uniformly available, those with positive HCV antibody results between 1 year prior to and 4 weeks after study entry were assumed to have chronic HCV infection prior to ART initiation. Patients with a first HCV serology result after 4 weeks after study entry, mainly from A5095, were

**Table 1. Summary of the antiretroviral treatment-naive studies included.**

| | ART regimens | | Sample size (% of total) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Parent study | NRTI | Protease inhibitor or NNRTI | By arm | Total | HCV/HIV | HIV | Missing | Follow-up (person-year) |
| A5073 | FTC + d4T XR or TDF[a] | LPV/r b.i.d. | 159 | 402 | 52 (12.9%) | 344 (85.6%) | 6 (1.5%) | 260 |
| | FTC + d4T XR or TDF[a] | LPV/r q.d. | 161 | | | | | |
| | FTC + d4T XR or TDF[a,b] | LPV/r q.d. | 82 | | | | | |
| A5095[c] | ABC/3TC/ZDV | EFV | 383 | 1147 | 55 (4.8%) | 415 (36.2) | 677 (59.0%) | 694 |
| | ABC/3TC/ZDV[d] | | 382 | | | | | |
| | 3TC /ZDV | EFV | 382 | | | | | |
| A5142 | | LPV/r b.i.d. + EFV | 250 | 753 | 84 (11.2%) | 649 (86.2%) | 20 (2.7%) | 1471 |
| | 3TC + ZDV or d4T XR or TDF[a] | LPV/r b.i.d. | 253 | | | | | |
| | 3TC + ZDV or d4T XR or TDF[a] | EFV | 250 | | | | | |
| A5202 | FTC/TDF | EFV | 464 | 1857 | 134 (7.2%) | 1705 (91.8%) | 18 (1.0%) | 4566 |
| | FTC/TDF | ATV/r | 465 | | | | | |
| | ABC/3TC | EFV | 465 | | | | | |
| | ABC/3TC | ATV/r | 463 | | | | | |

3TC, lamivudine; ABC, abacavir; ART, antiretroviral treatment; ATV/r, atazanavir/ritonavir; b.i.d., twice a day; d4T XR, stavudine-extended release; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; q.d., once a day; TDF, tenofovir disoproxil fumerate; ZDV, zidovudine.
[a]Nonrandomized NRTI regimens; all studies were stratified by RNA: <100 000 vs. ≥100 000 copies/ml.
[b]Direct observing treatment arm, excluded from the analysis.
[c]A5095 protocol version 1.0 did not require hepatitis C virus (HCV) antibody testing at study entry (was collected later).
[d]Terminated early by the study DSMB due to its inferiority for virologic outcome, excluded from the analysis.

excluded from the primary analyses but included in sensitivity analyses. Patients with positive HBV surface antigen were defined as having chronic HBV before initiation of ART. All four studies collected baseline aspartate aminotransferase (AST) and alanine transaminase (ALT) at entry. Entry criteria for the studies required that AST and ALT be five times or less than the upper limit of normal (ULN) and total bilirubin 2.5 or less than ULN (except A5095). In the absence of liver biopsy or transient elastometry results, baseline AST/Platelet Ratio Index (APRI) [37] and FIB-4 [38] were calculated to reflect the severity of the liver disease before ART initiation across studies, acknowledging that these surrogate biomarkers may not be as accurate as biopsy or transient elastometry results. All four studies specified any condition, including active drug/alcohol use, which at the discretion of the local investigator might compromise patients' ability to participate in the study as study entry exclusion criteria.

### Outcomes

Time-related endpoints were calculated from randomization. Virologic response for this analysis was measured by time to virologic failure, defined as two consecutive plasma HIV-1 RNA either at least 1000 copies/ml at or after week 16 and before week 24, or at least 200 copies/ml at or after week 24. Patients who discontinued the study at week 4 with HIV-1 RNA more than 50 copies/ml and less than 0.5 $\log_{10}$ copies/ml lower than baseline and those discontinued at week 8 with HIV-1 RNA more than 50 copies/ml and less than 1 $\log_{10}$ copies/ml lower than baseline were considered having virologic failures at weeks 4 and 8, respectively. Immunologic responses were analyzed as the average $CD4^+$ cell count, $CD4^+$%, and their changes from baseline. Clinical outcomes were times to first of new on-study AIDS-defining event or death regardless of cause, and to death alone. The safety-related endpoint was time to first grade 3/4 signs/symptoms or laboratory abnormality [toxicity rating scale developed by the Division of AIDS (version 1.0, December 2004)] that was at least one grade higher than at baseline. Adherence to the prior 7 days of ART was collected via self-report at 24-week intervals throughout the four studies. The adherence scores at each measurement time point for patients still in follow-up were grouped into four levels: 100% adherent; less than 100% adherent; not on medication; and unknown.

### Statistical analysis

Baseline demographics and clinical characteristics were compared between HCV/HIV-coinfected and HIV-monoinfected patients using Wilcoxon rank-sum test for continuous variables rather than normal distribution assumption-based parametric analysis to account for skewed data and $\chi^2$ test for categorical variables. Baseline covariates, including age, sex, race/ethnicity, HIV-1 RNA (grouped *a priori* into $<10\,000$, $10\,000 - <100\,000$, $100\,000 - <200\,000$, and $\geq 200\,000$ copies/ml), $CD4^+$ cell counts ($<50$, $50 - <200$, $200 - <350$, $350 - <500$ and $\geq 500$ cells/$\mu$l), prior AIDS history, previous or current intravenous drug user (IVDU), and chronic HBV infection, were controlled for in regression analyses regardless of their significance between groups at baseline. Time-to-event outcomes were compared based on log-rank tests stratified by treatment arms; event time percentiles were estimated by the Kaplan–Meier method. Cox proportional hazard models, stratified by treatment arms, were fit with and without adjusting for baseline covariates. Antiretroviral regimens were grouped according to their dual NRTIs and the third drug in the regimen, that is, protease inhibitors (all ritonavir boosted) vs. the non-NRTI EFV use. Whether HCV/HIV coinfection modifies the ART effect when comparing specific regimens, hereafter referred to as the 'treatment modification effect', was evaluated in Cox proportional hazard models stratified by study by testing for an interaction between antiretroviral regimen groups and HCV status. $CD4^+$ cell measurements in every 24-week interval were compared between groups using linear regressions controlling for baseline covariates. Repeated $CD4^+$ cell measurements during follow-up were modeled using linear mixed effects models with a random subject effect. In post-hoc regression analyses, interactions of HCV/HIV coinfection status with baseline HIV-1 RNA on virologic response and with baseline $CD4^+$ cell counts on $CD4^+$ cell responses were evaluated adjusting for other baseline covariates. Adherence (100% vs. <100%) of those who were still on ART was compared between HCV/HIV-coinfected and HIV-monoinfected patients using logistic regressions at weeks 24, 48, 72, and 96. Repeated measurements of adherence during follow-up were modeled using generalized estimating equations with a compound symmetry covariance structure. Additional analyses on patients' responses to ART controlled for the most recent adherence (with four categories) in addition to baseline covariates mentioned above. All comparisons were conducted with a two-sided significance level of 0.05, without adjusting for multiplicity.

## Results

### Baseline characteristics

Of 3041 white, black, or Hispanic patients with available baseline HCV serology, the majority were from A5202 and A5142 (57 and 23%, respectively); 279 (9.2%) were HCV-seropositive and assumed to be coinfected (Table 2). Compared with HIV-monoinfected, HCV/HIV-coinfected patients were significantly older (median age 44 vs. 37 years), more likely to be black non-Hispanic (47 vs. 36%), and prior/current IVDU (52 vs. 5%; all $P$ values $<0.001$). HCV/HIV coinfection was also associated with significantly higher AST, ALT, FIB-4,

**Table 2. Baseline characteristics of patients by hepatitis C virus coinfection status.**

| Characteristics | HIV ($N=2762$) | HCV/HIV ($N=279$) | Total ($N=3041$) | $P$ |
|---|---|---|---|---|
| ACTG study | | | | |
| A5073 | 258 (9%) | 38 (14%) | 296 (10%) | <0.001** |
| A5095 | 256 (9%) | 40 (14%) | 296 (10%) | |
| A5142 | 623 (23%) | 81 (29%) | 704 (23%) | |
| A5202 | 1625 (59%) | 120 (43%) | 1745 (57%) | |
| Age (years) | | | | |
| Median (Q1, Q3) | 37 (30, 44) | 44 (39, 49) | 38 (31, 45) | <0.001* |
| Race/ethnicity[a] | | | | |
| White non-Hispanic | 1107 (40%) | 90 (32%) | 1197 (39%) | <0.001** |
| Black non-Hispanic | 985 (36%) | 132 (47%) | 1117 (37%) | |
| Hispanic | 670 (24%) | 57 (20%) | 727 (24%) | |
| Sex | | | | |
| Male | 2245 (81%) | 227 (81%) | 2472 (81%) | 0.974** |
| Prior history of AIDS | | | | |
| Yes | 523 (19%) | 48 (17%) | 571 (19%) | 0.480** |
| Previous/current intravenous drug use | | | | |
| Yes | 142 (5%) | 144 (52%) | 286 (9%) | <0.001** |
| Baseline $\log_{10}$ RNA (copies/ml) | | | | |
| Median (Q1, Q3) | 4.72 (4.38, 5.20) | 4.74 (4.41, 5.10) | 4.72 (4.38, 5.18) | 0.688* |
| Baseline RNA (copies/ml) | | | | |
| <10 000 | 302 (11%) | 27 (10%) | 329 (11%) | |
| 10 000–<100 000 | 1601 (58%) | 167 (60%) | 1768 (58%) | |
| 100 000–<200 000 | 268 (10%) | 40 (14%) | 308 (10%) | |
| ≥200 000 | 591 (21%) | 45 (16%) | 636 (21%) | |
| Baseline $CD4^+$ cell count (cells/μl) | | | | |
| Median (Q1, Q3)(Q1, Q3) | 217.5 (76.5, 330.0) | 204.5 (76.5, 296.0 | 216.0 (76.5, 327.0) | 0.076* |
| <50 | 556 (20%) | 53 (19%) | 609 (20%) | |
| 50 to <200 | 714 (26%) | 80 (29%) | 794 (26%) | |
| 200 to <350 | 896 (32%) | 107 (38%) | 1003 (33%) | |
| 350 to <500 | 421 (15%) | 28 (10%) | 449 (15%) | |
| ≥500 | 171 (6%) | 11 (4%) | 182 (6%) | |
| AST (U/l) | | | | |
| *N* | 2639 | 254 | 2893 | |
| Median (Q1, Q3) | 29 (23, 39) | 39 (28, 67) | 30 (23, 41) | <0.001* |
| ALT (U/l) | | | | |
| *N* | 2641 | 254 | 2895 | |
| Median (Q1, Q3) | 31 (21, 46) | 39 (27, 64) | 31 (21, 48) | <0.001* |
| FIB-4 | | | | |
| *N* | 2611 | 249 | 2860 | <0.001* |
| Median (Q1, Q3) | 0.89 (0.60, 1.30) | 1.41 (0.92, 2.41) | 0.92 (0.61, 1.37) | |
| No/mild fibrosis (<1.45) | 2087 (80%) | 130 (52%) | 2217 (78%) | |
| Indeterminate (1.45–3.25) | 464 (18%) | 86 (35%) | 550 (19%) | |
| Fibrosis (>3.25) | 60 (2%) | 33 (13%) | 93 (3%) | |
| APRI | | | | |
| *N* | 2613 | 249 | 2862 | <0.001* |
| Median (Q1, Q3) | 0.32 (0.21, 0.49) | 0.45 (0.28, 0.90) | 0.32 (0.21, 0.51) | |
| No/mild fibrosis (<0.42) | 1771 (68%) | 117 (47%) | 1888 (66%) | |
| Indeterminate (0.42–1.5) | 781 (30%) | 106 (43%) | 887 (31%) | |
| Fibrosis (>1.5) | 61 (2%) | 26 (10%) | 87 (3%) | |
| HBsAg | | | | |
| *N* | 2748 | 268 | 3016 | |
| Positive | 86 (3%) | 12 (4%) | 98 (3%) | 0.235** |

AST, aspartate aminotransferase; ALT, alanine transaminase; FIB-4= $\frac{Age(years)\times AST(U/l)}{Platelet(10^9/l)\times ALT^{1/2}(U/l)}$ APRI = $\frac{\text{AST}}{\text{ULN}} \times \frac{100}{\text{Platelet}(\mu l)}$; HBsAg, hepatitis B virus surface antigen.
[a]Analysis was restricted to white, black, and non-Hispanic.
*Wilcoxon test.
**Chi-square test.

and APRI (all $P$ values <0.001). The median (25th, 75th percentile) FIB-4 and APRI scores among coinfected patients were 1.41 (0.92–2.41) and 0.45 (0.28–0.90), respectively, indicating mild-to-moderate liver fibrosis [37,38]. Thirteen percent of HCV/HIV-coinfected patients based on FIB-4, or 10% based on APRI, had high values of noninvasive markers, suggesting severe liver fibrosis.

## Virologic response

HCV/HIV-coinfected patients had significantly earlier time to virologic failure after initiating their ART than HIV-monoinfected patients (log-rank $P$ value <0.001, Fig. 1a), with the estimated time [95% confidence interval (CI)] to when 20% of patients have experienced a HIV virologic failure of 48 (32–72) weeks in HCV/HIV-coinfected compared with 112 (96–136) weeks in

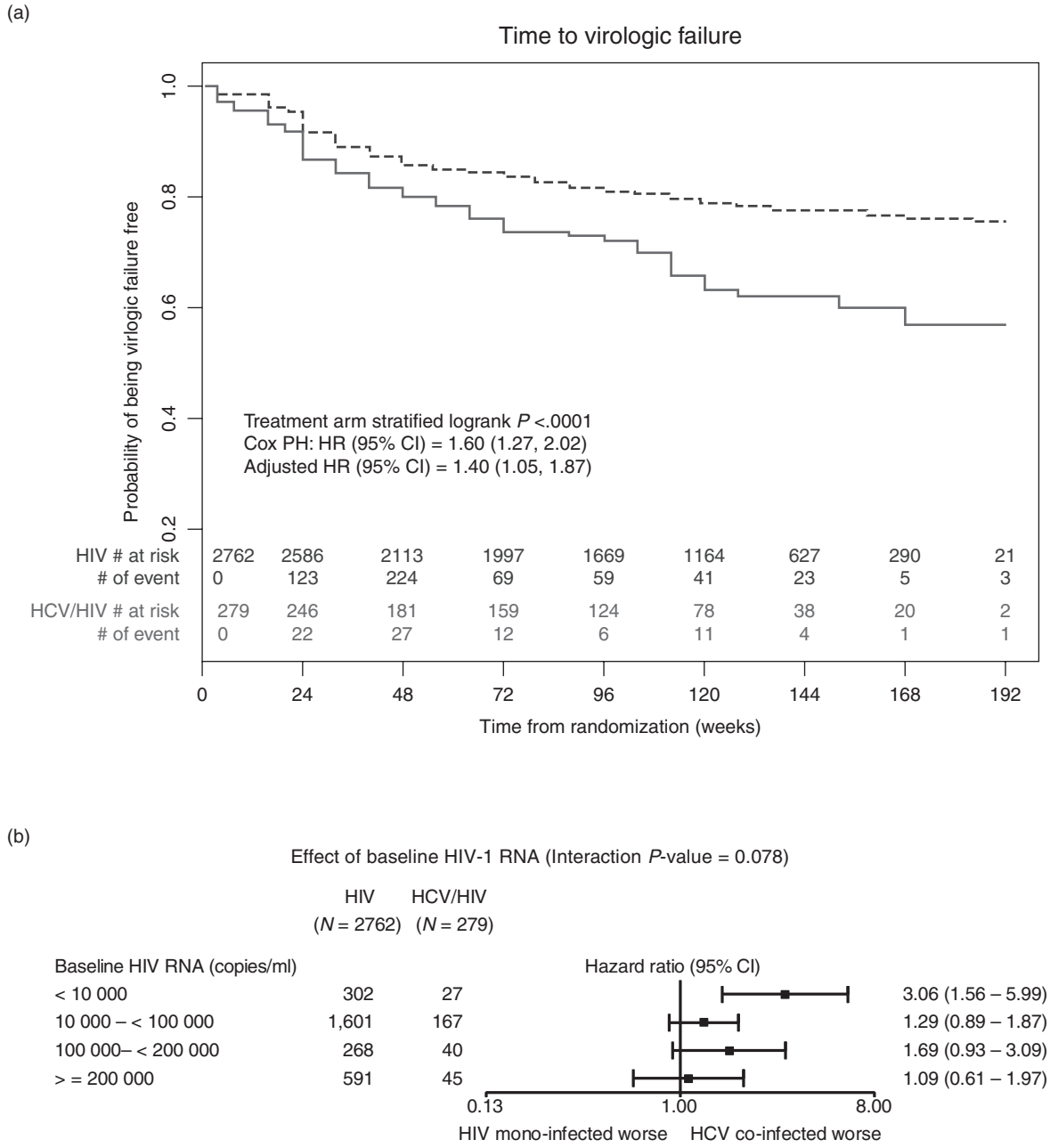


**Fig. 1. Time to virologic failure.** (a) Probability of virologic failure by hepatitis C virus (HCV) status (solid line: HCV/HIV; dotted line: HIV); (b) estimated hazard ratio for virologic failure between HCV/HIV-coinfected and HIV-monoinfected patients by baseline HIV-1 RNA viral load adjusted for baseline covariates.

HIV-monoinfected patients. The hazard ratios (95% CI) of having virologic failure for HCV/HIV-coinfected vs. HIV-monoinfected patients were 1.60 (1.27–2.02) and 1.43 (1.07–1.91) before and after adjusting for baseline covariates, respectively. The association of HCV/HIV coinfection with virologic failure was marginally significantly different by baseline HIV-1 RNA level (interaction $P$ value = 0.078), primarily among the 329 patients (27 coinfected vs. 302 monoinfected) with baseline HIV-1 RNA less than 10 000 copies/ml with a hazard ratio (95% CI) of 3.06 (1.56–5.99). These patients were more likely to be black non-Hispanic, current/history IVDU, and HBV-infected (Supplementary Table 1, http://links.lww.com/QAD/A381). Within groups with higher baseline HIV-1 RNA (≥10 000 copies/ml), the hazard ratio of time to virologic failure between HCV/HIV-coinfected and HIV-monoinfected patients did not individually reach statistical significance, although coinfected patients had consistently higher hazards (all hazard ratio point estimates >1.0, Fig. 1b). There was no significant treatment modification effect by HCV/HIV coinfection status ($P$ value = 0.75 for NRTI groups and 0.66 for the third drug in regimen

groups, Supplementary Table 2, http://links.lww.com/QAD/A381).

## CD4$^+$ cell response

At baseline, HCV/HIV-coinfected patients had on average slightly lower CD4$^+$ cell counts and lower CD4$^+$%, possibly due to advanced liver disease and hypersplenism, but the differences were not statistically significant ($P$ value = 0.14 and 0.44, respectively, Table 3). After ART initiation, HCV/HIV-coinfected patients had lower mean CD4$^+$ cell count and smaller CD4$^+$ cell increase from baseline, as well as lower mean CD4$^+$% and smaller CD4$^+$% increase from baseline than HIV-monoinfected patients at all follow-up weeks (Fig. 2). At week 48, based on the 2666 patients with CD4$^+$ cell data and data on baseline covariates, HCV/HIV-coinfected patients had a lower mean CD4$^+$ cell count of 32.8 (95% CI 9.7–56.9) cells/μl and a smaller increase from baseline of 27.8 (5.9–49.8) cells/μl compared with HIV-monoinfected patients, ($P$ value = 0.005 and 0.013, respectively). Similarly, the HCV/HIV-coinfected patients had a lower mean CD4$^+$% of 1.28 (0.16–2.40, $P$ value = 0.025) and a smaller mean increase in CD4$^+$% from baseline of 0.96 (0.08–1.84, $P$ value = 0.032). The differences were maintained through week 144 after controlling for baseline CD4$^+$ cell counts and other baseline covariates in the regression analyses (Table 3). In follow-up after week 144, the differences between HCV/HIV-coinfected and HIV-monoinfected patients did not reach statistical significance (results not included), but sample sizes were small, especially for the HCV/HIV-coinfected group. Among 3037 patients with baseline CD4$^+$ and at least one CD4$^+$ cell measurement after baseline, the median (25th, 75th percentile) follow-up time was 132 (88–168) weeks. Based on longitudinal modeling of all CD4$^+$ cell measurements during follow-up, HCV/HIV-coinfected patients had, over time, a mean of 39.2 (19.9–58.4) cells/μl lower CD4$^+$ cell count and 33.8 (15.4–52.2) cells/μl smaller CD4$^+$ cell increase from baseline, and a mean of 1.13 (0.82–1.44) lower CD4$^+$% and 1.16 (0.89–1.43) smaller CD4$^+$% increase from baseline than HIV-monoinfected patients (all $P$ values <0.001). Excluding CD4$^+$ cell measurements after patients experienced virologic failure, these differences decreased slightly and some cross-sectional associations were not as significant, in particular for change in CD4$^+$% (Table 3). However, in longitudinal modeling, HCV/HIV coinfection remained significantly associated with lower mean CD4$^+$ cell count and smaller CD4$^+$ cell count increase from baseline, as well as lower CD4$^+$% and smaller CD4$^+$% increase from baseline (all $P$ values <0.001, Table 3). The association of HCV/HIV coinfection with the blunted CD4$^+$ cell response was not significantly different by baseline CD4$^+$ cell levels (categorized, $P$ values >0.34 at different weeks and longitudinally). There was no evidence that HCV/HIV coinfection modified the treatment effect on CD4$^+$ cell responses when comparing specific ART regimens

**Table 3. Regression results of mean differences in CD4$^+$ cell count, CD4$^+$ cell change, CD4$^+$%, and CD4$^+$% change between HCV-coinfected vs. uninfected patients, adjusting for baseline covariates.**

| HCV/HIV vs. HIV | CD4$^+$ (cells/μl) | | CD4$^+$ cell change (cells/μl) | | CD4$^+$% | | CD4$^+$% change | |
|---|---|---|---|---|---|---|---|---|
| Week | Mean difference (95% CI) | $P$ value | Mean difference (95% CI) | $P$ value | Mean difference (95% CI) | $P$ value | Mean difference (95%) | $P$ value |
| All patients | | | | | | | | |
| Baseline | −6.46 (−15.0, 2.1) | 0.140 | – | – | −0.31 (−1.1, 0.5) | 0.443 | – | – |
| 24 | −29.8 (−48.7, −11.0) | 0.002 | −24.9 (−42.2, −7.5) | 0.005 | −1.06 (−2.11, −0.01) | 0.047 | −0.87 (−1.63, −0.12) | 0.024 |
| 48 | −32.8 (−56.9, −9.7) | 0.005 | −27.8 (−49.8, −5.9) | 0.013 | −1.28 (−2.40, −0.16) | 0.025 | −0.96 (−1.84, −0.08) | 0.032 |
| 72 | −46.8 (−76.9, −16.8) | 0.002 | −40.0 (−68.8, −11.2) | 0.007 | −1.46 (−2.73, −0.19) | 0.024 | −1.39 (−2.44, −0.34) | 0.009 |
| 96 | −35.6 (−69.7, −1.43) | 0.041 | −30.2 (−62.9, 2.6) | 0.071 | −1.35 (−2.76, 0.06) | 0.061 | −1.39 (−2.59, −0.2) | 0.022 |
| 120 | −78.2 (−117.3, −39.1) | <0.001 | −70.6 (−108.3, −32.8) | <0.001 | −2.51 (−4.10, −0.92) | 0.002 | −1.96 (−3.39, −0.54) | 0.007 |
| 144 | −62.5 (−110.0, −14.9) | 0.010 | −60.0 (−107.3, −12.7) | 0.013 | −2.89 (−4.73, −1.05) | 0.002 | −2.30 (−4.01, −0.60) | 0.008 |
| Longitudinal | −39.2 (−58.4, −19.9) | <0.001 | −33.8 (−52.2, −15.4) | <0.001 | −1.13 (−1.44, −0.82) | <0.001 | −1.16 (−1.43, −0.89) | <.001 |
| Excluding observations after patient experienced virologic failure | | | | | | | | |
| Baseline | −6.5 (−15.0, 2.1) | 0.140 | – | – | −0.31 (−1.1, 0.48) | 0.443 | – | – |
| 24 | −24.1 (−43.7, −4.5) | 0.016 | −21.2 (−39.0, −3.4) | 0.020 | −0.71 (−1.79, 0.38) | 0.200 | −0.56 (−1.34, 0.21) | 0.153 |
| 48 | −21.8 (−46.0, 2.4) | 0.077 | −19.1 (−42.0, 3.8) | 0.102 | −1.00 (−2.17, 0.17) | 0.094 | −0.67 (−1.58, 0.24) | 0.148 |
| 72 | −44.1 (−75.6, −12.6) | 0.006 | −38.2 (−68.1, −8.2) | 0.013 | −1.10 (−2.42, 0.23) | 0.104 | −0.69 (−1.76, 0.37) | 0.203 |
| 96 | −40.5 (−76.4, −4.6) | 0.027 | −35.2 (−69.4, −0.9) | 0.044 | −1.67 (−3.14, −0.20) | 0.026 | −1.21 (−2.42, 0.00) | 0.049 |
| 120 | −82.0 (−125.0, −39.1) | <0.001 | −74.0 (−115.3, −32.7) | <0.001 | −2.57 (−4.26, −0.87) | 0.003 | −1.28 (−2.79, 0.23) | 0.100 |
| 144 | −73.6 (−124.5, −22.7) | 0.005 | −72.6 (−123.0, −22.1) | 0.005 | −3.25 (−5.21, −1.28) | 0.001 | −2.30 (−4.07, −0.53) | 0.011 |
| Longitudinal | −30.6 (−47.5, −13.7) | <0.001 | −25.3 (−39.3, −11.3) | <0.001 | −1.03 (−1.34, −0.72) | <0.001 | −0.83 (−1.08, −0.57) | <0.001 |

CI, confidence interval; HCV, hepatitis C virus.

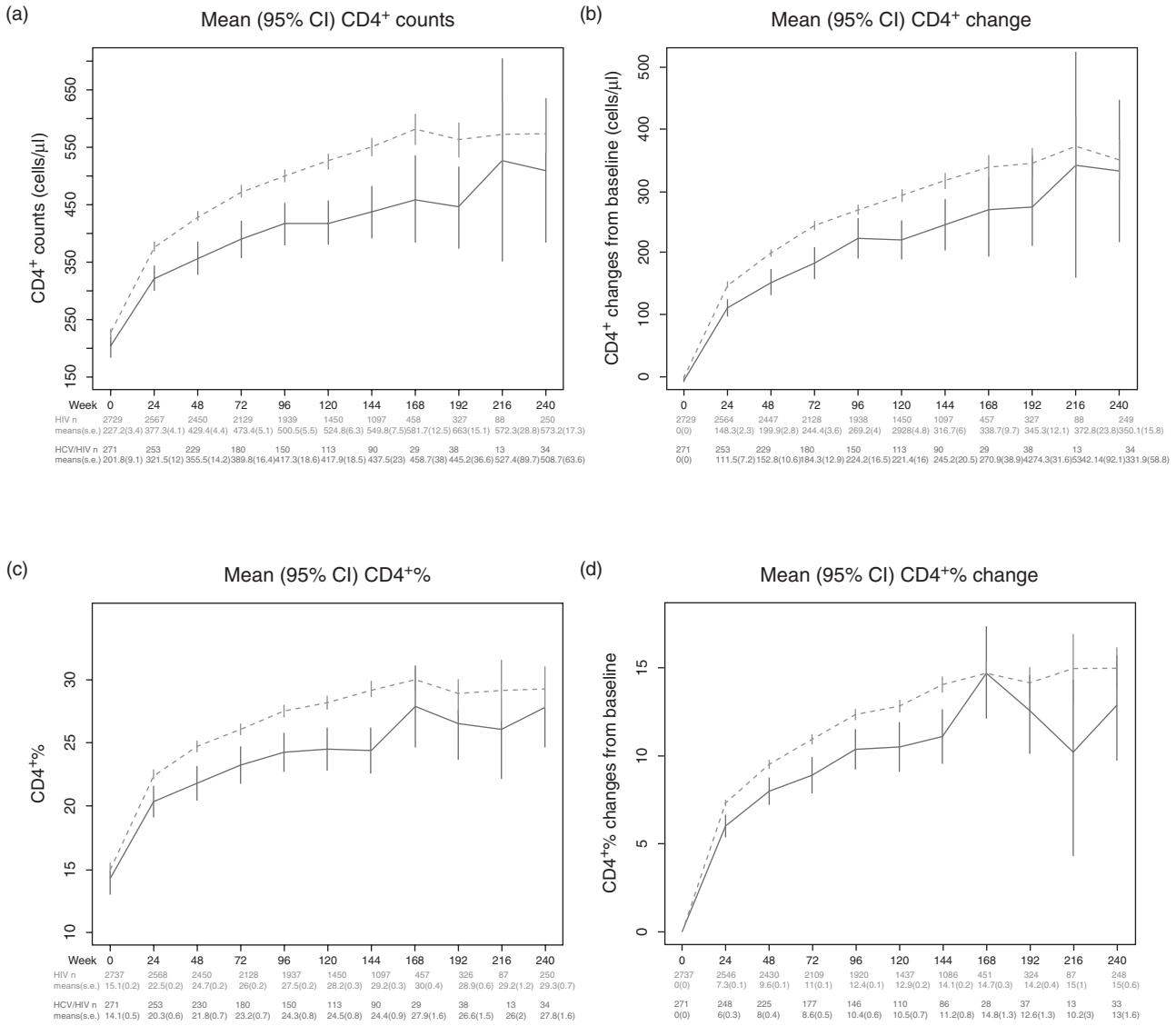


**Fig. 2. CD4$^+$ cell response.** Estimated mean (95% confidence interval, CI) of (a) CD4$^+$ cell counts; (b) CD4$^+$ cell increase from baseline; (c) CD4$^+$%; (d) CD4$^+$% increase from baseline after initiation of antiretroviral treatment (ART) at different scheduled weeks by hepatitis C virus (HCV) status (solid line: HCV/HIV; dotted line: HIV).

($P$ value = 0.20 for NRTI groups and 0.88 for the third drug in regimen groups).

## AIDS-defining event or death

Eleven percent of HCV/HIV-coinfected patients developed an AIDS-defining event or died while in study follow-up, compared with 5% in HIV-monoinfected patients ($P$ value < 0.001, Supplementary Table 3, http://links.lww.com/QAD/A381), with a hazard ratio (95% CI) of 2.11 (1.42–3.13) and 2.10 (1.31–3.37) before and after controlling for baseline covariates (Supplementary Figure 1A, http://links.lww.com/QAD/A381). The increased hazard was primarily driven by mortality (Supplementary Figure 1B, http://links.lww.com/QAD/A381), with a hazard ratio (95% CI) of mortality at 5.45 (3.01–9.85) and 5.14 (2.48, 10.67) before and after adjusting for baseline covariates. HCV/HIV-coinfected patients had more accidents, suicides, or substance abuse-related deaths compared with HIV-monoinfected patients (41.2 vs. 20.6%, Supplementary Table 4, http://links.lww.com/QAD/A381).

## Occurrence of grade 3/4 safety events

Of the 279 HCV/HIV-coinfected patients, 65% experienced at least one grade 3/4 safety event compared with 53% in HIV-monoinfected group ($P$ value <0.001), largely due to elevated AST or ALT (14 vs. 3%, $P$ value <0.001, Supplementary Table 5, http://links.lww.com/QAD/A381). The median time to experiencing a grade 3/4 safety event was 33 (24–50) weeks in HCV/HIV-coinfected compared with 97 (86–112) weeks in HIV-monoinfected patients (Supplementary

Figure 2, http://links.lww.com/QAD/A381). The hazard ratios (95% CIs) were 1.57 (1.34–1.84) and 1.51 (1.26–1.81) before and after adjusting for baseline covariates, respectively. Excluding AST and ALT, the occurrence of other grade 3/4 safety events was not significantly different between HCV/HIV-coinfected vs. HIV-monoinfected patients ($P$ value = 0.37). However, HCV/HIV-coinfected patients experienced non-ALT/AST grade 3/4 safety events earlier than HCV-uninfected patients (PH model $P$ value = 0.016 and 0.068 before and after adjusting for baseline covariates, Supplementary Table 5, http://links.lww.com/QAD/A381 and Fig. 2). There was no significant HCV treatment modification effect for the occurrence of grade 3/4 safety events, both excluding AST/ALT: $P$ value = 0.14 for NRTI groups and 0.48 for the third drug in regimen groups; and considering AST/ALT alone: $P$ value = 0.80 for NRTI groups and 0.83 for the third drug in regimen groups (Supplementary Table 6, http://links.lww.com/QAD/A381). The earlier time to grade 3/4 safety event in the atazanavir/ritonavir-containing regimens as compared with EFV-containing regimens was primarily due to expected elevated total bilirubin (Supplementary Table 6, http://links.lww.com/QAD/A381). Excluding total bilirubin, this difference was no longer statistically significant.

### Adherence

Supplementary Table 7, (http://links.lww.com/QAD/A381) summarizes self-reported adherence (100% adherent vs. <100% adherent) among those who were still on ART at weeks 24, 48, 72, and 96, by HCV/HIV coinfection status. At week 24 among those on ART, 91% of HCV/HIV-coinfected patients had 100% adherence compared with 87% among HIV-monoinfected patients. Controlling for baseline covariates, HCV/HIV coinfection was associated with increased odds of self-reported perfect adherence with an odds ratio (95% CI) of 1.73 (1.02–2.93), $P$ value = 0.012. At subsequent follow-up weeks, HCV/HIV-coinfected patients were less likely to adhere perfectly, although such adherence remained high. Adjusting for baseline covariates, the difference in adherence between HCV/HIV-coinfected and HIV-monoinfected patients was not significant at weeks 48 ($P$ = 0.73), 72 ($P$ = 0.35), 96 ($P$ = 0.48), or longitudinally ($P$ = 0.09). The observed significant differences between HCV/HIV-coinfected and HIV-monoinfected patients in time to HIV-1 virologic failure, patients' $CD4^+$ cell response, time to AIDS-defining endpoint or death, time to death only, and time to grade 3/4 safety events were retained after controlling for the most recent adherence score in addition to baseline covariates (all $P$ values $\leq$0.009).

## Discussion

The reported analyses combined data from four ACTG randomized ART trials with relatively homogeneous populations. The randomization, rigorous study monitoring, and extensive and similar data collection from these clinical trials (Supplementary Table 8, http://links.lww.com/QAD/A381) provided a unique opportunity to systematically examine the association of HCV/HIV coinfection with response to ART. HCV/HIV coinfection before ART initiation was significantly associated with earlier time to virologic failure and attenuated $CD4^+$ cell responses including both blunted $CD4^+$ cell count recovery and smaller $CD4^+$% increase through 144 weeks. The association of HCV/HIV coinfection with attenuated $CD4^+$ cell responses was retained when restricting analysis to data from patients while not failing virologically. This may be clinically relevant as HCV/HIV coinfection was also significantly associated with accelerated HIV disease progression with a higher risk of developing a new AIDS-related diagnosis or death.

Our results from data on randomized trials were consistent with results from the large observational Swiss HIV cohort study [11] as well as with other smaller cohort studies [12,13]. The observed persistently attenuated $CD4^+$ T-cell responses could be related to worse adherence and higher rates of virologic failure, but this is unlikely as the association remained strong even when limiting analysis to those not failing virologically. Alternative mechanisms may be related to the chronic immune activation reflected by elevated CD38/HLA-DR T cells in HCV/HIV-coinfected patients [39–41]. Regardless of the mechanism, these findings have important implications in the clinic. Both the International Antiviral Society-USA Panel [42] and the Department of Health and Human Services' HIV treatment guidelines [43] suggest that HCV infection might influence the decision as to when ART should be started, which is primarily justified by the fact that it might influence HCV disease progression. The results from this study further demonstrate that HCV/HIV coinfection is associated with increased risk of clinical progression and an attenuated $CD4^+$ cell response to ART, both of which would also argue for earlier initiation of therapy in this patient population based upon parameters relevant to HIV disease progression.

The better adherence at week 24 among HCV/HIV-coinfected patients may reflect a selection bias, that is, HCV/HIV-coinfected patients, considered having a high risk of poorer adherence due to substance abuse, for example, may have been scrutinized more closely prior to enrollment. Consequently, HCV/HIV-coinfected patients enrolled into the randomized trials may have been more likely to adhere to their ART than those who were not enrolled. The exclusion criteria of select conditions, including active drug/alcohol usage that might affect patients' adherence, may also contribute to such a selection bias.

The analyses took advantage of the randomization of the ART regimens and assessed the possible treatment

modification effects of ART by HCV/HIV coinfection status. As there was no significant evidence that HCV/HIV coinfection was a treatment effect modifier when comparing antiretroviral regimens, our results do not indicate that HCV/HIV coinfection would need to be considered when choosing among the regimens included in the studies analyzed. However, the relatively small sample size in the HCV/HIV-coinfected group resulted in wide CIs for outcome measures, in particular in subgroup analyses. Consequently, important modification effects could be missed.

Our analyses have several limitations. First, HCV/HIV coinfection status was determined by the serology result alone without confirmation by detection of HCV RNA and due to the lack of liver biopsy or transient elastometry results, severity of liver disease was limited to APRI and FIB-4 measurements. Patients with positive HCV serology results may have included both patients with cleared HCV and chronic HCV infections, although literature indicates that over 90% of HCV infections progress to chronic infection in HIV-infected patients [19]. Nevertheless, our results may be conservative because true associations between HCV coinfection and reduced ART responses might have been diluted by the inclusion of those that had cleared HCV infection self-clearers in the HCV-coinfected group [2]. The opposite may also happen, in which HCV/HIV-coinfected patients with low $CD4^+$ cell counts could have false-negative serology result. Misclassification of these patients as HIV-monoinfected would also dilute the detected difference between HCV/HIV-coinfected and HIV-monoinfected patients. The impact of using surrogate markers for severity of liver disease on the outcome of this study is less clear but certainly would not substantially alter the primary findings of the study. Second, in our primary analyses, only data from patients with HCV infection status assessed between 1 year prior to and within 4 weeks after randomization at study entry were included. Sensitivity analyses of time to virologic failure and $CD4^+$ cell responses including data from additional 411 patients with HCV serology results obtained after 4 weeks after study entry, mainly from A5095 in which serology was not carried out under protocol version 1.0, showed consistent results (data not shown). Third, explicit laboratory-based inclusion criteria in all four trials could have resulted in exclusion of patients with significant transaminase elevation or hyperbilirubinemia, to whom the current result may not be applicable. The trial inclusion criteria may also explain the smaller proportion of HCV/HIV coinfection (9.2%) than the prevalence previously reported [1]. Finally, among the 3041 patients, 17 patients were reported to have received pegylated interferon and ribavirin on study, although use of these drugs was not specifically targeted to be collected by the protocols. Excluding these patients from the analysis did not change the results (data not shown). With the rapidly evolving field of direct antiviral agents for treatment of chronic HCV infection, the association of HCV/HIV coinfection with HIV disease progression also needs to be evaluated in the context of HCV treatment.

This study provides unique data from well characterized patients on the relationship between HCV/HIV coinfection and response to ART. The earlier time to virologic failure results argue for close monitoring of ART treatment effect and HIV disease progression in this population and the blunted immunologic responses support an earlier initiation of ART in HCV/HIV-coinfected patients to optimize their on-treatment $CD4^+$ cell counts. Further research is needed to determine whether early treatment of HCV in HCV/HIV-coinfected patients would be associated with improved responses to ART and clinical outcomes.

## Acknowledgements

The project described was supported by National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) funding to the AIDS Clinical Trial Group (ACTG) including U01AI068636 and 5 UM1 AI068634–07. M.J.G. was also supported by K24 AI078884. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIAID or the NIH.

### Conflicts of interest

L.H. is currently a full time employee of Vertex Pharmaceuticals Inc. E.D. received research support from Abbott, Merck, Gilead, ViiV, Pfizer and is a consultant/advisor for Gilead, Bristol Myers Squibb, Janssen, ViiV, and Merck. C.T. is a paid member of a Data Monitoring Committee for a Hepatitis C drug for Tibotec.

*The present work has been presented at CROI 2012, Poster #779.*

## References

1. Sherman KE, Rouster SD, Chung RT, Rajicic N. **Hepatitis C virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US Adult AIDS Clinical Trials Group.** *Clin Infect Dis* 2002; **34**:831–837.
2. Potter M, Odueyungbo A, Yang H, Saeed S, Klein MB. **Impact of hepatitis C viral replication on $CD4^+$ T-lymphocyte progression in HIV-HCV coinfection before and after antiretroviral therapy.** *AIDS* 2010; **24**:1857–1865.
3. Agbaji O, Thio CL, Meloni S, Graham C, Muazu M, Nimzing L, *et al.* **Impact of hepatitis C virus on HIV response to antiretroviral therapy in Nigeria.** *J Acquir Immune Defic Syndr* 2013; **62**:204–207.
4. Motta D, Brianese N, Foca E, Nasta P, Maggiolo F, Fabbiani M, *et al.* **Virological effectiveness and $CD4^+$ T-cell increase over early and late courses in HIV infected patients on antiretroviral therapy: focus on HCV and anchor class received.** *AIDS Res Ther* 2012; **9**:18.

5. Pineda J, Romero-Gómez M, Díaz-García F, Girón-González J, Montero J, Torre-Cisneros J, *et al*. **HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis.** *Hepatology* 2005; **41**:779–789.
6. Thein H, 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.
7. Thein H, Yi Q, Dore GJ, Krahn MD. **Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression.** *Hepatology* 2008; **48**:418–431.
8. Sulkowski MS, Mehta SH, Torbenson MS, Higgins Y, Brinkley SC, de Oca RM, *et al*. **Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults.** *AIDS* 2007; **21**:2209–2216.
9. Rossi SJ, Volberding PA, Wright TL. **Does hepatitis C virus infection increase the risk of HIV disease progression?** *JAMA* 2002; **288**:241–243.
10. Operskalski EA, Kovacs A. **HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies.** *Curr HIV/AIDS Rep* 2011; **8**:12–22.
11. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, *et al*. **Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study.** *Lancet* 2000; **356**:1800–1805.
12. Luca AD, Bugarini R, Lepri AC, Puoti M, Girardi E, Antinori A, *et al*. **Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects.** *Arch Intern Med* 2002; **162**:2125–2132.
13. Lincoln D, Petoumenos K, Dore G. **HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy.** *HIV Med* 2003; **4**:241–249.
14. Seminari E, Tinelli C, Ravasi G, Ripamonti D, Ladisa N, Mario N, *et al*. **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.
15. Chen T, 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.
16. 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.
17. Law WP, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, Lange JM, *et al*. **Impact of viral hepatitis co-infection on response to antiretroviral therapy and HIV disease progression in the HIV-NAT cohort.** *AIDS* 2004; **18**:1169–1177.
18. Kaufmann GR, Perrin L, Pantaleo G, Opravil M, Furrer H, Telenti A, *et al*. **CD4$^+$ T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study.** *Arch Intern Med* 2003; **163**:2187–2195.
19. Matthews GV, Dore GJ. **HIV and hepatitis C coinfection.** *J Gastroenterol Hepatol* 2008; **23**:1000–1008.
20. Sulkowski MS, Moore rD, Meehta SH, Chaisson RE, Thomas DL. **Hepatitis C and progression of HIV disease.** *JAMA* 2002; **288**:199–206.
21. Stebbing J, Waters L, Mandalia S, Bower M, Nelson M, Gazzard B. **Hepatitis C virus infection in HIV type 1-infected individuals does not accelerate a decrease in the CD4$^+$ cell count but does increase the likelihood of AIDS-defining events.** *Clin Infect Dis* 2005; **41**:906–911.
22. Weimer LE, Fragola V, Floridia M, Guaraldi G, Ladisa N, Francisci D, *et al*. **Response to raltegravir-based salvage therapy in HIV-infected patients with hepatitis C virus or hepatitis B virus coinfection.** *J Antimicrob Chemother* 2013; **68**:193–199.
23. Rockstroh J, Teppler H, Zhao J, Sklar P, Harvey C, Strohmaier K, *et al*. **Safety and efficacy of raltegravir in patients with HIV-1 and hepatitis B and/or C virus co-infection.** *HIV Med* 2012; **13**:127–131.
24. Than N, Sungkanuparph S, Maek-A-Nantawat W, Kaewkungwal J, Pitisuttithum P. **Comparison of clinical outcomes between HIV-infected patients with and without HCV co-infection in a resource-limited setting.** *Southeast Asian J Trop Med Public Health* 2011; **43**:646–651.
25. Collazos J, Carton JA, Asensi V. **Evaluation of the possible influence of hepatitis C virus and liver fibrosis on HIV type 1 immunological and virological outcomes.** *HIV Med* 2011; **12**:308–315.
26. Rockstroh J, Mocroft A, Soriano V, Tural C, Losso M, Horban A, *et al*. **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.
27. Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. **HIV and hepatitis C co-infection within the CAESAR study.** *HIV Med* 2004; **5**:174–179.
28. Bonacini M, Louie S, Bzowej N, Wohl AR. **Survival in patients with HIV infection and viral hepatitis B or C: a cohort study.** *AIDS* 2004; **18**:2039–2045.
29. Monforte AD, Cozzi-Lepri A, Castagna A, Antinori A, Lua AD, Mussini C, *et al*. **Risk of developing specific AIDS-defining illnesses in patients coinfected with HIV and hepatitis C virus with or without liver cirrhosis.** *Clin Infect Dis* 2009; **49**:612–622.
30. Gross R, Tierney C, Andrade A, Lalama C, Rosenkranz S, Eshleman SH, *et al*. **Modified directly observed antiretroviral therapy compared with self-administered therapy in treatment-naive HIV-1-infected patients: a randomized trial.** *Arch Intern Med* 2010; **169**:1224–1232.
31. Flexner CW, Tierney C, Gross R, Andrade A, Lalama C, Eshleman SH, *et al*. **Comparison of once-daily versus twice-daily combination antiretroviral therapy in treatment-naive patients: results of AIDS clinical trials group (ACTG) A5073, a 48-week randomized controlled trial.** *Clin Infect Dis* 2010; **50**:1041–1052.
32. Gulick R, Ribaudo H, Shikuma CM, Lustgarten S, Squires KE, Meyer WA, *et al*. **Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection.** *N Engl J Med* 2004; **350**:1850–1861.
33. Riddler SA, Haubrich RH, DiRienzo G, Peeples L, Powderly WG, Klingman KL, *et al*. **Class-sparing regimens for initial treatment of HIV-1 infection.** *N Engl J Med* 2008; **358**:2095–2106.
34. Sax PE, Tierney C, Collier AC, Fischl MA, Mollan K, Peeples L, *et al*. **Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy.** *N Engl J Med* 2009; **361**:2230–2240.
35. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, *et al*. **Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1.** *Ann Intern Med* 2011; **154**:445–456.
36. Sax P, Tierney C, Collier A, Daar E, Mollan K, Budhathoki C, *et al*. **Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results.** *J Infect Dis* 2011; **204**:1191–1201.
37. Snyder N, Gajula L, Xiao S, Grady J, Luxon B, Lau D, *et al*. **APRI: an easy and validated predictor of hepatic fibrosis in chronic hepatitis C.** *J Gastroenterol Hepatol* 2006; **40**:535–542.
38. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A. **FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with Liver Biopsy and FibroTest.** *Hepatology* 2007; **46**:32–36.
39. Kovacs A, Karim R, Mack WJ, Xu J, Chen Z, Operskalski E, *et al*. **Activation of CD8 T cells predicts progression of HIV infection in women coinfected with hepatitis C virus.** *J Infect Dis* 2010; **201**:823–834.
40. Hunt PW, Brenchley J, Sinclair E, McCune JM, Roland M, Shafer KP, *et al*. **Relationship between T cell activation and CD4$^+$ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy.** *J Infect Dis* 2008; **97**:126–133.
41. Gonzalez VD, Falconer C, Blom KG, Reichard O, Morn B, Laursen AL, *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.
42. Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, *et al*. **Antiretroviral treatment of adult HIV infection: 2012 Recommendations of the International Antiviral Society–USA Panel.** *JAMA* 2012; **308**:387–402.
43. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf [Accessed 09 June 2012].