

Impact of Hepatitis C Co-Infection on Response to Antiretroviral Treatment

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Abstract

The MONET study, comparing darunavir/ritonavir-based triple therapy and monotherapy, has found higher risk of failure in patients with positive HCV serology, but the effects of HCV co-infection on the efficacy of antiretroviral treatment have not been clearly established.

A detailed MEDLINE search was conducted to identify cohort studies and clinical trials with published analyses of the efficacy of antiretroviral treatment by HCV co-infection. A meta-analysis of the clinical trials was conducted, with the standardized endpoint of HIV RNA < 50 copies/ml at week 48 (intent to treat, time to loss of virologic response algorithm).

Twelve cohort studies, seven clinical trials in antiretroviral-naïve patients and three in pretreated patients were identified. In the clinical trials, 637/5,408 (12%) patients had HIV/HCV co-infection by HCV antibody tests; this percentage was in the lower range of the percentage of HIV/HCV co-infected patients reported in cohort studies in North America and Europe (median 37%, range 9-64%). In the meta-analysis of the clinical trials, the mean percentage of patients achieving HIV RNA < 50 copies/ml at week 48 was 68.2% for HIV/HCV co-infected patients versus 80.4% for HIV mono-infected patients. The absolute difference in efficacy was 11.5% (95% CI: 7.7-15.3%; $p < 0.001$). However, a high proportion of endpoints in the time to loss of virologic response analysis were discontinuations of randomized treatment for adverse events or other reasons.

The cause of the lower efficacy of antiretroviral treatment in HIV/HCV co-infected patients is unclear. The low percentage of HIV/HCV co-infected patients in this analysis, compared with published cohort studies, suggests that HCV co-infected patients are underrepresented in HIV clinical trials. (AIDS Rev. 2012;14:124-31)

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Key words

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Introduction

In North America and Europe the percentage of HIV-positive people who are co-infected with hepatitis C (HCV) ranges from 72-95% among intravenous (IV)

drug users, 1-12% among men who have sex with men, and 9-27% among heterosexual men and women¹. Worldwide, an estimated 4-5 million people are co-infected with HIV and HCV². Patients co-infected with HIV and HCV have higher HCV RNA levels, and accelerated liver disease progression compared to patients infected with HCV alone².

The MONET trial, a randomized study which evaluated darunavir/ritonavir either with or without nucleoside analogues, has shown a correlation between HCV seropositivity and therapeutic failure as defined by the endpoint of time to loss of virologic response (TLOVR). These results raised questions about the role of HCV co-infection on the efficacy of antiretroviral regimens^{3,4}.

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In this systematic review of clinical trials and cohort studies, we aimed to answer two questions:

- Are HIV/HCV co-infected patients underrepresented in HIV clinical trials compared with cohort studies?
- In cohort studies and clinical trials, is the efficacy of antiretroviral treatment different between HIV/HCV co-infected patients and those infected with HIV alone?

HIV clinical trials typically exclude patients who have hepatitis B or C co-infection. For example in the MONET trial, patients currently using IV drugs were excluded. Active misuse of recreational drugs increases the likelihood of non-adherence to study procedures and is a standard exclusion criterion in HIV clinical trials. Patients co-infected with hepatitis B were also excluded from the MONET trial because of the potential risk of hepatic flares if nucleoside analogue treatment was discontinued at the baseline visit in the darunavir/ritonavir monotherapy arm. Patients with HCV co-infection were excluded if their medical condition was unstable and/or required treatment during the study period. In addition, any patient could be discontinued from the trial if they became acutely infected with hepatitis A, B, or C³. These procedures are likely to lead to underrepresentation of patients with co-infection in HIV clinical trials.

MEDLINE review

A systematic MEDLINE review was conducted for prospective clinical trials and cohort studies of HAART regimens in antiretroviral-naïve and pretreated HIV-infected individuals published between January 1, 2000 and November 1, 2011. The search aimed to identify studies that included analysis of antiretroviral efficacy by HCV co-infection. This search used the generic names of each antiretroviral, followed by “cohort” or “clinical trial” and “hepatitis C”.

This search was further extended by a review of the proceedings and abstract books of the following international scientific conferences organized during the abovementioned index period: the Conference on Retroviruses and Opportunistic Infections (CROI), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Conference on Clinical Aspects and Treatment of HIV Infection (EACS), the International AIDS Conference (also known as the “World AIDS Conference”), the International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment, the International Conference on Drug

Therapy in HIV Infection (ICDT), and the Annual Meeting of the Infectious Diseases Society of America (IDSA).

Finally, the latest US Food and Drug Administration (FDA)-approved package inserts for each antiretroviral currently licensed for the treatment of HIV infection were examined and listed trials were reviewed.

Trials derived from this systematic review of public domain data and conference presentations were included in this analysis if they met all of the following eligibility criteria:

- At least 100 chronically infected treatment-naïve or pretreated HIV-infected individuals aged 16 years or over at any stage of HIV infection.
- The minimum duration of follow-up had to be 48 weeks.
- Efficacy data from clinical trials had to be reported for the week 48 time point using the TLOVR algorithm for the virologic response (% of patients with plasma HIV RNA < 50 copies/ml). Where this was not reported, the closest equivalent efficacy endpoint was used.
- Cohort studies needed to include analyses of antiretroviral drug efficacy by HCV co-infection to be included in this review. Efficacy data from cohort studies was collected using either: effects on HIV RNA suppression, effects on CD4 counts, or survival data. The efficacy results in cohort studies were not available using the standardized TLOVR algorithm.

HCV co-infection and intravenous drug use

Results from 12 cohort studies⁴⁻¹⁵ and 10 clinical trials^{3,4,16-24} were reviewed. Two clinical trials (START-MRK and BENCHMRK)²⁵ included analyses of efficacy by an endpoint different from the standard TLOVR analysis and could not be included. Across the clinical trials and cohort studies, HIV/HCV co-infected patients were significantly more likely to be either former or current IV drug users compared with patients infected with HIV alone. Results are shown in table 1. Intravenous drug use was reported in different ways: some trials reported IV drug use as a risk factor for HIV transmission, while others reported either a history of IV drug use, current IV drug use, or use of “hard drugs”. The majority of IV drug users in HIV clinical trials or cohort studies were co-infected with HCV, with co-infection rates ranging from 62-95%; among non-IV drug users, the percentage with HCV co-infection ranged from 0.5% in the MONET trial^{3,4} to 33% in the Vietnam cohort study¹³.

Table 1. History of intravenous drug use by hepatitis C co-infection by previous or current use of intravenous drugs in HIV clinical trials and cohort studies

Clinical trial/cohort study	HCV Ab positive/IV drug users	HCV Ab positive/non-IV drug users
MONET trial ³	31/39 (79%)	1/217 (0.5%)
OK-04 trial ²⁴	80/94 (87%)	12/104 (13%)
Vietnam cohort ¹³	369/485 (76%)	436/1,321 (33%)
Treat Asia cohort ¹⁴	47/71 (66%)	106/1,398 (8%)
Danish National cohort ⁹	261/276 (95%)	182/2,350 (8%)
US Veteran Affairs cohort ⁵	4,687/7,548 (62%)	966/4,668 (21%)
Italian MASTER cohort ⁸	572/630 (91%)	264/2,605 (10%)

Ab: antibody; IV: intravenous.

HCV co-infection and outcomes in HIV cohort studies

Table 2 shows the correlation between hepatitis C co-infection and response to antiretroviral treatment in 12 HIV cohort studies. Three of these cohort studies were from North America, five were from Europe or

Russia, one was Australian, and three were from developing countries (Vietnam, the Treat Asia cohort, and a treatment access program in Tanzania). The prevalence of HCV co-infection was highest in Russian (64%) versus North American cohorts (37-51%), slightly lower in Europe (9-34%) and lowest in Tanzania (1.4%). In some cases, these cohorts used the data from patients

Table 2. Prevalence of hepatitis B or C co-infection in HIV cohort studies, and associations between HCV co-infection and response to antiretroviral treatment

Cohort (country, year)	(n)	% HCV positive	HCV co-infection and outcomes on antiretroviral treatment
ACTG (USA, 2011) ⁴	2,495	–	Higher risk of HIV RNA rebound > 200 copies/ml
VA (USA, 2004) ⁵	12,216	37%	Significantly lower survival
British Columbia (Canada, 2006) ⁶	1,186	51%	Smaller rises in CD4 cell count
EuroSida (Europe, 2004) ⁷	5,883	34%	No effects on time to first HIV RNA < 400 No effects on CD4 cell rises Significantly lower survival
MASTER (Italy, 2011) ⁸	3,262	26%	Slower time to HIV RNA < 500 No effects on CD4 cell rises
National Cohort (Denmark, 2006) ⁹	2,734	16%	Significantly lower survival
CHIC (UK, 2010) ¹⁰	20,365	8.9%	No effects on HIV RNA suppression or CD4 cell rises
Russian study (Russia, 2011) ¹¹	416	64%	Smaller rises in CD4 cell count
AHOD (Australia, 2003) ¹²	2,086	13.1%	Smaller rises in CD4 cell count No effects on HIV RNA suppression or survival
Outpatient clinics (Vietnam, 2011) ¹³	1,806	27%	Smaller rises in CD4 cell count Higher loss to follow-up
Treat Asia (SE Asia, 2007) ¹⁴	2,979	10%	No effects on time to first HIV RNA < 400, CD4 cell rises or survival
PEPFAR (Tanzania, 2010) ¹⁵	4,935	1.4%	Smaller rises in CD4 cell count No effects on survival

tested for HCV antibodies; however, not all patients were tested in some cohorts. In the cohorts with incomplete testing for HCV, it is not clear whether the subset of patients tested for HCV are a representative sample of the whole cohort.

The cohorts used three measures of efficacy: HIV RNA suppression, rises in CD4 counts, and survival. However, the 12 cohort studies did not analyze all three measures of efficacy and did not use consistent methods. For example, some cohort studies used univariate analyses, while others used multivariate analyses, adjusting for potential confounders. Four cohorts showed no association between HCV co-infection and reductions in HIV RNA during antiretroviral treatment. However, the reductions in HIV RNA were measured as the time until HIV RNA was first < 400-500 copies/ml, and not the TLOVR algorithm, as used in clinical trials. By contrast, the AIDS Clinical Trials Group cohort study, combining data from several clinical trials, showed a significantly higher risk of virologic rebound to > 200 copies/ml for patients with HCV co-infection in a multivariate analysis⁴.

One other cohort (MASTER, Italy) showed a significant association between HCV co-infection and a longer time from starting antiretroviral treatment to first HIV RNA reduction to < 500 copies/ml⁸. Five cohorts showed hepatitis C co-infection to be associated with smaller rises in CD4 counts during antiretroviral treatment, while four showed no correlations between HCV co-infection and changes in CD4 count. Three large cohorts (The US Veteran Affairs cohort⁵, EuroSida⁷, and the Danish National cohort⁹), with a combined sample size of approximately 20,000 patients, showed an independent association between HCV co-infection and lower survival rates during antiretroviral treatment. Three smaller cohorts (AHOD in Australia¹², Vietnam¹³, and PEPFAR, Tanzania¹⁵), with a combined sample size of 10,000 patients and a lower prevalence of HCV co-infection, showed no association between HCV co-infection and survival on antiretroviral treatment.

HCV co-infection and efficacy outcomes in randomized clinical trials

Table 3 shows a summary of the efficacy data from 10 randomized clinical trials, analyzed by HCV co-infection: seven in antiretroviral-naïve patients (Gilead 934, KLEAN, ECHO, THRIVE, SENSE, ARTEMIS, CASTLE), and three in pretreated patients (MONET, OK-04, TITAN). There were 5,408 patients included in the analysis, of whom 637 (12%) were HCV antibody

positive. These clinical trials were conducted mainly in North America and Europe. However, the percentage of patients with HIV/HCV co-infection in the clinical trials (12%) was smaller than in the cohort studies in North America and Europe (median 37%, range 9-64%).

In each trial, treatment success was defined as HIV RNA suppression to < 50 copies/ml at week 48, using the TLOVR algorithm, or a similar endpoint. With the TLOVR algorithm, treatment failure is either virologic rebound or discontinuation of treatment for adverse events or discontinuation for other reasons. There were a few trials analyzed using slightly different methods: in the TITAN trial, the < 400 copies/ml threshold was used for HIV RNA; in the OK-04 trial, efficacy was analyzed at week 96. In several trials (ECHO/THRIVE, ARTEMIS, CASTLE and TITAN), the results were analyzed by co-infection with either hepatitis B or C.

Individually, each trial could be too small to detect statistically significant differences in efficacy by HCV co-infection. However, there was a consistent pattern across the 10 trials for lower efficacy in patients co-infected with HCV. In the meta-analysis of these clinical trials, the mean percentage with HIV RNA < 50 copies/ml at week 48 was 68.2% for patients with HIV/HCV co-infection versus 80.4% for patients with HIV infection alone. The absolute difference in efficacy was 11.5% (95% CI: 7.7-15.3%). This difference was statistically significant in the meta-analysis ($p < 0.001$). The difference in efficacy was consistent in trials of treatment-naïve patients (difference: 11.1%; 95% CI: 6.5-15.6%) and in pretreated patients (difference: 13.2%; 95% CI: 4.6-21.1%). There was no evidence for heterogeneity of this difference between clinical trials (Breslow-Day tests, $p = \text{ns}$).

The TLOVR algorithm, a composite endpoint, may be a limitation of this meta-analysis. In previous clinical trials, a high percentage of failure endpoints can be discontinuation of randomised treatment rather than true virological failure. Most of the published sub-analyses of efficacy by HIV/HCV co-infection have been presented using the TLOVR endpoint or similar analysis, but provide no information on what types of failure were seen in each group. In an analysis of the STARTMRK and BENCHMRK trials of raltegravir using only virologic endpoints²⁵, there was no difference in efficacy between HIV/HCV co-infected patients and those with HIV infection alone. These two trials could not be included in the meta-analysis because they had not been analyzed using the TLOVR endpoint. In the OK-04

Table 3. Efficacy by hepatitis B or C co-infection in clinical trials of first-line treatment and pretreated patients: HIV RNA < 50 copies/ml at week 48 (TLOVR endpoint)

Clinical trial	Treatment arm	% HCV positive	HIV RNA < 50 copies/ml HCV positive	HIV RNA < 50 copies/ml HCV negative
<i>Naive patients</i>				
Gilead 934 ¹⁶	ZDV/3TC/EFV	7%	7/16 (44%)	164/228 (72%)
	TDF/FTC/EFV	4%	8/10 (80%)	186/233 (80%)
ECHO/THRIVE ¹⁷	2 NRTI/EFV	9% (B/C)	50/63 (79%) [†]	497/602 (83%) [†]
	2 NRTI/RPV	7% (B/C)	36/49 (74%) [†]	528/621 (85%) [†]
SENSE ¹⁸	2 NRTI/EFV	10%	5/8 (63%)	53/70 (76%)
	2 NRTI/ETR	11%	5/9 (56%)	55/70 (79%)
KLEAN ¹⁹	ABC/3TC/FPV/r	12%	20/47 (43%)*	277/358 (77%)*
	ABC/3TC/LPV/r	9%	23/38 (61%)*	282/386 (73%)*
ARTEMIS ^{20,21}	TDF/FTC/DRV/r	8%	32/42 (76%) [†]	255/300 (85%) [†]
	TDF/FTC/LPV/r	9%	32/48 (67%) [†]	239/299 (80%) [†]
CASTLE ²²	TDF/FTC/ATV/r	9%	42/61 (69%) [†]	300/378 (79%) [†]
	TDF/FTC/LPV/r	7%	37/51 (73%) [†]	301/397 (77%) [†]
<i>Pre-treated patients</i>				
TITAN ²³	2 NRTI/DRV/r	13% (B/C)	35/52 (67%) [†]	193/244 (79%) [†]
	2 NRTI/LPV/r	12% (B/C)	19/37 (51%) [†]	179/259 (69%) [†]
MONET ³	2 NRTI/DRV/r	9%	10/12 (83%)	103/117 (88%)
	DRV/r	17%	16/22 (71%)	94/105 (89%)
OK-04 ²⁴	2 NRTI/LPV/r	50%	37/50 (74%)	39/48 (81%)
	LPV/r	44%	31/44 (70%)	46/56 (82%)

*HIV RNA < 400 copy endpoint; †Response in HBV and/or HCV co-infected patients combined.

TLOVR: time to loss of virologic response; ZDV: zidovudine; 3TC: lamivudine; EFV: efavirenz; TDF: tenofovir; FTC: emtricitabine; NRTI: nucleoside reverse transcriptase inhibitor; RPV: rilpivirine; ETR: etravirine; ABC: abacavir; FPV: fosamprenavir; LPV: lopinavir; DRV: darunavir; r: ritonavir.

trial of lopinavir/ritonavir monotherapy²⁴, the HIV/HCV co-infected patients had rates of HIV RNA suppression 12% worse than HIV-infected patients at week 96 using a TLOVR type endpoint, but 3% better than HIV-infected patients when only virologic endpoints were included.

HCV co-infection and efficacy in the MONET trial

In the MONET trial^{3,4}, we had detailed follow-up for almost all the patients to the end of the trial, after discontinuation of randomized treatment or elevations in HIV RNA. We therefore re-analyzed the data from the MONET trial of darunavir/ritonavir, with or without nucleoside analogues, to assess what types of treatment failure were seen in the two groups.

The MONET trial recruited 256 patients with HIV RNA < 50 copies/ml at screening and no history of

virologic failure. The patients were randomized to receive darunavir/ritonavir 800/100 mg once daily, either as monotherapy or in combination with two nucleoside analogues. Patients with virologic failure, defined as two consecutive HIV RNA levels > 50 copies/ml, could intensify with nucleoside analogues or re-start the antiretrovirals taken before the trial. All patients were followed up to week 144, whether on or off randomized treatment. Patients with major protocol violations, such as prior virologic failure or taking the wrong randomized treatment, were excluded from the per protocol population.

Figure 1 A shows the analysis of efficacy using the TLOVR endpoint at week 144. In this analysis, patients are failures if they discontinue randomized treatment or have two consecutive HIV RNA elevations > 50 copies/ml at any time, even if there is subsequent re-suppression. When all the patients enrolled in the study are included in the analysis, the HCV co-infected patients had

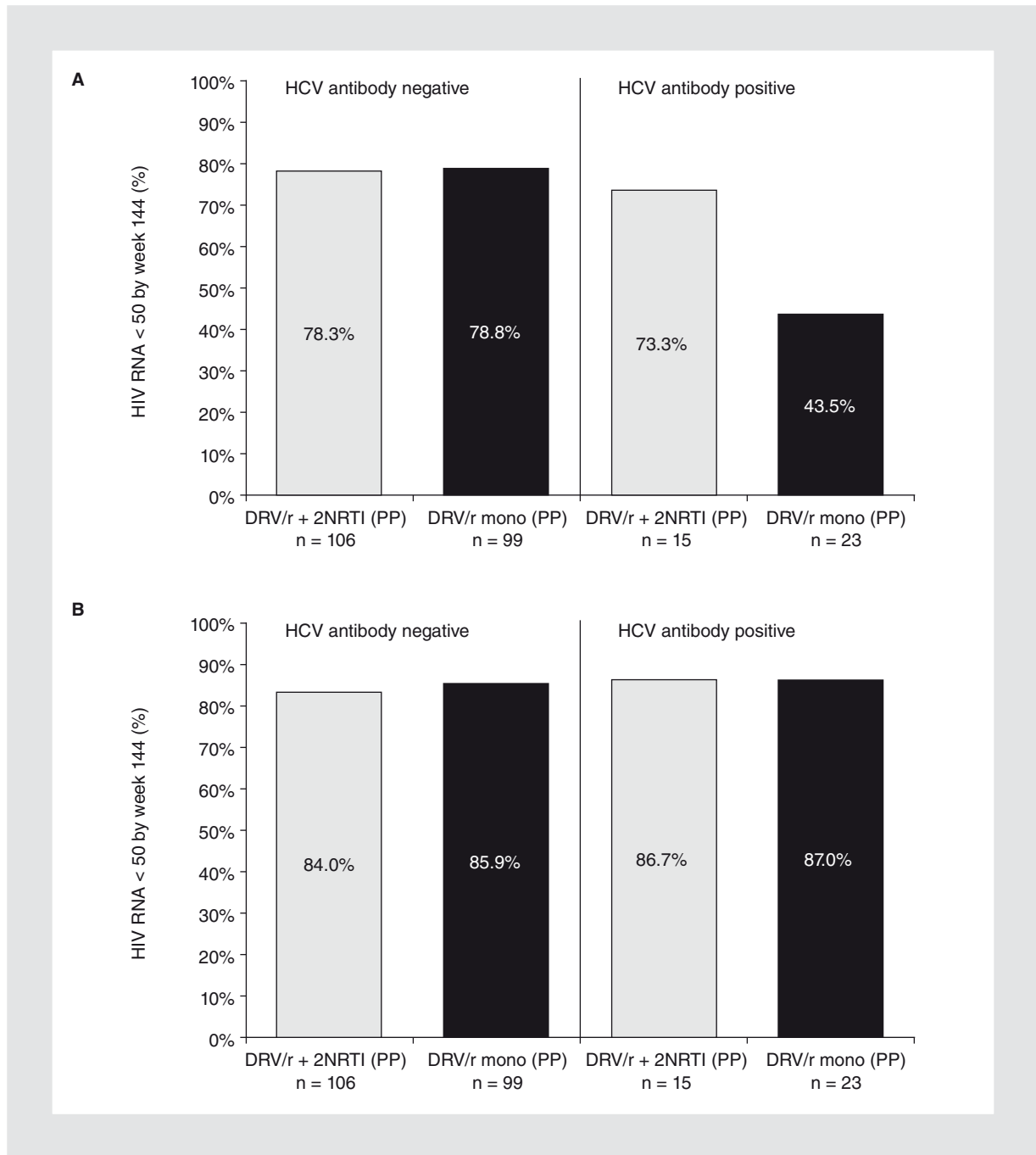


Figure 1. A: MONET trial, HIV RNA < 50 copies/ml at week 144, TLOVR, switch = failure by hepatitis C co-infection at baseline. **B:** MONET trial, HIV RNA < 50 copies/ml at week 144, switch included analysis by hepatitis C co-infection at baseline. DRV/r: darunavir/ritonavir; NRTI: nucleoside reverse transcriptase inhibitor; PP: per protocol; TLOVR: time to loss of virologic response.

lower rates of efficacy than those infected with HIV alone ($p < 0.01$ in multivariate analysis). For HCV-positive patients, there is a trend to a higher rate of failure in those treated with monotherapy (26.7% with triple therapy vs. 56.5% with monotherapy), but differences do not reach statistical significance ($p = 0.11$) although the number of patients with a positive serology

of HCV is small and the study did not have enough power for this analysis. However, in this trial only 47.9% of the failure endpoints were actual elevations in HIV RNA – the other 52.1% were discontinuations of randomized treatment for adverse events or other reasons.

Figure 1 B shows an analysis based only on the HIV RNA result at week 144. Patients are classified as

successes if their HIV RNA was < 50 copies/ml at week 144, whether on or off randomized treatment. Patients who discontinued randomized treatment, or showed confirmed elevations in HIV RNA, but then responded to subsequent treatments were included in this analysis. These patients with prior treatment failure were counted as responders if their HIV RNA levels were < 50 copies/ml at week 144. In this analysis there was no significant difference in efficacy by HCV co-infection, and overall success rates were higher. Therefore, it seems that the additional failures seen in HIV/HCV co-infected patients can be re-suppressed if they are switched to other antiretrovirals.

Discussion

The results of clinical trials seem consistent, showing lower antiretroviral efficacy when patients are co-infected with HCV. However, it is not possible to clarify the reason for this finding using data from those trials.

There are many confounding factors related with sociodemographic characteristics of the co-infected patients. The most evident of them is the high proportion of use of drugs (former or current) among HIV/HCV co-infected patients, as has been reaffirmed in our review of the cohort studies. A higher proportion of IV drug users is associated with higher rates of lack of adherence and loss to follow-up^{26,27}. However, HIV/HCV co-infected patients cannot be seen as a homogenous group as epidemiology is changing due to a new epidemic of HCV infection among gay men²⁸. In the US WIHS study, female partners of IV drug users also show a high prevalence of HCV co-infection²⁹.

There are two other possible reasons why the efficacy of antiretroviral treatment might be lower for HIV/HCV co-infected patients. Firstly, HIV/HCV co-infection might be associated with baseline characteristics correlated with lower response rates such as low CD4 counts or high HIV RNA levels. Secondly, it may be harder for HIV/HCV co-infected patients to tolerate antiretroviral treatment if they have frequent rises in liver enzymes^{30,31}, if hepatic impairment increases pharmacokinetic exposures of antiretrovirals, or if there are interactions with the treatments they use for HCV infection^{32,33}.

The analyses of the cohort studies are hard to interpret, given that they have used different endpoints for measuring HIV RNA suppression, and the influence of confounding factors is difficult to avoid. The analyses of the clinical trials used a standardized efficacy endpoint, but there was underrepresentation of HIV/HCV

co-infected patients. This may be due to the strict entry criteria for trials, which do not allow patients to enter if they are currently using recreational drugs (some trials define this criteria depending on the opinion of the investigator), or if the liver enzymes are increased (a surrogate marker of co-infection), or if therapy for HCV infection is expected to be necessary before the end of the trial. Cohort studies should be re-analyzed to assess the efficacy of antiretroviral treatment among patients who would not normally be permitted to enter HIV clinical trials.

The combined analysis of HIV RNA suppression rates in the clinical trials suggests that there is lower overall efficacy for HIV/HCV co-infected patients, but the reasons for this remain unclear as the commonly used TLOVR analysis does not show what type of treatment failure occurred, related or not with the biological effect of the therapy. Some indirect evidence suggests reasons other than biological factors as virologic endpoints are not significantly different between co-infected and mono-infected HIV patients in the OK-04, MONET, STARTMRK and BENCHMRK trials^{3,4,24,25}. However, this type of analysis is not available for the majority of the trials and no definitive evidence can be obtained in the meta-analysis.

There may be more discontinuations from treatment in HIV/HCV co-infected patients. In clinical trials it is important to follow-up all patients to the end of the randomized phase, whether they are on or off randomized treatment. This would allow a more detailed analysis of the consequences of treatment failure.

In the MONET trial, patients who had temporary elevations in HIV RNA were classified as treatment failures by the conventional efficacy endpoint of TLOVR. However, most of these patients then showed re-suppression of HIV RNA by the end of the trial on the same or intensified treatment.

Another limitation of these analyses from trials and cohorts is that HCV co-infection is usually defined by seropositivity of anti-HCV antibody. Ten to 30% of the patients with positive serology against HCV do not have actual replication of HCV as measured by viral load assays, suggesting spontaneous clearance of the HCV³⁴. These patients are systematically misclassified in these trials as co-infected. Also, serology does not take into account the possibility of former effective anti-HCV therapy, identifying patients with positive antibodies anti-HCV but no longer HCV activity (sustained viral responders). Further analysis of the impact of HCV co-infection on antiretroviral efficacy will have to be performed, defining co-infected patients as those with

active HCV replication. As this information is not available in the analyzed trials and cohorts, new studies are warranted.

In conclusion, our results show a higher risk of failure of antiretroviral therapy in patients co-infected with HIV and HCV, although the reasons for this situation remain unclear. Improving the knowledge and understanding of these related factors could play an important role in optimizing the efficacy of antiretroviral treatment for co-infected patients.

References

- Alter M. Epidemiology of viral hepatitis and HIV co-infection *J Hepatol*. 2005;44(Suppl 1):S6-9.
- Rotman Y, Liang J. Co-infection with hepatitis C virus and human immunodeficiency virus: virological, immunological, and clinical outcomes. *J Virol* 2009;83:7366-74.
- Arribas J, Clumeck N, Nelson M, et al. The MONET trial: Week 144 analysis of efficacy of darunavir/ritonavir monotherapy versus DRV/r + 2NRTIs, for patients with HIV RNA <50 copies/mL at baseline. 6th IAS Conference on HIV Pathogenesis and Treatment, Rome, Italy, 2011. [Abstract MOPE216].
- Ribaudo H, Smith K, Robbins G, et al. Race Differences in the efficacy of initial ART on HIV infection in randomized trials undertaken by ACTG. Presented at 18th CROI, Boston, USA, 2011. [Abstract 50].
- Backus L, Phillips B, Boothroyd D, et al. Hepatitis C co-infection increases mortality in HIV-infected U.S. veterans treated with highly active antiretroviral therapy. 11th CROI, San Francisco, USA, 2004. [Abstract 800].
- Braitstein P, Zala C, Yip B, et al. Immunologic response to antiretroviral therapy in hepatitis C virus-coinfected adults in a population-based HIV/AIDS treatment programme. *J Infect Dis*. 2006;193:259-68.
- Rockstroh J, Konopicki D, Soriano V, et al. Hepatitis B and hepatitis C in the EuroSida cohort: prevalence and effect on mortality, AIDS progression and response to HAART. 11th CROI, San Francisco, USA, 2004. [Abstract 799].
- Torti C, Quiros-Roldan E, Maggiolo F, et al. Viro-immunological effectiveness of HAART by HCV antibody status in the Italian MASTER cohort over short-term follow up. International Conference on HIV Pathogenesis and Treatment, Rome, Italy, 2011. [Abstract TuPE106].
- Weis N, Lindhardt B, Kronberg G, et al. Impact of Hepatitis C virus co-infection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. *Clin Infect Dis*. 2006;42:1481-7.
- Turner J, Bansil L, Gilson R, et al. 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;17:569-77.
- Gochitashvili N, Chkhartishvili L, Sharvadze N, et al. Impact of HCV coinfection and virological and immunological response to antiretroviral treatment in a cohort of patients in Georgia. 6th IAS Conference on HIV pathogenesis, treatment and prevention, Rome, Italy, 2011. [Abstract CDB190].
- D Lincoln, Petoumenos K, Dore G; on behalf of the Australian HIV Observational Database. HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. *HIV Med*. 2003;4:75-84.
- Nguyen D, Do N, Cosimi L, et al. Response to antiretroviral therapy (ART) of HIV/HCV co-infected patients at outpatient clinics in Vietnam. 17th CROI, San Francisco, USA, 2010. [Abstract 817].
- Zhou J, Dore G, Zhang F, et al. Hepatitis B and C virus co-infection in the Treat Asia HIV Observational Database. *Hepatology*. 2007; 22:1510-18.
- Christian B, Okuma J, Hawkins C, et al. Prevalence of hepatitis B and C co-infection and response to antiretroviral therapy among HIV-infected patients in an urban setting in Tanzania. 17th CROI, San Francisco, USA, 2010. [Abstract 694].
- Arribas J, Gallant J, DeJesus E, et al. Response to antiretroviral therapy with tenofovir DF and emtricitabine versus zidovudine/lamivudine in combination with efavirenz in Hepatitis C (HCV) co-infected antiretroviral naïve patients. European AIDS Clinical Society Conference, Dublin, Ireland, 2004. [Abstract PE13.2/16].
- Nelson M, Amaya G, Clumeck N, et al. Efficacy and safety of rilpivirine in treatment-naïve, HIV-1 infected patients with HBV/HCV co-infection enrolled in the ECHO/THRIVE trials. 7th International Workshop on HIV and HCV Co-infection, Milan, Italy, 2011. [Abstract O-02].
- Gazzard B, Duvivier C, Zagler C, et al. Phase 2 double-blind, randomized trial of etravirine versus efavirenz in treatment-naïve patients: 48-week results. *AIDS*. 2011;25:2249-58.
- Norris D, Patel L, Rizzardini G, et al. Efficacy and safety of fosamprenavir/ritonavir (FPV/r) BID or lopinavir/ritonavir (LPV/r) BID in antiretroviral treatment-naïve subjects co-infected with hepatitis B (HBV) or C (HCV) and HIV (The KLEAN Study). 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2007), Sydney, Australia. [Abstract MOPEB059].
- Ortiz R, Fourie J, Andrade-Vilanova J, et al. Tolerability of darunavir/ritonavir once daily versus lopinavir/ritonavir in treatment-naïve patients co-infected with hepatitis B and/or C in the ARTEMIS Trial. Presented at: HEP DART: Frontiers in Drug Development for Antiretroviral Therapies, Hawaii, USA, 2007. [Abstract 91].
- Fourie J, Flamm J, Rodriguez-French A, et al. Effect of baseline characteristics on the efficacy and safety of DRV/r 800/100 mg QD in HIV-1 infected, treatment naïve ARTEMIS patients at Week 96. *HIV Clin Trial*. 2011;12:313-32.
- Absalon J, Thal G, Thiry A, et al. Atazanavir is safe and efficacious in HBV and HCV co-infected patients: results of A1424138 (CASTLE). 9th International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 2008. [Abstract P136].
- Bánhegyi D, Suter F, De Paepe E, et al. Tolerability of darunavir/r versus lopinavir/r in lopinavir/r-naïve, treatment-experienced, hepatitis B and/or C co-infected patients in TITAN. Presented at the 11th European AIDS Conference, Madrid, Spain, 2007. [Abstract P7.3/03].
- Pulido F, Arribas J; the OK-04 Study Group. No effect of HCV infection on virological response 96 weeks after simplification to lopinavir/ritonavir (LPV/r) monotherapy in the OK04 trial. 6th IAS Conference on HIV Pathogenesis and Treatment, Rome, Italy, 2011. [Abstract MOPE217].
- Rockstroh J, Tepler H, Zhao J, et al. Hepatic safety and efficacy of raltegravir in patients co-infected with HIV and Hepatitis B (HBV) and/or C (HCV) virus. 11th CROI, San Francisco, USA, 2010. [Abstract 662].
- Escobar I, Campo M, Martin J, et al. Factors affecting patient adherence to highly active antiretroviral therapy. *Ann Pharmacother*. 2003;37: 775-81.
- Bassetti S, Battegay M, Furrer H, et al. Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued? Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr*. 1999;21:114-19.
- Taylor LE, Holubar M, Wu K, et al. Incident hepatitis C virus infection among US HIV-infected men enrolled in clinical trials. *Clin Infect Dis*. 2011;52:812-18.
- Frederick T, Burian P, Terrault N, et al. Factors associated with prevalent hepatitis C infection among HIV-infected women with no reported history of injection drug use: the Womens Interagency HIV Study (WIHS). *AIDS Patient Care STDs*. 2009;23:915-23.
- Saves M, Vandentorren S, Daucourt V, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort, France, 1996-1998. *Groupe d'Epidemiologie Clinique de Sida en Aquitaine (GECSA)*. *AIDS*. 1999;13:F115-21.
- Aranzabal L, Casado JL, Moya J, et al. Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection. *Clin Infect Dis*. 2005;40:588-93.
- FDA Drug Safety Communication: Important drug interactions between Victrelis (boceprevir) and ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitor drugs. <http://www.fda.gov/Drugs/DrugSafety/ucm291119.htm> [accessed Feb 21 2012].
- Soriano V, Sherman K, Rockstroh J, et al. Challenges and opportunities for hepatitis C drug development in HIV-hepatitis C virus-co-infected patients. *AIDS*. 2011;25:2197-208.
- Hernandez M, Sherman K. HIV/hepatitis C co-infection natural history and disease progression. *Curr Opin HIV AIDS*. 2011;6:478-82.