

**639-M**

**Poorer immunological response to HAART in HCV+ve individuals co-infected with hepatitis C virus (HCV)**

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## Background

- **Many individuals infected with HIV are co-infected with HCV. Rates of co-infection vary by risk group, with 50-90% of injecting drug users (IDU) and 60-90% of haemophilic men infected with HCV, but only 3-5% of those infected by homosexual or heterosexual sex.**
- **Whilst individuals co-infected with HCV experience a similar virological response to HAART, they may experience a poorer immunological response than those who are not co-infected with HCV (1).**

## **Aim of study**

- **To describe the effect of HCV infection on virological and immunological responses to HAART in 576 patients attending a large HIV clinic in Frankfurt, Germany.**

## **Patients**

- **Patients were followed from the date of starting HAART (defined as the first regimen including a PI or NNRTI) to the date of virological or immunological response. These were defined as follows:**

- ***Virological response:***

- **Time to first HIV RNA < 500 copies/ml**

- ***Immunological response:***

- **Time to 100 cell/mm<sup>3</sup> increase in CD4 count from pre-HAART levels.**

- **Cox regression models were used to assess the effects of HCV antibody status on time to virological and immunological response after adjusting for other possible confounding factors.**

## **HCV antibody status**

- **HCV antibody status was determined from the most recent test result before starting HAART, or from the first available HCV measure after starting HAART in patients whose only HCV determinations were after HAART.**
- **Of the 4758 patients aged > 14 years included in the Frankfurt HIV Clinic Cohort and under follow-up on 1/1/1996, 2118 started HAART between 1996 and 2001. Of these, 576 (27%) had at least one HCV antibody determination.**

## Results

- The 576 patients with known HCV status were predominantly male (76%) and the main risk factors for HIV infection were homo/bisexual sex (45%), injecting drug use (15%) and heterosexual sex (27%) (Table 1).
- Compared to those with unknown HCV status, patients included started HAART later ( $p=0.001$ ), were more likely to be ARV-naïve ( $p=0.001$ ), less likely to be male ( $p=0.04$ ) and homosexual ( $p=0.001$ ), and were younger ( $p=0.008$ ). CD4 counts and HIV RNA levels at the time of starting HAART were similar.

## Table 1: Comparison of individuals with and without a HCV antibody determination

	HCV antibody determination		p-value
	No	Yes	
Number of patients	1542	576	
Date of starting ART			
≤1996	520 (34)	114 (20)	
1997-1998	781 (51)	241 (42)	
≥1999	241 (16)	221 (38)	0.001
Male	1234 (80)	437 (76)	0.04
Homo/bisexual	836 (54)	258 (45)	0.001
Previous AIDS	398 (26)	132 (23)	0.19
ARV-naïve	856 (56)	396 (69)	0.001
Age at start of HAART	36 (17-76)	35 (18-76)	0.008
CD4 count at start of HAART	181 (1-1035)	164 (1-895)	0.08
HIV RNA at start of HAART	5.1 (1.3-8.0)	5.2 (1.3-6.7)	0.79

- **Of the 576 patients, 120 (21%) were HCV antibody positive.**
- **As expected, HCV+ve patients were more likely to report IDU as their risk for HIV infection ( $p=0.0001$ ). In addition, HCV+ve individuals were less likely to be male ( $p=0.006$ ) and had been infected with HIV for longer periods ( $p=0.0001$ ) than those who were HCV-ve (Table 2a)**
- **HCV+ve patients also started HAART later ( $p=0.02$ ) and were less likely to be ARV-naïve ( $p=0.03$ ) (Table 2b).**

## Table 2a: Demographics of HCV antibody positive and negative individuals

	HCV Antibody status		p-value
	Positive	Negative	
Number of patients	120	456	
Male gender	79 (66)	358 (79)	0.006
Risk group			
Homo/bisexual	12 (10)	246 (54)	
IDU	84 (70)	3 (1)	
Heterosexual	13 (11)	144 (32)	
Other/unknown	11 (9)	63 (14)	0.0001
Years since HIV diagnosis	5.1 (0-15.8)	1.3 (0-17.8)	0.0001
Age at start of HAART (years)	35 (20-52)	36 (18-76)	0.13

\* Entries are n (%) or median (range) as appropriate

## Table 2b: Clinical status HCV antibody positive and negative individuals

	HCV Antibody status		p-value
	Positive	Negative	
Number of patients	120	456	
Date of starting ART			
≤1996	16 (13)	98 (22)	
1997-1998	63 (53)	178 (39)	
≥1999	41 (34)	180 (39)	0.02
ARV-naive	72 (60)	324 (71)	0.03
Previous number of NRTIs received	2 (1-5)	2 (1-4)	0.48
Previous AIDS diagnosis	21 (18)	111 (24)	0.14
CD4 count (cells/mm <sup>3</sup> )	149 (1-642)	164 (1-895)	0.57
HIV RNA (log <sub>10</sub> copies/ml)	5.2 (1.8-6.6)	5.2 (1.3-6.7)	0.97

\* Entries are n (%) or median (range) as appropriate

- **Of HCV+ve individuals, 59% started a regimen including a PI, 40% started a regimen containing an NNRTI and 1% started a regimen including both classes of drugs.**
- **Of HCV-ve individuals, the proportions were 73%, 23% and 3%, respectively (p=0.001)**
- **More specifically, HCV+ve individuals were less likely to start regimens including ritonavir (p=0.005) and indinavir (p=0.01) and were more likely to start regimens including nevirapine (p=0.001) than HCV-ve individuals (Table 3)**

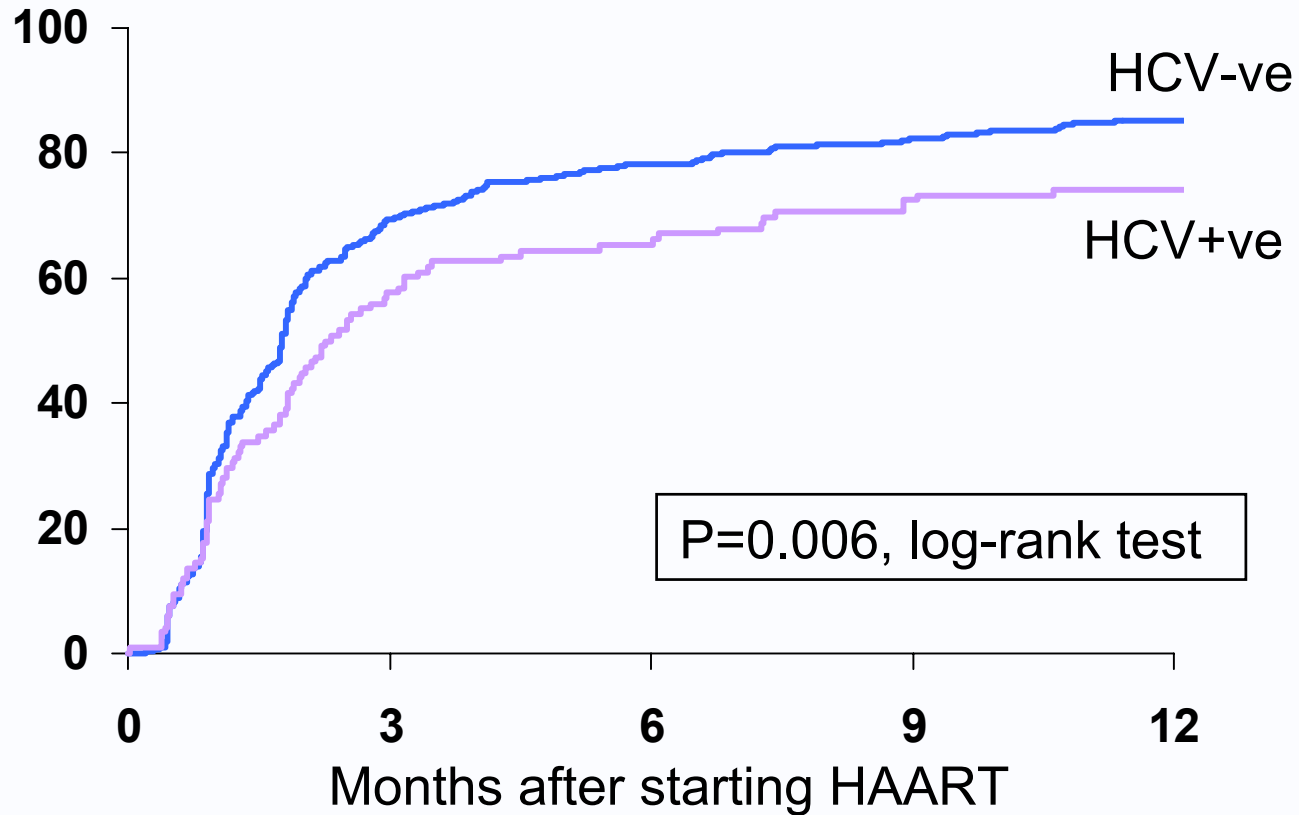
## Table 3: ARV drugs started as part of initial HAART regimen

		HCV Antibody status		p-value
		Positive	Negative	
<i>PIs</i>				
	Ritonavir	14 (12)	110 (24)	0.005
	Indinavir	30 (25)	174 (38)	0.01
	Saquinavir	13 (11)	48 (11)	1.00
	Nelfinavir	17 (14)	68 (15)	0.95
	Other PI	5 (4)	17 (4)	0.79
<i>NNRTIs</i>				
	Nevirapine	39 (33)	77 (17)	0.001
	Efavirenz	10 (8)	43 (9)	0.85
	Other NNRTI	0 (-)	2 (1)	1.00

- Overall, 75% and 55% of individuals experienced virological and immunological responses by 6 months after starting HAART (Kaplan-Meier estimates of response rates).
- In univariate analyses, those who were HCV+ve were less likely to achieve a virological response than those who were HCV-ve (**Figure 1**, relative hazard [RH] 0.74, 95% CI 0.60 - 0.92, p=0.007).
- This effect did not remain significant after adjusting for baseline HIV RNA levels, previous treatment history and gender (**Table 4**), all of which were associated with virological response.

**Figure 1: Cumulative virological response rate, monthly after starting HAART, stratified by HCV status**

% with virological response



P=0.006, log-rank test

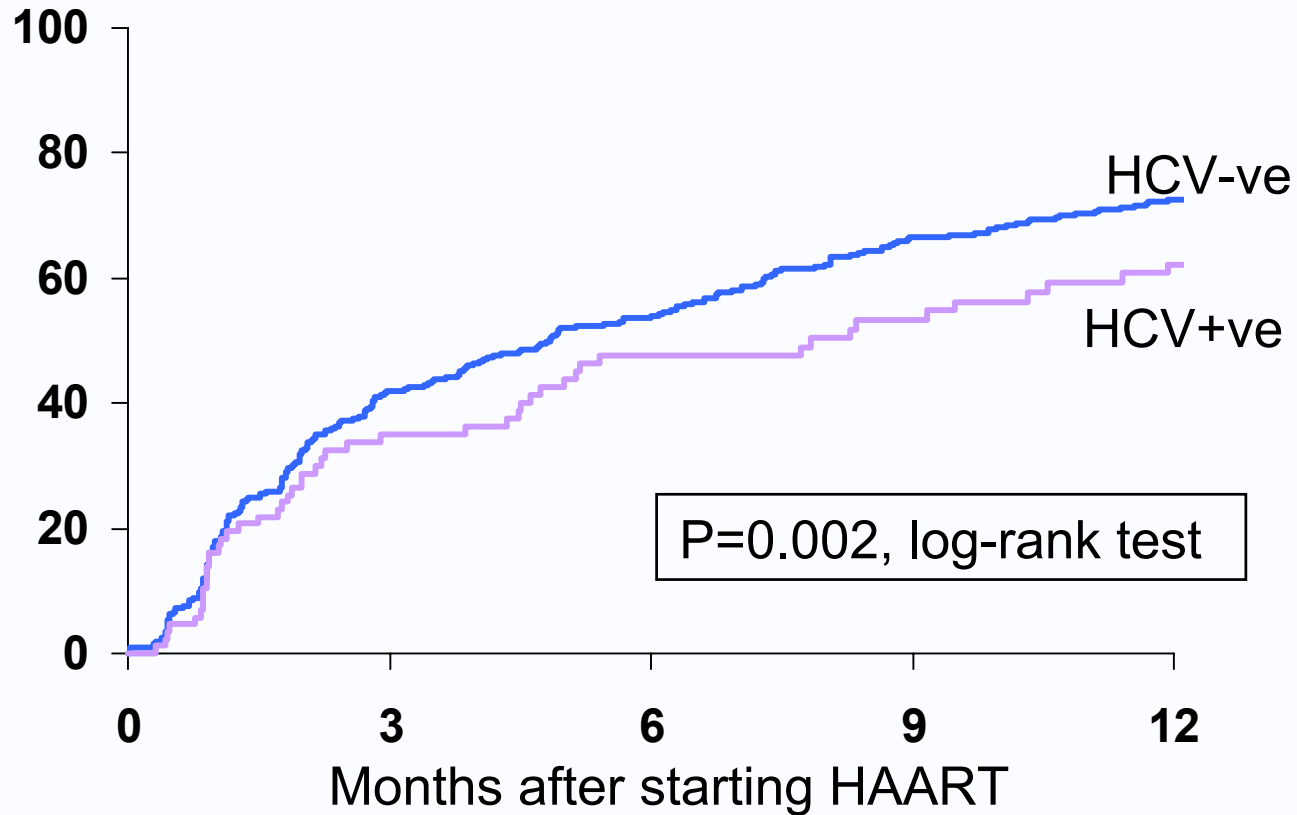
## Table 4: Factors associated with virological response - results from multivariable regression models

	RH	95% CI	p-value
<b>HCV status</b>	<b>0.92</b>	<b>(0.72-1.17)</b>	<b>0.47</b>
HIV RNA at start of HAART (per log higher)	0.77	(0.70-0.84)	0.0001
Number of drugs previously received	0.82	(0.75-0.89)	0.0001
Female	1.34	(1.08-1.67)	0.009

- In contrast, those who were HCV+ve were less likely to experience an immunological response than those who were HCV-ve (**Figure 2**, unadjusted RH 0.64, 95% CI 0.48-0.85,  $p=0.002$ ).
- This effect did remain significant after adjusting for other baseline factors (**Table 5**).
- In multivariable regression analyses, other factors associated with an improved immunological response were non-heterosexual risk group, having received fewer drugs in the past and a shorter time since HIV diagnosis.

## Figure 2: Cumulative immunological response rate, monthly after starting HAART, stratified by HCV status

% with immunological response



## Table 5: Factors associated with immunological response - results from multivariable regression models

	RH	95% CI	p-value
<b>HCV status</b>	<b>0.67</b>	<b>(0.50-0.90)</b>	<b>0.008</b>
Heterosexual risk group	0.60	(0.47-0.76)	0.0001
Number of drugs previously received	0.81	(0.74-0.89)	0.0001
Time since HIV diagnosis (per year)	0.95	(0.93-0.98)	0.0008

- **One limitation of this study is that the effect of HCV status is strongly confounded with risk group**
- **Although we have adjusted for risk group, the very small number of injecting drug users who are HCV-ve (n=3) means that it is doubtful that this adjustment will have been successful.**
- **Thus the apparent effect of HCV status could simply reflect some other factor associated with injection drug use (eg. poor adherence to therapy), which cannot be captured in an observational database.**

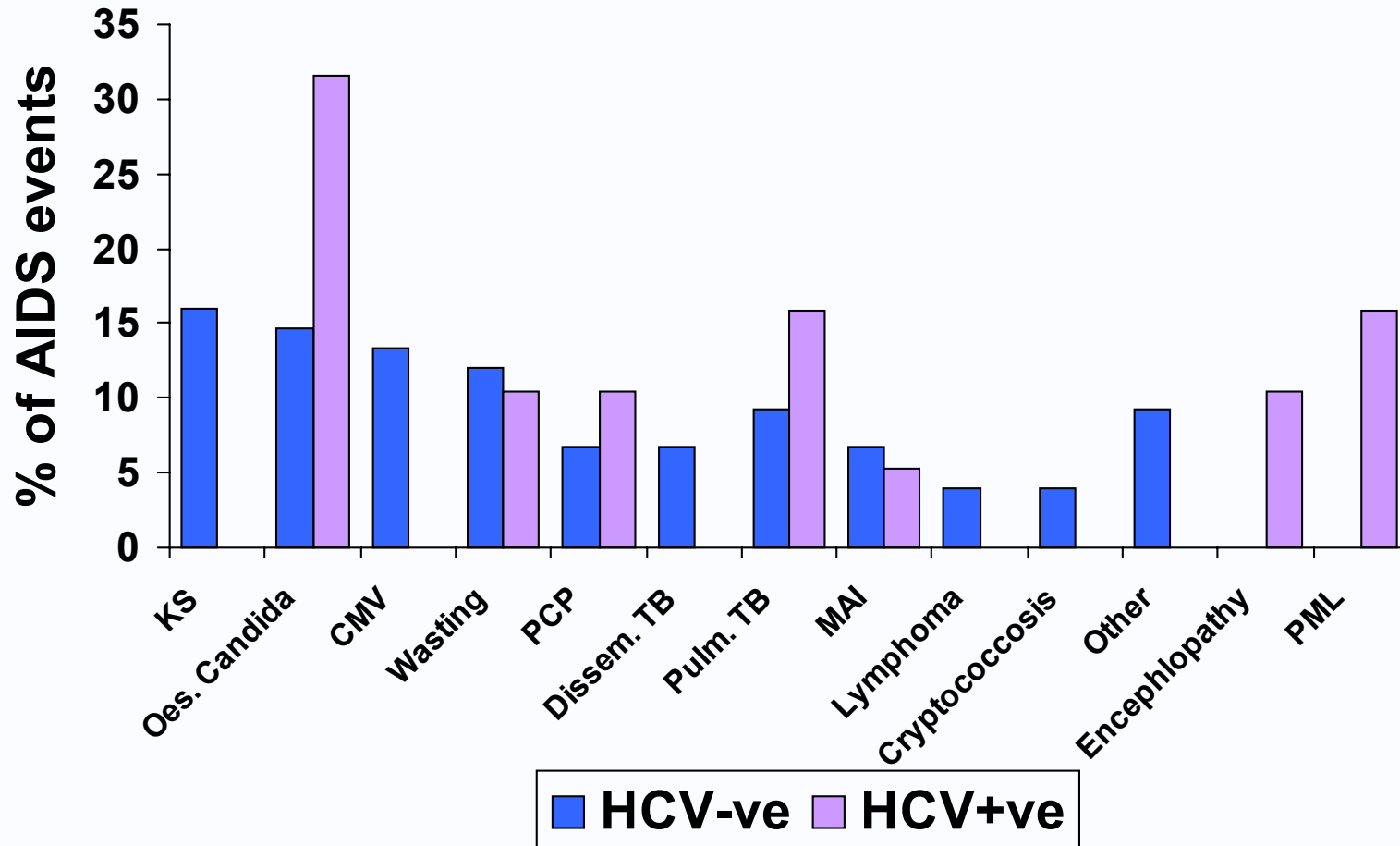
- **One surrogate measure for adherence, is the frequency of CD4 monitoring in the cohort. Those who were HCV+ve had less frequent CD4 monitoring after starting HAART than those who were HCV-ve:**

**HCV+ve: 48 [34-74]  
HCV-ve: 42 [34-57], p=0.0001**

- **A longer time between CD4 measures was associated with a poorer immunological response (RH per additional 10 days: 0.90 [0.86-0.93], p=0.0001), but after adjusting for this factor in multivariable analyses, the effect of HCV status remained significant (RH 0.70 [0.51-0.95], p=0.02)**

- **After starting HAART, 54 (12%) of the HCV-ve individuals developed an AIDS event compared to 13 (11%) of the HCV+ves (p=0.71, log-rank test)**
- **Where events occurred, oesophageal candida, pulmonary tuberculosis, encephalopathy and PML tended to occur proportionately more frequently in those who were HCV+ve, whereas Kaposi's sarcoma, cytomegalovirus and disseminated TB occurred more frequently in those who were HCV-ve (Figure 3).**
- **These differences are more likely to reflect risk group differences, than any effect of HCV status.**

**Figure 3: AIDS events occurring after start of HAART in HCV-ve and HCV+ve individuals**



## Conclusions

- **Individuals co-infected with HCV have a worse immunological response to HAART than those who remain HCV-ve, despite having a similar virological response**
- **The effect of HCV status is independent of other baseline factors, such as HIV RNA, and is independent of the frequency of CD4 monitoring**
- **However, the strong confounding between risk group and HCV status means that we cannot rule out the possibility that some other factor associated with IDU, could explain our findings**

- **In this study, clinical events appeared to occur at a similar rate in the two groups and differences in the type of event seen were more likely to be due to risk group differences than to any real effect of HCV.**
- **These findings are generally in agreement with those published from another large cohort study (1). Whilst the reason for these findings remains unclear, possible explanations may include increased toxicity in those who are HCV+ve, or a direct pathogenic effect of HCV on lymphocytes.**

## **Reference**

1. Greub G, Ledergerber B, Battegay M et al. Lancet (2000); 356: 1800-5.