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## A randomized, controlled trial of triple antiviral therapy as initial treatment of chronic hepatitis C in HIV-infected patients<sup>☆</sup>

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**Background/Aims:** Interferon and ribavirin combination therapy for chronic hepatitis C induces a low response rate in human immunodeficiency virus (HIV) infected patients. To assess the impact of intensification of interferon administration and of the addition of amantadine on the efficacy and safety of standard anti-hepatitis C virus (HCV) treatment in HIV-infected patients.

**Methods:** Multicentre, prospective, open-label, randomized, phase III clinical trial. Eighty co-infected patients were randomized to receive ribavirin 800–1000 mg/day in combination with, group A: interferon alpha2a 3 MIU thrice weekly; group B: IFN $\alpha$ 2a 3 MIU daily, plus amantadine 200 mg/day; treatment duration was 24–48 weeks according to HCV genotype.

**Results:** Forty-one patients were randomized in group A and 39 in group B. Intention-to-treat analysis showed a sustained virological response, defined as HCV-RNA negativization, 6 months after stopping treatment in 22% of patients from group A and 13% from group B ( $P > 0.05$ ). The lack of a 2-log drop in HCV-RNA levels after 12 weeks of treatment showed a 100% predictive value of lack of sustained response.

**Conclusions:** Amantadine addition and interferon intensification do not improve the low efficacy of combination of interferon alfa plus ribavirin in HIV/HCV co-infected patients. Patients with no early virologic response did not have any probability of sustained response.

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**Keywords:** Human immunodeficiency virus; Chronic hepatitis C; Interferon alpha; Ribavirin; Amantadine

### 1. Introduction

Prevalence of hepatitis C virus (HCV) infection among anti-human immunodeficiency virus (HIV) seropositive patients with a history of intravenous drug use (IDU) or transfusion is greater than 80%. The extensive use of highly active antiretroviral therapy (HAART) has dramatically changed the prognosis of HIV infection, prolonging and improving life of anti-HIV seropositives [1]. On the other hand, mortality and morbidity for liver disease have increased significantly [2].

Consequently, treatment of chronic hepatitis C in

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co-infected patients has become mandatory. Interferon in combination with ribavirin was the gold standard for treatment of chronic hepatitis C in HIV-uninfected patients, inducing a 40% rate of sustained response [3]. However, a cumulative sustained virological response (SVR) was observed in only 22% (95% Confidence interval (CI), 14–30%) of 111 patients enrolled in four pilot uncontrolled studies aiming to assess the efficacy and tolerability of ribavirin plus interferon alfa administered thrice weekly in HIV/HCV co-infected patients [4–7]. So there is an urgent need for new and more effective treatment schedules for hepatitis C in HIV co-infected patients. Among patients treated with interferon alfa three times weekly an intermittent increase of HCV viral load is observed on treatment-free days [8]. Daily administration of interferon could maintain a sustained antiviral effect on HCV; this schedule is expected to increase the efficacy of interferon alfa 2. Amantadine (1-aminoamantadan) is a tricyclic amine with antiviral activity against toga-, myxo-, arena-, flavi- and coronavirus [9]. A comparative study recently demonstrated a statistically significant advantage of the addition of amantadine to interferon and ribavirin combination in HIV-uninfected patients with chronic hepatitis C and non-responders to a previous cycle of interferon monotherapy [10]. Thus addition of amantadine and intensification of interferon schedule with daily administration could be expected to increase the efficacy of standard combination treatment with ribavirin and interferon administered thrice weekly. In order to test this hypothesis we designed a multicentre, randomized controlled trial to compare the efficacy and safety of a new treatment schedule for chronic hepatitis C including ribavirin, amantadine and daily interferon alfa administration with the standard combination treatment.

## 2. Methods

### 2.1. Patient selection

From April 2000 to October 2001, 80 HIV/HCV co-infected patients were consecutively enrolled in a multicentre, prospective, open-label, randomized, phase III clinical trial.

The study was conducted by the MASTER HIV/HCV co-infection study group.

Eligibility criteria included: age between 18 and 60 years; alanine aminotransferase (ALT) levels above the upper limit of normal (ULN) 6 months before enrolment in the study; detectable plasma HCV RNA by qualitative test (polymerase chain reaction (PCR) with Amplicor<sup>®</sup> Roche Diagnostic System, Hoffman-La Roche, Basel, Switzerland); proven HIV Ab seropositivity by ELISA confirmed by western blot; stable HIV disease with CD4 cell count persistently over 300/ $\mu$ l during the last 8 months; anti-retroviral treatment (ART) started at least 3 months before enrolment and demonstrated to be effective or no need for ART; exclusion of hepatocellular carcinoma by imaging and alphafetoprotein level lower than 100 ng/ml; willingness not to consume alcohol during the treatment period.

Exclusion criteria were: reactivity for Hepatitis B surface antigen (HBsAg), neutropenia (fewer than 1500 neutrophils per  $\mu$ l), anaemia (less than 12 g/dl of haemoglobin in women and less than 13 g/dl in men), thrombocytopenia (fewer than 90,000 platelets per  $\mu$ l), decompensated

liver disease, serum creatinine level more than 1.5 times the ULN, poorly controlled psychiatric disease, alcohol or drug dependence in the year prior to enrolment; substantial coexisting medical conditions except HIV co-infection, previous treatment with IFN alfa or ribavirin or amantadine; systemic anti-neoplastic or immunomodulatory treatment in the preceding 6 months; current/present HIV-related opportunistic infection or malignancy classified as AIDS defining events (according to 1993 CDC AIDS Surveillance Case Definitions); concomitant medication with rifampicin and/or rifabutin and/or isoniazid and/or pyrazinamide and/or gancyclovir; evidence of excessive alcohol consumption (>40 g in males and 20 g in females) and/or illegal substance abuse within the last 6 months; coexisting causes of liver disease; any additional contraindication to any of the drugs used in the study.

Additional exclusion criteria were pregnancy or lactation, and refusal to practise effective contraception during treatment and follow-up.

### 2.2. Study design

This randomized controlled clinical trial was conducted at 15 Italian centres from April 2000 to December 2002. Patients were randomly assigned at a 1:1 ratio (with a block size of five) to receive: group A: Interferon alpha 2a (IFN $\alpha$ ) 3 million units (MIU) subcutaneously (sc) three times per week plus daily per oral (po) ribavirin (Copegus<sup>®</sup>, Roche, 200 mg tablets) or group B: IFN $\alpha$  2a 3 MIU sc daily plus ribavirin (Copegus<sup>®</sup>, Roche, 200 mg tablets) and Amantadine (Mantadan<sup>®</sup>, Boehringer Ingelheim, 100 mg tablets) po 100 mg every 12 h. Ribavirin was given orally with food at a dose of 800 mg/day (two tablets bid every 12 h) for patients <75 kg of body weight and 1000 mg/day (two tablets in the morning and three in the evening after 12 h) for patients >75 kg of body weight. Treatment duration differed according to HCV genotype: 24 weeks for HCV genotype 2 or 3, and 48 weeks for HCV genotype 1 or 4, only if HCV RNA was negative at week 24 according to international guidelines [11].

Randomization was centralized in the coordinating centre and stratified according to HCV genotype (genotype 1 or 4 vs. 2 or 3). Genotype was performed by reverse hybridization assay (Inno LiPA HCV II; Innogenetics, Ghent, Belgium). Patients were followed up for a treatment-free period of 24 weeks after cessation of therapy.

The institutional review boards of the participating centres approved the protocol and all patients provided written informed consent. The study was conducted according to the Declaration of Helsinki, the applicable regulatory requirements and the ICH/CPMP guidelines 'Good Clinical Practice'.

### 2.3. Assessment of efficacy and safety

Clinical examination, laboratory testing (including lactic acid and bicarbonate) and haematological count, including CD4 cell count, were performed monthly; plasma HCV RNA was monitored every 3 months using commercially available tests (Quantiplex HIV-1 RNA v.3.0 Assay Chiron Corporation Emeryville California, USA); HCV RNA was measured at time 0 and after 1, 2, 4 and 12 weeks by a commercially available second-generation RT-PCR test (Amplicor Monitor version 2.0, Roche Diagnostic System, Pleasanton, CA) according to the manufacturer's instructions. Presence of HCV RNA in plasma was determined at weeks 4, 12 and 24, at the end of treatment and 24 weeks after cessation of therapy using a commercially available second-generation RT-PCR test (Amplicor HCV 2.0; Roche Diagnostic Systems, Pleasanton, CA) with a low end detection limit of 50 IU/ml according to the manufacturer's instructions.

Primary measures of efficacy were end-of-treatment response (EOTR) and SVR, respectively, defined as HCV RNA levels below 50 IU/ml at the end of treatment, and 24 weeks after treatment. Measures of safety were: any change in CD4 cell count, HCV RNA level, rate of withdrawal for adverse events (AE) or drop-out (DO), rate of withdrawal from ART or switch of anti-retrovirals.

### 2.4. Statistical analysis

In difficult-to-treat patients (such as 'non-responders' to interferon monotherapy), triple therapy has been proven to increase by at least three times the sustained viral response rate obtained with standard interferon and ribavirin combination [10]. In order to establish that the SVR in the triple therapy arm is at least three times higher than the 18% sustained response

rate observed in HIV-co-infected patients treated with interferon and ribavirin in pilot studies [4–7], it was calculated that at least 64 patients should have been enrolled. A confidence probability of 80% and a significance level of 0.05 were used.

Intention to treat (ITT) and per protocol (PP) analyses were performed. Categorical variables were compared using Fisher's exact test; distribution of continuous variables was compared using the *t*-test, Mann–Whitney two-sample statistic test or Wilcoxon ranksum test. Relationship between patients' baseline characteristics and SVR was examined by univariate logistic regression analysis. To assess the independence of these factors, a multivariate logistic regression analysis was performed with backward selection ( $P > 0.2$ ). All *P* values reported are two-sided, and *P* was considered significant when  $< 0.05$ . Statistical analysis was performed using STATA software, version 7.0 (Stata Corporation, College Station, TX, USA).

### 3. Results

#### 3.1. Patient demographics

Eighty patients were enrolled in the study; 41 were randomly assigned to group A and 39 to group B; their baseline characteristics are shown in Table 1. No difference was found in demographics or clinical and immunovirological characteristics between the two groups. Sixty patients (75%) were taking ART, all for more than 3 months according to inclusion criteria, when they started anti-HCV treatment.

#### 3.2. Virologic response

The rates of HCVRNA clearance in both groups are shown in Table 2. ITT analysis showed 32.5% EOTR, 31.7% in group A and 33.3% in group B. At the end of 6 months, follow-up response rates had decreased by about half: SVR was observed in 17.5, 22% in group A and 12.9% in group B. Differences in absolute HCVRNA levels or HCVRNA change-over baseline between the two groups at any time were not statistically significant.

#### 3.3. Factors associated with a sustained virologic response

Table 3 shows the distribution of some baseline characteristics in patients with and without SVR; viroimmunologic and ART characteristics were also analyzed, but the tests did not reveal a relationship with SVR; genotype 2 or 3 and gamma glutamyl transferase (GGT) baseline level less than 1.5 times the upper limit of the normal range were more frequent in patients with SVR ( $P < 0.05$  Fisher's exact test); univariate logistic regression showed their role as predictive factors of SVR, with an odds ratio of 6 (1.2–28.9 CI 95%) and 13.5 (1.6–111.8 CI 95%), respectively. Aspartate aminotransferase (AST) and neutrophil baseline levels were, respectively, lower and higher in patients who obtained an SVR ( $P < 0.05$  with Mann–Whitney test). By performing a multivariate logistic regression we found that genotype 2 or 3 and GGT baseline

value were independent predictive factors for SVR (Table 4).

#### 3.4. Predictive value of 12-week virologic response

By week 12, 32 of the 68 patients (47%) still on active treatment had a virologic response defined as a 2-log decrease from baseline HCVRNA levels or no detectable serum HCVRNA (Fig. 1). Of those with a 12-week virologic response 14 (44%) subsequently had an SVR, 5 dropped out (2 because of an adverse event and 3 spontaneously stopped treatment), 5 did have sustained HCVRNA negativization, 2 showed a breakthrough after reducing the dose of ribavirin, and 6 patients relapsed after stopping treatment. Eighteen out of 32 tested HCVRNA negative at 12 weeks. The sustained response rate in this group (9/18, 50%) did not differ significantly from that observed in subjects with detectable HCVRNA at 12 weeks (5/14; 36%). By contrast, of the 36 patients who did not have a 12-week virologic response 20 dropped out (8 because of AE and 12 prematurely stopped treatment), and 14 did not show HCVRNA negativization; only two patients showed an ETR, but none showed an SVR.

#### 3.5. Safety

Twenty-five out of 80 patients (31.3%) stopped treatment prematurely: 10 patients (18.8%) withdrew due to AE and 15 independently stopped therapy: distribution of AE and DO was similar in the two treatment groups. PP analysis showed 32.1% of SVR in group A and 14.8% in group B: there was not a significant difference between the two treatment arms.

The treatment schedule was modified for more than

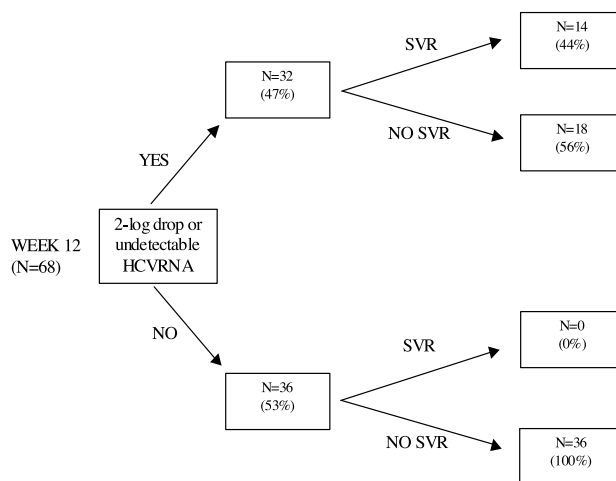


Fig. 1. At week 12, 47% of the patients treated had a 2-log drop in HCVRNA levels or had undetectable levels of HCVRNA. Of these patients 44% went on to have an SVR. Of the 36 patients who did not have a 2-log drop or undetectable levels of HCVRNA at week 12, 100% did not have an SVR. None of the 36 patients not showing a 2-log drop in HCVRNA had an SVR.

**Table 1**  
Baseline characteristics of study population

	Total	Group A	Group B
Number	80	41	39
Sex [Males % (n)]	76.3 (61)	80.5 (33)	71.8 (28)
Age (years ± SD)	37 ± 5	38 ± 5	37 ± 5
BMI (± SD)	23.8 ± 3	23.6 ± 2.8	24.1 ± 3.2
Estimated HIV infection duration [years (range)]	11 (10–13)	12 (9–14)	11 (9–13)
Estimated HCV infection duration [years (range)]	5 (4–7)	5 (4–8)	5 (3–7)
Fibrosis score F3–4% (n) <sup>a</sup>	47.1 (32)	42.1 (16)	53.3 (16)
HCV genotype % (n)			
1	46.3 (35)	43.9 (16)	48.7 (19)
2	6.3 (5)	4.9 (2)	7.7 (3)
3	40 (31)	46.3 (18)	33.3 (13)
4	10 (7)	9.8 (3)	10.3 (4)
Mixed	2.5 (2)	4.9 (2)	0 (0)
Risk factor % (n)			
Transfusion	1.3 (1)	0 (0)	2.6 (1)
Injection drugs use (IDU)	91.3 (73)	92.7 (38)	89.7 (35)
Anti HCV positive partner	6.3 (5)	4.9 (2)	7.7 (3)
Partner with history of IDU	13.8 (11)	4.9 (2)	23.1 (9)
Promiscuous Heterosexual activity (>3 partners/year)	22.5 (18)	24.2 (10)	20.5 (8)
Male homosexual activity	5 (4)	4.9 (2)	5.1 (2)
ALT (IU/l ± SD)	150 ± 102	138 ± 88	161 ± 115
AST (IU/l ± SD)	120 ± 89	109 ± 73	131 ± 103
GGT (IU/l ± SD)	159 ± 178	155 ± 208	164 ± 141
HCV RNA % (n)			
< 850,000 IU/ml	66.3 (53)	70.7 (29)	61.5 (24)
> 850,000 IU/ml	33.7 (27)	29.3 (12)	38.5 (15)
HIV RNA <50 cp/ml % (n)	40 (32)	39 (16)	41 (16)
CD4 cell count (cells/mm <sup>3</sup> ± SD)	574 ± 232	585 ± 241	563 ± 225
Nadir CD4 [median cells/μl (range)]	285 (234–322)	291 (183–331)	279 (202–330)
Naive for ART % (n)	16.3 (13)	19.5 (8)	12.5 (5)
Ongoing ART % (n)			
None	25 (20)	24.4 (10)	25.6 (10)
Two drugs	12.5 (10)	14.6 (6)	10.3 (4)
Three drugs with PI	22.5 (18)	29.3 (12)	15.4 (6)
Three drugs with NNRTI	40 (32)	31.7 (13)	48.7 (19)

<sup>a</sup> Liver biopsy was available for 68 out of 80 patients.

4 weeks in 6 patients (15%) from group A (3 reduced ribavirin dose and 3 stopped ribavirin because of anaemia) and in 19 (49%  $P = 0.02$  vs. group A) patients from group B (13 reduced interferon dose: 3 had a decrease in CD4, 6 neutropenia and 4 intolerance to flu-like symptoms, and

6 stopped ribavirin because of anaemia). Absolute CD4 cell count increased during treatment in 10 patients (mean increase  $92 \pm 86$ , range 1–218) and dropped in 65 patients (mean decrease  $176 \pm 98$ , range 15–416), without a significant change in CD4 cell proportion. Only 17 patients

**Table 2**  
Treatment outcomes stratified by treatment group and HCV genotypes

Treatment group	Number	Genotype 2 and 3				Number	Genotype 2 and 3			
		DO (%)	Number of patients with AE (%)	Number of patients with EOTR (%)	Number of patients with SVR (%)		DO (%)	Number of patients with AE (%)	Number of patients with EOTR (%)	Number of patients with SVR (%)
A	21	7 (33%)	4 (19%)	3 (14%)	2 (10%)	20	1 (5%)	1 (5%)	10 (50%)	7 (35%)
B	23	5 (22%)	4 (17%)	4 (17%)	0	16	2 (13%)	1 (6%)	8 (35%)	5 (31%)

DO, drop-out; AE, adverse events; EOTR, end-of-treatment response; SVR, sustained virologic response.

**Table 3**  
Baseline characteristic stratified according to presence or absence of SVR

	SVR	No SVR
Number	14	66
Sex [Males (%)]	57	80.3
BMI (mean $\pm$ SD)	23 $\pm$ 2	24 $\pm$ 3
Estimated HIV infection duration [years (range)]	14 (2–16)	11 (10–13)
Estimated HCV infection duration [years (range)]	5 (3–7)	5 (4–8)
Genotype 2 or 3 (%)	85.7 <sup>#</sup>	50
Nadir CD4 counts <250/ $\mu$ l %	50%	42%
HCV RNA <8,50,000 UI/ml (%)	57.1	68.2
Fibrosis score F3–4 (%) <sup>a</sup>	50	46.3
CD4 cell count (cells/mm <sup>3</sup> $\pm$ SD)	613 $\pm$ 236	566 $\pm$ 233
Neutrophil [median cells/ $\mu$ l (range)]	3560 (2683–4247) <sup>§</sup>	2398 (2180–2702)
ALT (IU/l $\pm$ SD)	119 $\pm$ 59	156 $\pm$ 109
AST (IU/l $\pm$ SD)	81 $\pm$ 58 <sup>^</sup>	128 $\pm$ 93
GGT (IU/l $\pm$ SD)	60 $\pm$ 62 <sup>*</sup>	180 $\pm$ 187
GGT <1.5 fold UL normal range (%)	91.7 <sup>°</sup>	44.8

<sup>#</sup> $P = 0.005$ , <sup>°</sup> $P = 0.004$  (Fisher's exact test two sided); <sup>§</sup> $P = 0.004$ , <sup>^</sup> $P = 0.03$ , <sup>\*</sup> $P < 0.001$  ( $t$ -test).

<sup>a</sup> In SVR 7 out of 14 showed fibrosis stage F3 or F4 at liver biopsy; liver biopsy was available in 54 out of 66 patients without SVR; 25 out of 54 showed fibrosis stage F3 or F4.

showed an increase in HIV RNA level at any time during treatment and only 4 of them needed a switch of ART due to loss of efficacy. No statistically significant difference was found in CD4 and HIV RNA levels between the two treatment groups at any time. Eleven patients were undergoing treatment with didanosine, 39 with stavudine, and six with both of them; lactic acidosis was not observed in any patients.

#### 4. Discussion

The main finding of this study was the very poor rate of SVR to combination of standard interferon and ribavirin observed in both treatment arms, with and without amantadine and interferon dose intensification. Cumulatively 17.5% of treated patients and 23.6% of those who completed the treatment course cleared HCV RNA. This response rate is significantly lower than the 40% SVR rate reported in trials performed on HIV seronegatives [12]. The high withdrawal rate (31%), the large number of subjects requiring adjustment of the treatment schedule (31%) and the low response rate observed in those who completed the treatment schedule suggest that the tolerability and efficacy

of interferon alfa and ribavirin in combination are reduced in HIV-co-infected subjects. The proportion of patients who needed interferon dose reduction was significantly higher in group B.

We did not find a statistically significant difference in the rates of EOTR and SVR between the two treatment arms. Therefore, the combination of interferon alfa schedule intensification and amantadine addition neither increase the efficacy nor improve the tolerability of combination therapy in co-infected HIV/HCV patients. Clinical trials with pegylated interferon formulations [13,14] in combination with ribavirin are ongoing in HIV/HCV-co-infected patients; preliminary results suggest that increased interferon levels induced by pegylated interferons could improve response rates in HIV/HCV-co-infected patients [15,16].

Amantadine addition did not improve the efficacy or tolerability of interferon alfa and ribavirin in chronic HCV infection. However, given the low power of this study, additional studies are needed before this drug is discarded from the therapeutic armamentarium for HIV/HCV co-infection.

Univariate logistic regression analysis of factors predictive of SVR did not confirm that of age, sex, degree of fibrosis or baseline HCV RNA levels, reported in HIV

**Table 4**  
Logistic regression: multivariate analysis of pre treatment predictive factors of SVR

	Univariate (not adjusted)	Multivariate (adjusted for all other variables)
Variables	OR (95% CI) $p$ -value	OR (95% CI) $p$ -value
Pre treatment:		
Genotype 2 and 3	16.8 (1.8–157.1) $p = 0.026$	6 (1.2–28.9) $p = 0.013$
GGT <1.5 nv vs. >1.5	15.7 (1.4–178.7) $p = 0.016$	13.5 (1.6–111.8) $p = 0.026$

seronegative patients, but this was probably due to the small size of the sample under study [17].

The results of our study show that half of the patients with SVR had in the past reached a CD4 cell count of less than 250/ $\mu$ l; such a low nadir of CD4 count in the years preceding treatment did not preclude achievement of a SVR. These findings, together with the absence of an association between fibrosis score and CD4 counts and SVR, suggest that progression of both HCV and HIV infections does not decrease the response rate to interferon and ribavirin combination in patients without severe immune depletion. We can therefore hypothesize that in patients without a high probability of response and early stage of liver fibrosis a watchful waiting strategy would not reduce the potential efficacy of anti-HCV treatment. This hypothesis needs to be confirmed by larger studies or by a meta-analysis of multiple pilot studies. HCV genotype, early HCVRNA clearance and GGT levels were significant predictors of SVR in multivariate analysis.

The association between HCV genotypes 2 and 3 and a higher rate of SVR is well known and has been confirmed in anti-HIV seropositives by pilot studies [4–7]. All but two responders were infected by HCV genotype 2 or 3 and the SVR rate in patients infected by genotype 1 or 4 was 5%. So, taking into account the side effects of treatment, these data suggest a very low cost effectiveness of treatment with standard interferon and ribavirin in HIV seropositives infected by HCV genotype 1 or 4. The association between earlier HCV clearance and SVR suggests that suppression of HCV replication in the early phase of treatment is necessary but not sufficient to induce an SVR.

High serum GGT in chronic hepatitis C patients was frequently associated with more severe hepatic fibrosis or cirrhosis, or with steatosis, and may in part account for poor response to interferon therapy [18–21]. GGT alteration in HIV seropositive patients is frequent and possibly correlated with one or more of the following factors: hepatic steatosis and/or lipidic dismetabolism, drug-related hepatic toxicity (especially in patients undergoing ART), excessive alcoholic consumption, HCV-related hepatic damage (especially genotype 3) and immuno-mediated biliary duct damage. Although all the included patients denied alcohol abuse, we cannot rule out that high GGT levels were due to undeclared excessive alcohol consumption. Body mass index was not significantly associated with treatment response. Only one of the SVRs showed high GGT at baseline; in this patient GGT normalized the third month after HCVRNA negativization. Evaluation of ART toxicity, careful assessment of alcohol intake and correction of alcohol abuse, diagnosis and treatment of altered lipid metabolism are factors to evaluate before starting treatment for chronic hepatitis C in patients co-infected with HIV.

In this study the lack of a 2-log drop in HCVRNA levels after 12 weeks of treatment showed a 100% negative predictive value of SVR. Although this data should be interpreted with caution, given the high proportion of

DOs, this result reinforces/supports the observation of a nearly absolute negative predictive value of the lack of a 12-week virologic response in HCV non-infected patients treated with pegylated interferons [13,14]. As we enter an era in which HCV treatment is going to be pursued aggressively in HIV/HCV-co-infected persons, more and more emphasis must be placed on identifying at an early stage subjects who will not benefit from an expensive and poorly tolerated therapy. If these results are confirmed by larger studies, anti-HCV treatment could be stopped after 12 weeks, without decreasing the expected rate of SVR, in HIV-infected patients who did not show at least a 2-log drop in HCVRNA level.

In conclusion, intensification of interferon alpha schedule and amantadine addition do not appear to improve the limited efficacy of standard combination therapy including interferon thrice weekly plus ribavirin for the treatment of chronic hepatitis C in HIV-co-infected patients. The best candidates for anti-HCV treatment are patients infected by HCV genotype 2 or 3 with normal GGT levels. The lack of a 2-log drop in HCVRNA level after 12 weeks of treatment seems to be highly predictive of the poor efficacy of anti-HCV treatment.

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## Appendix

THE MASTER HIV/HCV Co-infection study group also includes L. Biasi, S. Rossi, A. Spinetti, V. Putzolu, M. Airoidi, C. Baiguera, K. Prestini, MG. Antonini, P. Pagani, S. Casari, G. Parainfo, MA. Forleo, E. Quiros, C. Torti, A. Patroni, P. Nasta, F. Moretti, C. Uccelli (Clinica di Malattie Infettive e Tropicali, AO Spedali Civili, Università degli Studi di Brescia), G. Scalise, F. Ancarani, S. Di Cesare (Clinica di Malattie Infettive Università di Ancona), A. Paladini and A. Nerli (Divisione di Malattie Infettive, ASL Toscana 4, Prato), G. Pagano, F. Dodi (Divisione di Malattie Infettive Ospedale S. Martino, Genova) G. Di Perri, G. Cariti (Clinica di Malattie Infettive, Ospedale Amedeo di Aosta, Università di Torino), R. Cavaliere and N. Ladisa (Clinica di Malattie Infettive Università di Bari), E. Francavilla and A. Guzzo (Divisione di malattie Infettive Ospedale di Belluno) Silvia Boni, M. Guerra (Divisione di Malattie Infettive, Ospedale di La Spezia), F. Chiodo, M. Nafissi (Clinica di Malattie Infettive Università di Bologna), A. Scalzini and D. Tomasoni (Divisione di Malattie Infettive Ospedale Carlo Poma, Mantova), P. Rocchetto and S. Panese (Divisione di Malattie Infettive e Tropicali Ospedali SS Giovanni e

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