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SPECIAL ARTICLE

Treatment of acute hepatitis C virus infection in HIV+ patients: Dutch recommendations for management

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ABSTRACT

With a rising incidence of acute hepatitis C virus (HCV) infection in patients coinfected with the human immunodeficiency virus (HIV), there is a need for evidence-based treatment recommendations. There are no randomised trials available and published studies differ with respect to design, patient characteristics and number of patients included, making a comparison between studies difficult. However, it is critical to standardise treatment for this group of patients in order to optimise the outcome of therapy. The Dutch Society for HIV Physicians proposed to write recommendations for the treatment of acute HCV in HIV-coinfected patients. Combination therapy with pegylated interferon-alpha and ribavirin is the preferred regimen initiated preferably within 12 weeks after the diagnosis of acute HCV. A treatment duration of 24 weeks is recommended in case of a favourable virological response (either achievement of a rapid virological response or a >2log10 decrease plus undetectable HCV-RNA at week 12). In all other patients prolonging the duration of therapy to 48 weeks should be considered.

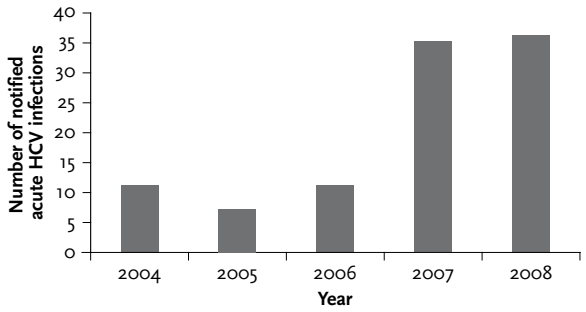
KEYWORDS

Acute hepatitis C, HIV, peginterferon-alfa, ribavirin, therapy

INTRODUCTION

In recent years, the incidence of acute hepatitis C virus (HCV) infections among men having sex with men coinfected with the human immunodeficiency virus (HIV) has markedly increased (*figure 1*).[1-4] HIV-infected patients with an acute HCV infection hardly ever present with overt clinical symptoms, thereby hampering early detection of acute HCV infection. Frequent routine laboratory assessment of transaminases is the most commonly used method of detection.[5,6] In contrast to

Figure 1. *Number of notified acute HCV infections per year, among HIV-infected MSM in the Netherlands*



Source: RIVM-report 210261005 'Sexually Transmitted Infections, including HIV, in the Netherlands in 2008'. RIVM-OSIRIS notification data.

treatment of acute HCV mono-infected patients, where sustained virological response (SVR) rates between 72 to 94% are reached with pegylated interferon-alpha (peg-IFN-α) monotherapy,[7-11] the optimal treatment strategy for acute HCV in HIV-coinfected patients is less clear.[12,13] Therefore, there is a need for evidence-based treatment recommendations, guiding clinicians in the field to treat acute HCV in this population. Here, we summarise the available literature, after which recommendations are made regarding the case definition for acute HCV (*textbox 1*), the preferred treatment regimen, the time to start therapy and the duration of therapy (*textbox 2*).

Textbox 1. *Case definition of acute hepatitis C virus*

Preferred criteria (Level II)

1) Positive anti-HCV IgG in the presence of a documented negative anti-HCV IgG in the previous 12 months

or

2) Detectable HCV-RNA in the presence of either a documented negative HCV-RNA or a documented anti-HCV IgG seroconversion within the previous 12 months

Alternative criteria (If historical data/ stored samples are lacking) (Level III)

1) Detectable HCV-RNA or positive anti-HCV IgG in association with:
   a) an acute rise in ALAT with a documented normal ALAT and no change in antiretroviral regimen within the past six months

   and

   b) anti-HAV IgM negative and anti-HBV core IgM negative, and exclusion of other causes of an acute hepatitis

Textbox 2. *Recommendations regarding acute HCV treatment*

Treatment regimen:

- Combination therapy pegylated interferon alpha-2a/2b and ribavirin (weight based 800-1400 mg)
  → level III

When to start

- Preferably within 12 weeks after the diagnosis of acute HCV
  → level III

Treatment duration

- 24 weeks in case of either
  1) a rapid virological response (RVR, HCV-RNA <50 IU/ml) or
  2) >2log10 drop of HCV-RNA at week 4 and undetectable HCV-RNA at week 12
  → level III
- in all other patients prolonging the duration of treatment to 48 weeks should be considered
  → level IV
- treatment should be stopped when <2log10 drop in HCV-RNA at week 12 of therapy
  → level IV

LITERATURE SEARCH

An English-language literature search was conducted using the PubMed database through 1 April 2010. As search terms "hepatitis C or acute hepatitis C or HCV or acute HCV" AND "peginterferon-alfa or interferon-alfa or ribavirin or combination therapy or mono-therapy or RBV or HCV treatment or HCV therapy" AND "HIV or human immunodeficiency virus or Acquired Immunodeficiency Syndrome" were used. Titles and/or abstracts were screened to determine the relevance of the studies. Of all relevant studies, full-text publications were reviewed. Furthermore, references of full-text studies were reviewed for missing publications. Lastly, conference abstracts of the annual meetings of the American Association for the Study of Liver Diseases (AASLD), the Conference on Retroviruses and Opportunistic Infections (CROI) and the European Association for the Study of the Liver (EASL) were reviewed for treatment of acute HCV.

DEFINITION OF THE DIAGNOSIS ACUTE HCV IN HIV-COINFECTED PATIENTS

To date, there is no uniform definition for the diagnosis of acute HCV. Most studies use a raise in transaminases from a previous measurement, during routine lab monitoring of HIV patients, as criterion for acute HCV.[14-21] However, sometimes a cut-off value is defined above which acute HCV is suspected (for example, >10x above the upper limit of normal or a pre-defined value of >300 U/l). Other studies combine a raise in transaminases with clinical symptoms and/or exposition to HCV as criterion for acute HCV.[22-25] Furthermore, all studies use a documented seroconversion from negative to positive anti-HCV IgG with subsequently detectable HCV-RNA as criterion for acute HCV. The time frame of seroconversion differs per study though; within six months,[25-30] 12 to 24 months[18,31-33] or unknown.[34-36]

HCV SEROCONVERSION

In the past, the sensitivity of HCV serology in HIV-infected patients has been questioned. In a large cohort study conducted in the USA, 3.2% of HIV-infected patients coinfected with *chronic* HCV were anti-HCV negative but plasma HCV-RNA positive.[37] Thomson *et al.* retrospectively tested stored serum samples of HIV patients on the presence of HCV antibodies. At the time point that HCV-RNA was first detectable, only 25% of the samples were anti-HCV IgG positive. This percentage subsequently increased to 63%, 87% and 90% at month 3, 6 and 9 respectively after the first positive HCV-RNA,[38] suggesting

that relying solely on HCV antibody testing induces the risk of missing patients with acute HCV infections. Furthermore, the study showed that at the time of HCV diagnosis, 76% of patients had an elevated alanine aminotransferase (ALAT) value (40 U/l being the upper limit of normal) making this a valuable method for detecting acute HCV. In the Utrecht cohort study, 18 of the 23 HIV-infected patients with acute HCV experienced an HCV seroconversion within the previous six months whereas extending this interval to 12 months resulted in a 100% seroconversion rate.[39]

Based on the available literature, we recommend the following case definition for acute HCV (modified from future European AIDS Treatment Network (NEAT) recommendations; *textbox 1*)

TREATMENT OF ACUTE HCV IN HIV-COINFECTED PATIENTS

What to treat with

In recent years, several retrospective studies have been published on the efficacy of peg-IFN-α monotherapy for the treatment of acute HCV in HIV-infected patients. SVR rates (i.e. HCV-RNA negative 24 weeks after discontinuation of therapy) varied from 0%,[40] 8%,[36] 67%[41] to 100% (*table 1*).[42,43] In two prospective non-randomised studies, patients were treated with either peg-IFN-α monotherapy or peg-IFN-α/ribavirin combination therapy.[25,44] Vogel *et al.* treated 21 patients with combination therapy and 15 patients with monotherapy, resulting in higher SVR rates of 73% (24 weeks) and 100% (48 weeks) for peg-IFN-α monotherapy compared with 38% (24 weeks) and 80% (48 weeks) for the patients treated with combination therapy. A protocol violation (treatment duration was extended from 24 to 48 weeks in nine patients) and a small number of patients per treatment arm (ribavirin, length of treatment) make the results from this study difficult to interpret. From 1999 through 2007, Morin *et al.* registered all patients with acute HCV, of whom 15 were also coinfected with HIV. The choice of therapy was left to the treating physician, resulting in five patients being treated with peg-IFN-α monotherapy and seven patients with peg-IFN-α/ribavirin combination therapy. In this study combination therapy was more successful than monotherapy (57 *vs* 40%). Due to the long period of inclusion, some patients were treated with conventional interferon-α again leading to very small numbers of patients in both treatment arms. In a recent study by Arends *et al.*,[45] treatment with peg-IFN-α monotherapy for acute HCV in 19 HIV-infected patients resulted in an SVR rate of only 37%. Remarkably, a large percentage of 47% of patients were null-responders to peg-IFN-α monotherapy (defined as <2log10 decline in HCV-RNA at week 12 of treatment).

All these studies differ with respect to design, patient characteristics and numbers of included patients making comparison between studies difficult. However, studies including mostly or exclusively HCV genotype 1 and 4 infected patients reported lower SVR rates after peg-IFN-α monotherapy,[36,46-48] compared with studies that also included HCV genotype 2 and 3 infected patients.[25,49-51]

Does addition of ribavirin to peg-IFN-α lead to a higher SVR rate? In most studies performed with peg-IFN-α/ribavirin combination therapy, SVR rates varied between 50 and 80% (*table 1*). For example, in a recent prospective study by Matthews *et al.* (n=27), an SVR rate of 80% was reported after 24 weeks of therapy.[52] Likewise, combination-therapy studies differ with respect to patient characteristics (percentage genotype 1 infected patients, time between seroconversion and treatment, CD4 cell count and amount of patients treated with antiretroviral therapy) and the definition of acute HCV. For example, in the prospective study by Dominquez *et al.* (n=14),[53] with an SVR of 71%, a low dose of ribavirin (800 mg) was used, the median CD4 count was low and the median time between diagnosis and treatment was 14 weeks. In contrast, in the study by Gilleece *et al.* (n=27),[54] reporting an SVR of 59%, combination therapy was already initiated after a median of four weeks after the diagnosis, the median CD4 count was not mentioned and ribavirin was dosed according to body weight. Despite these differences, the reported SVR rates were very similar.

Besides a probably higher SVR rate, there might be another argument favouring the addition of ribavirin to peg-IFN-α. A recent conference abstract by Matthews *et al.* demonstrated that the viral kinetics of HCV were better (i.e. steeper decline in HCV viral load during therapy) in patients treated with peg-IFN-α/ribavirin combination therapy compared with peg-IFN-α monotherapy.[55]

In conclusion, based on the available literature, treatment with peg-IFN-α/ribavirin combination therapy is the preferred treatment regimen with achievable success rates above 60%. Since this is considerably higher than SVR rates reached in HIV-infected patients with chronic HCV, treatment of HCV in the acute phase of the infection should be pursued.

When to start

Deciding at which time point one should start treatment in patients with acute HCV is difficult. On the one hand a chance of spontaneous viral clearance should be awaited while on the other hand deferring treatment to the chronic phase of HCV diminishes the chances of achieving a high SVR.

Studies in patients with an acute HCV mono-infection have shown that the rate of spontaneous viral clearance can be as high as 40% occurring mostly within 12 weeks after the diagnosis.[56] In HIV-infected patients with acute HCV

Table 1. *Overview of studies evaluating the efficacy of peg-IFN-alpha with or without ribavirin in HIV-infected patients with acute hepatitis C virus infection*

	Number of treated patients (total number of patients)	Patient characteristics	Genotype	Median time between diagnosis and start of therapy	CD4/HAART	Treatment regimen	SVR rate
Vogel *et al.*[66] 2005 (retrospective)	11 (16)	Male: 91% MSM: 91% Symptomatic: 82%	1 & 4: 91% 2: 9%	2.6 weeks	507 / 73%	Peg-IFN-α + RBV (n=5), peg-IFN-α (n=4) and IFN-α (n=2) Duration varied between 24 and 48 weeks	80% (peg-IFN-α + RBV) and 100% (peg-IFN-α)
Danta *et al.*[36] 2005 (retrospective)	23 (39)	Male: NM% MSM: NNM% Symptomatic: NM%	1 & 4: 85%	0 weeks for peg-IFN-α monotherapy; 12 weeks for peg-IFN-α/ RBV	549 / NM	Peg-IFN-α monotherapy (centre 1); Peg-IFN-α / RBV (centre 2)	60% (peg-IFN-α / RBV) 8% (peg-IFN-α monotherapy)
Serpaggi *et al.*[67] 2006 (retrospective)	10 (12)	Male: 100% MSM: 100% Symptomatic: 20%	1 & 4: 92% 3: 8%	49 days	625 / 90%	IFN (n=7), IFN + RBV (n=2) and peg-IFN (n=1)	0%
Luetkemyer *et al.*[68] 2006 (retrospective)	4 (9)	Male: 100% MSM: 67% Symptomatic: 44%	1: 75% 2: 25%	8 weeks	329 / 89%	Peg-IFN-α + RBV (WB) 1 patient 24 weeks and 3 patients 48 weeks	50% (1 patient only end-of-treatment available)
De Rosa *et al.*[69] 2009 (retrospective)	6 (7)	Male: 57% MSM: NB% Symptomatic: 14%	1 & 4: 71% 2: 29%	31 days	539 / 43%	Peg-IFN-α monotherapy 12 weeks	67%
Lambers *et al.*[18] 2010 (retrospective)	50 (52)	Male: 100% MSM: 100% Symptomatic: NM%	1: 65% 2 and 3: 4% 4: 19% Unknown: 12%	27 weeks	450 / NM	Peg-IFN-α + RBV Duration: 24 weeks (n=21) and 48 weeks (n=29)	75% (24 weeks) 86% (48 weeks)
Schulze zur Wiesch *et al.*[70] 2009 (case-series)	3 (3)	Male: 67% MSM: 33% Symptomatic: 0%	1: 33% 3: 67%	10 weeks	323 / 0%	Peg-IFN-α (n=2) and peg-IFN-α + RBV (n=1) Duration: mono (22 and 28 weeks) and combination 48 weeks	100% for mono and combination therapy
Fierer *et al.*[60] 2008 (prospective)	10 (31)	Male: 100% MSM: 100% Symptomatic: NM%	NM	'Acute phase'	527 / NM	Peg-IFN-α + RBV for 24 weeks	80%
Gilleece *et al.*[71] 2005 (prospective)	27 (50)	Male: NM% MSM: 100% Symptomatic: NM%	1: 74% 2, 3 and 4: NM	4 week	NB / 56%	Peg-IFN-α + RBV (WB) 24 weeks	59%
Dominquez *et al.*[72] 2006 (prospective)	14 (25)	Male: 100% MSM: 96% Symptomatic: 36%	1 & 4: 50% 3: 50%	14 weeks	345 / 86%	Peg-IFN-α + RBV (WB) 24 weeks	71%
Vogel *et al.*[25] 2006 (prospective)	36 (47)	Male: 100% MSM: 81% Symptomatic: 47%	1 & 4: 75% 2 & 3: 20%	7 weeks	416 / 61%	peg-IFN-α (n=15) and peg-IFN-α + RBV (n=21) Duration: 24 weeks (11 peg-IFN and 16 RBV) and 48 weeks (4 peg-IFN and 5 RBV)	Peg-IFN 24 weeks:73% Peg-IFN 48 weeks: 100% Peg-IFN+RBV 24 weeks: 38% Peg-IFN+RBV 48 weeks: 80%
Matthews *et al.*[73] 2009 (prospective)	22 (27)	Male: 100% MSM: 49% Symptomatic: 46%	1: 60% 2 & 3: 33 %	> 30 weeks	614 / 59%	Peg-IFN-α (n=2) Peg-IFN-α + RBV (n=20) 24 weeks	0% for peg-IFN-α; 80% for peg-IFN-α/RBV
Schnuriger *et al.*[74] 2009 (prospective)	20 (38)	Male: 100% MSM: NM% Symptomatic: 30%	1 & 4: 95% 3: 5%	4 weeks	509 / 75%	Peg-IFN-α + RBV (800 mg) 24 weeks	75% (2 patients with SVR became re-infected)
Morrin *et al.*[75] 2010 (prospective)	12 (15)	Male: 93% MSM: 67% Symptomatic: 27%	1 & 4: 73% 3: 13%	Less than 12 weeks (n=10) and more than 12 weeks (n=2)	NM	Peg-IFN-α: 5 (42%) Peg-IFN-α + RBV : 7 (58%) 7 patients 24 weeks and 5 patients 48 weeks	Mono: 2 (40%) Combi: 4 (57%)
Arends *et al.*[76] 2010 (prospective)	19 (23)	Male: 100% MSM: 100% Symptomatic: 0%	1: 68% 4: 32%	12 weeks	500 / 42%	Peg-IFN-α monotherapy 24 weeks (n=9) and 48 weeks (n=3)	37% (2 patients with SVR became re-infected)

MSM = men who have sex with men; NM = not mentioned; peg-IFN-α = pegylated interferon-alpha; SVR = sustained virological response; RBV = ribavirin.

chances of spontaneous viral clearance were lower (around 10 to 15%), but also highest within the first 12 weeks after the diagnosis.[57-60] However, in a recent study by Vogel *et al.*, evaluating spontaneous viral clearance rates in 92 HIV-infected patients with acute HCV, an unusually high clearance rate of 40% was reported.[61] An intent-to-treat (ITT) analysis on week 12 after the initial diagnosis showed a positive predictive value of 89% for development of chronic HCV in case of HCV-RNA positivity. Furthermore, patients not experiencing a 2log10 drop in HCV-RNA at week 4 after the diagnosis had an 85% chance of becoming chronically infected with HCV. The PCR used for HCV-RNA detection had a relatively high lower limit of detection of 600 IU/ml in contrast to the currently used detection limits of 10 to 50 IU/ml. This is important since it has been observed in acute HCV-infected patients that HCV-RNA fluctuates, sometimes even briefly becoming undetectable.[62]

Although the absence of spontaneous viral clearance might be predicted four weeks after the infection, this does not imply that treatment should be started thereafter. To date, no randomised study has compared the outcome of therapy in HIV-infected patients with an acute HCV infection starting treatment very early after the diagnosis compared with those who initiated treatment 12 weeks after the diagnosis. In the study by Matthews *et al.*[63] a high SVR rate of 80% was reported with treatment being initiated more than 30 weeks after the diagnosis of acute HCV. Furthermore, a recent retrospective cohort study in 50 patients from Amsterdam, evaluated the effect on SVR in patients with initiation of therapy within six months (24 weeks) after the diagnosis versus deferral of treatment thereafter.[18] In this study, the time of infection was defined as the midpoint between the last negative and first positive HCV test (serology or PCR). Although statistically not significant, in both the 24- and 48-week treatment arms a higher SVR rate was reported in patients starting treatment within six months after the diagnosis. Furthermore, in most intervention studies, treatment of acute HCV in HIV-infected patients was initiated after a median of 12 weeks after the diagnosis. In a cohort of acute HCV mono-infected Japanese patients a significantly lower SVR rate was noted when the start of therapy was postponed for one year compared with initiating therapy within eight weeks after the diagnosis (40% versus 81%).[64] Taken together, although spontaneous viral clearance generally occurs within 12 weeks after an acute HCV infection and the chances of persistence of acute HCV might be predicted already four weeks after the infection, evidence for very early initiation of therapy is lacking.

In conclusion, after establishing the diagnosis of acute HCV in HIV-coinfected patients, it is recommended to await spontaneous viral clearance for a period of no more than 12 weeks. If no spontaneous clearance occurs, anti-HCV therapy should be started.

Treatment duration

Most studies in HIV-infected patients with acute HCV achieved SVR rates above 60% after 24 weeks of treatment (*table 1*). This is supported by the previously mentioned Amsterdam cohort study evaluating the outcome of therapy in 50 HIV-infected patients with acute HCV.[18] No significant difference in SVR rates was demonstrated between 24 and 48 weeks of therapy (75 *vs* 86% in all patients starting therapy within six months after the diagnosis). In contrast, in a German study higher SVR rates were seen in the 48-week arm compared with the 24-week arm (89 *vs* 52%; p=0.062).[25] It must be noted that these patients were erroneously treated for 48 weeks due to a protocol violation and that both patients treated with peg-IFN-α monotherapy and combination therapy with ribavirin were pooled together for this analysis.

A recent re-analysis by Vogel *et al.*[65] of previously published studies, evaluated the treatment outcome and the role of HCV viral kinetics during therapy in a group of 111 HIV-infected patients treated for acute HCV. Longer treatment duration did not significantly improve SVR rates. Both achievement of a rapid virological response (in this study defined as HCV-RNA <600 IU/ml) and a complete early virological response (cEVR, undetectable HCV-RNA (<600 IU/ml) at week 12) were strong predictors of achieving an SVR. In other words, in case of favourable viral kinetics (fast decline of HCV-RNA until undetectable at week 4 (RVR) or week 12 (cEVR)), 24 weeks of treatment seems sufficient. On the other hand, only 9% of patients without a cEVR reached an SVR.

Quality of studies on which a recommendation is based:

Grade	Definition
A1	Meta-analysis of at least two independent studies of A2 level
A2	Randomised double-blind, placebo-controlled study of adequate quality and size
B	Comparative study not fulfilling the characteristics of an A2 level study (including case-control studies and cohort studies)
C	Non-comparative studies
D	Expert opinion

Level of evidence based on the quality of the study on which a recommendation is based

Level	Definition
I	Study of level A1 or at least two independent studies of level A2
II	Single level A2 study or at least two independent level B studies
III	Single level B or C study
IV	Expert opinion

CONCLUSION

In conclusion, 24 weeks of therapy is the preferred duration of treatment in HIV-infected patients with acute HCV achieving either an RVR or a >2log10 drop in HCV-RNA with an undetectable HCV viral load at week 12 of therapy (cEVR). In all other patients extending treatment duration to 48 weeks should be considered. In patients without a >2log10 drop in HCV-RNA at week 12 of therapy, treatment can be stopped.

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