Acute hepatitis C in HIV-infected individuals – recommendations from the NEAT consensus conference

The European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel

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Hepatitis C virus (HCV) infection is a transmissible disease with potentially severe consequences on morbidity and mortality. Although there is increasing awareness of an ongoing epidemic of acute HCV infection in HIV-infected men who have sex with men (MSM), there exists no guidance on the best management of acute HCV infection in HIV-infected individuals. As data from clinical trials and cohort studies has become available, evidence based guidelines are timely to permit best management of these individuals. To address this issue, the European AIDS Treatment Network (NEAT) invited members of the European AIDS Clinical Society (EACS) Hepatitis Group, the European Association for the Study of the Liver (EASL), the European Study Group on Viral Hepatitis (ESGVH) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European AIDS Treatment group (EATG) and other experts to attend a consensus conference on acute HCV infection in HIV-infected individuals in Paris, France, on May 21st, 2010. This review reports the results of the conference and recommendations issued on the diagnosis, epidemiology, natural course and treatment of HIV-infected patients with acute hepatitis C infection.

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Introduction

There is increasing awareness of an ongoing epidemic of acute hepatitis C virus (HCV) infection in HIV-infected men who have sex with men (MSM). The epidemiology has been reviewed in this journal recently [1], however there is a lack of guidance on the management of acute HCV infection in HIV-infected individuals. To address this issue, the European AIDS Treatment Network (NEAT) invited members of the European AIDS Clinical Society (EACS) hepatitis group, the European Association for the Study of the Liver (EASL), the European Study Group on Viral Hepatitis (ESGVH) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European AIDS Treatment group (EATG) and other experts to draw up a consensus statement at a conference held in Paris, France, in May, 2010. Four working groups prepared draft guidelines for consideration at the conference on: case definition and diagnosis, transmission risk and epidemiology, pathogen-

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esis and natural history, and acute HCV infection management in the HIV-infected population. A literature search, using the PubMed database of the National Library of Medicine, and abstract databases of the Conference on Retroviruses and Opportunistic Infections (CROI), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), and the Liver Meetings of the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL) was utilized by all groups. Statements and recommendations were graded by the strength of recommendation and level of evidence (Table 1). A consensus was reached if 80% or more of the participants were in favour.

Case definition and diagnosis of acute HCV infection in HIV-infected patients

Acute hepatitis C virus (HCV) infection is defined as the first six months after exposure to HCV. This definition is arbitrary as there is a lack of evidence on when 'acute' infection becomes 'chronic' and determining the precise timing of infection is usually problematic. As the majority of individuals with acute HCV infection are asymptomatic [3,4], clinical diagnosis has a low sensitivity. Differentiating between acute HCV infection and an exacerbation of chronic HCV infection clinically, virologically and immunologically is difficult in the absence of recent negative HCV RNA and antibody results. A serological test does not exist to differentiate between acute and chronic infection [5–7].

One third to a half of individuals with acute HCV infection experience symptoms attributable to an acute illness [3,4], although symptoms are non-specific. Eighty-eight percent experience elevated alanine aminotransferases (ALT) within three months of infection [8] with peak ALT levels $>$ 5 times the upper limit of normal in 55% [4]. Patients in this study were sampled at 1–3 monthly intervals, so the rate of ALT elevation could be an underestimation. HIV-infected patients with chronic HCV develop hepatic flares with a rise of ALT $>5 \times$ ULN in less than 2 % [9], minimizing the possibility of classifying "chronic" HCV infection as "acute". The first marker of HCV infection is serum or plasma HCV RNA detected via nucleic acid test (NAT) as early as one week post infection [10]. HCV antibody responses may be delayed or absent in HIV-infected individuals with two thirds positive at three months and 5% remaining negative up to one year after infection [8]. Fluctuations in HCV-RNA levels during the acute phase of HCV infection are characteristic in HIV-uninfected individuals and may be of value in suggesting a diagnosis of acute hepatitis C [11].

A definitive diagnosis of acute hepatitis C can be made by documented seroconversion from negative to positive in a test for HCV antibodies. Due to the asymptomatic nature of the illness seroconversion often occurs prior to diagnosis. Even if annual antibody screening is performed, a prior HCV antibody test may not have been performed within the previous six months. Due to delayed and occasionally absent HCV antibody seroconversion, the window period where HCV RNA will be detectable in peripheral blood without the presence of anti-HCV antibodies cannot be used with accuracy to diagnose acute hepatitis C. Advanced serologic assays for HCV including HCV-antigen tests improve the sensitivity of serological testing [12,13], but are inferior to testing for HCV-RNA (Table 2).

Consensus recommendation: case definition acute HCV infection

Preferred criteria *(Grade A, Level II)*

(1) Positive anti-HCV IgG in the presence or absence of a positive HCV RNA and a documented negative anti-HCV IgG in the previous 12 months or
(2) Positive HCV RNA and a documented negative HCV RNA and negative anti-HCV IgG in the previous 12 months

Alternative criteria *(Grade B, Level III)*

If historical data is lacking and relevant test results within the past year unavailable, acute hepatitis C may be diagnosed if the following criteria are met

Table 1. Grading strength of recommendation and level of evidence.

Strength of recommendation	
Grade A	Strong – good evidence to support a statement
Grade B	Moderate – moderate evidence to support a statement
Grade C	Optional – poor evidence to support a statement
Quality of evidence	
Level I	Evidence from at least one randomized controlled study
Level II	Evidence from at least one well-designed non-randomized study;one or more cohort or case-controlled studies; or from dramatic results of uncontrolled studies
Level III	Evidence from expert opinion only

∗adapted from the Canadian Task Force on the Periodic Health Examination Health Canada [2].

Table 2. Sensitivity of serum-based assays for the detection of hepatitis C virus compared to HCV-RNA.

Markers for acute hepatitis C virus in serum	Rate of positive /equivocal tested samples [12]*
Nucleic acid testing (NAT, HCV-RNA)	100%
HCV Antigen/HCV Antigen and Antibody	68%
HCV Antibody	20%

*serum of 25 HIV-infected patients with acute hepatitis C were retrospectively tested for the diagnostic sensitivity of antibody and antibody/antigen test kits. HCV-RNA was the reference, thus 100% of samples were HCV-RNA positive. Due to the diagnostic window a repeat test later on in the course of acute hepatitis C infection will enhance sensitivity of the test [8].

Positive HCV RNA regardless of anti-HCV IgG with:

(1) A) an acute rise in ALT greater than 10 times the upper limits of normal (ULN) B) an acute rise in ALT greater than five times the ULN, with documented normal ALT within twelve months. In individuals with a previously high ALT, an acute rise to 3.5 × their previous ALT is acceptable [14] and
(2) anti-hepatitis A virus IgM negative and anti-hepatitis B core IgM antibody negative, and exclusion of other causes of acute hepatitis.

No consensus (20 in favour, 6 against with 3 abstentions) was reached to include a history of transmission risk factors for acute HCV in the alternative case definition.

Epidemiology and transmission

Prevalence of HCV infection

The prevalence of HCV infection in the HIV-infected is higher than in the uninfected population [15]. Within the HIV-infected population the highest prevalence is in those with a history of intravenous drug use (IVDU) or haemophilia and other bleeding disorders. The Euro-SIDA cohort reported a prevalence of anti-HCV antibody or HCV RNA positivity of 33%, ranging from 6.6% in MSM to 75% in IVDUs [16]. This is similar to other cohorts and cross sectional studies in HIV-infected populations [17–26].

Incidence of acute hepatitis C

The most efficient means of HCV transmission is through parenteral exposure in IVDUs who share needles, syringes or other paraphernalia for drug use. Cases of sexual transmission of HCV infection in heterosexuals remain uncommon [27,28]. Since 2000 there have been reports from Europe, Australia and the USA of an increasing incidence of acute hepatitis C infection in HIV-infected MSM (Table 3). In Amsterdam incidence has risen 10-fold from an estimated 0.08 per 100 person years in 1984–99 to 0.87 in 2000–2003 in HIV-infected MSM attending a sexually transmitted infection (STI) clinic [29].

HCV transmission in MSM

Studies in MSM have shown HIV infection and intravenous drug use to be independently associated with the presence of HCV antibodies [29,33–35]. In early reports, evidence for sexual transmission was weak with conflicting evidence of an association with sexual risk behaviour [33–39].

Recent studies investigating factors underlying HCV transmission in HIV-infected MSM have provided further evidence for an association with certain sexual practices including fisting, using sex toys, and group sex [29,36,37]. Non-injecting drug use is also associated, probably because of the influence on sexual behaviour but transmission through sharing contaminated devices may also contribute. There is an association with bacterial sexually transmitted infections notably syphilis and lymphogranuloma venereum. The mechanism of sexual transmission remains uncertain but the association with traumatic sexual practices and ulcerative STIs affecting the mucosa of the rectum provides some clues. HCV RNA has been detected in semen and more often in the HIV-infected [38], although one study failed to detect HCV RNA in the semen of most HIV-infected men even during acute HCV infection [39]. Group sex may facilitate transfer of infected material [36]. Other causes of disruption of the ano-rectal mucosa, including surgery, may contribute to the risk [Schmidt]. There is no evidence that HIV-infected men are more susceptible to HCV infection due to immunological deficits, or that a more virulent HCV strain is being selected. Phylogenetic analyses of transmitted HCV strains show clustering consistent with transmission among a social and sexual network of HIV-infected MSM, which extends nationally and internationally [40]. Although the majority of patients present with two or more risk factors described above, cases of acute HCV infection are seen in MSM who report only unprotected anal intercourse. Although current outbreaks have been largely confined to HIV-infected MSM, cases have also been reported in HIV-uninfected individuals.

Public health implications

The recognition of ongoing transmission of HCV requires measures to reduce rates of transmission. This involves identification of undiagnosed HCV infection and ensuring appropriate risk-reduction advice is provided to the infected and those at risk.

Table 3. HCV incidence among people who are HIV infected.

Study	Time period	Sample size or person years	Population group	Number of Patients with HCV seroconversion	Incidence per 100 person years (95%CI)
Swiss HIV cohort [22]	1988-2004	N = 3327	History IVDU	69	7.4 (5.7–9.3)
			Heterosexual male, no IVDU	5	0.18 (0.06–0.42)
			Heterosexual female, no IVDU	6	0.17 (0.06–0.37)
			MSM, no IVDU, unsafe sex		
			MSM, no IVDU, safe sex	8	0.7 (0.3–1.4)
				6	0.2 (0.07–0.43)
Omega study cohort, Montreal [26]	1996-2001	2610 PY	MSM, non IVDU	0	0.038 (0.001,0.21)
		43 PY	MSM/IVDU	1	0.5 (0.06,12.9)
PRIMO cohort, France [30]	1996-2005	1405 PY	MSM	4	0.35
			Women	2	0.78
Positive Health cohort, Sydney, Australia [23]	2005-2007	n = 159 238 PY	MSM	0	0 (97% CI 0,1.54, single sided)
UK	2002	42985 PY	MSM	56	0.69
20 clinics in London and Brighton [31,32]	2006		MSM	84	1.16
	2007		MSM	101	0.82
Amsterdam cohort studies (ACS) [29]	1984-2003	4408 PY	MSM	8	0.18 (0.08,0.36)
	2000–3	572 PY	MSM	5	0.87 (0.28,2.03)

While unselected screening for acute hepatitis C in HIV-infected individuals may not be cost-effective in regions with a low prevalence [41], annual testing in populations at high risk may detect seroconversions in those with normal transaminases and permit improved estimation of the time of infection. Liver transaminases at routine visits with subsequent HCV-RNA testing in suspected cases will identify 90% of those with acute HCV [8]. HIV-infected individuals with severe immunodeficiency may lose anti-HCV antibodies but may regenerate antibodies after initiation of HIV therapy with subsequent immune reconstitution.

Consensus recommendation Screening for acute HCV infection (Grade A, Level II, ∗Grade C, Level II)

(1) All newly diagnosed HIV individuals should be screened for anti-HCV antibody [42].
(2) HIV-infected MSM at risk for contracting acute hepatitis C infection should be screened six monthly with ALT and annually with anti-HCV antibody.
(3) HIV-infected patients with newly diagnosed sexually transmitted infection or continued intravenous drug use should be screened 3 months after diagnosis/last exposure
(4) A NAT test for HCV RNA should be performed if a diagnosis of acute HCV infection is suspected.

The management of those diagnosed with acute HCV infection should include encouraging partner notification to identify potential sources of infection and those at risk of exposure. Screening for other sexually transmitted diseases is required.

Consensus recommendation risk-reduction advice (Grade B, Level II)

(1) Although the mode of HCV transmission remains unclear, epidemiological studies suggest that the following risk behaviours be considered in risk-reduction advice: fisting, recreational drug use, group sex, use of sex toys, unprotected anal sex, sharing of paraphernalia (for IVDU and permucosal drug use) and sexual practices with risk for blood-blood contact or mucosal damage
(2) Information regarding risk of HCV transmission should be given to all HIV-infected individuals after HIV diagnosis and on an ongoing basis. Advice regarding risk factors for transmission must be given to all those newly diagnosed with HCV infection including risk-reduction.

Pathogenesis, natural history and implications for treatment of acute hepatitis C

Innate and adaptive immune responses

The immune response in acute hepatitis C, and correlates of spontaneous clearance, have been studied predominantly in HCV-monoinfected individuals and in chimpanzees. Acute hepatitis C infection induces a range of innate and adaptive immune responses. Single nucleotide polymorphisms near the IL28B gene, encoding for interferon lambda, provide strong evidence for an important role of the innate immune system in the

natural defence against HCV [43–45]. Individuals with the CC genotype were more than three times likely to clear HCV-RNA compared with individuals with C/T and T/T genotypes [43]. A similar association is observed in HIV/HCV coinfected individuals [44]. The frequency of the protective allele varies across ethnic groups with a lower frequency in those of African origin compared to European patients, which could explain observed differences in spontaneous clearance between races [43]. The cellular immune response is important for the outcome of acute hepatitis C. Clearance in HIV-uninfected individuals is associated with a broad, vigorous and sustained memory CD4+ and CD8+ T-cell response [46,47]. In one study, memory T-cell responses to NS4 correlated with HCV clearance [48], whereas in a comparative study of HIV-infected and uninfected, HIV-infected patients had CD4+ T-cell IFNγ ELISpot responses against non-structural (NS3-5) proteins, but were reduced in frequency, breadth and magnitude [49]. Successful antiretroviral therapy can restore HCV specific cellular immune responses [50]. The importance of CD4/CD8 HCV antigen-specific responses in determining spontaneous clearance and patterns of viraemia post HCV acquisition has been demonstrated in HIV negative [51] and HIV co-infected individuals [52,53]. A lack of antigen-specific responses early in the course of acute infection determines progression to chronic HCV and may be associated with the pattern of viraemia observed [51]. Spontaneous clearance was associated with early antigen-specific responses and rapid HCV clearance.

The role of humoral immune responses in acute hepatitis C is not well defined [52–58]. Evoked cellular and humoral immune responses after first acute HCV infection diminish following spontaneous resolution or successful antiviral therapy [58], though data is inconsistent.

Rates and predictors of spontaneous HCV-RNA clearance

The rate of and factors associated with spontaneous viral clearance in HIV infected patients with acute hepatitis C have been studied in prospective cohorts. In the Johns Hopkins cohort [59] of predominantly black men with prior or current IVDU, HCV-RNA clearance was observed in 14% of HIV uninfected and 7% of HIV infected with the lowest rate (5%) associated with CD4+ cell counts <200 cells/ml. Viral clearance was associated with non-black ethnicity, younger age (<45 years) and HBsAg positivity [59]. In the EuroSIDA cohort spontaneous HCV-RNA clearance was 23% in 1940 HCV antibody positive individuals [60]. Factors associated with spontaneous viral clearance were female sex, mode of transmission (sexual vs. IVDU), HBsAg positivity and region (other European regions vs. southern Europe/Argentina). Viral clearance was not associated with age, ethnicity or HIV-related variables [60].

Rates of spontaneous viral clearance in those with established HIV infection range from 0 to 40%, but due to small sample sizes, and the majority being MSM, factors associated with spontaneous viral clearance are not well defined [49,61–63]. Gilleece et al. [62] reported lower HCV-RNA titers and CD4+ T-cell count >500 cells/microliter were predictive of spontaneous clearance.

Consensus statement on the natural history of acute hepatitis C infection

(1) Acute hepatitis C takes a chronic course more frequently in HIV infected individuals (II)
(2) Spontaneous clearance of acute HCV in HIV patients occurs in 0 – 40% (III) and is associated with
   (i) Host genetic factors (eg IL28b-CC genotype) and stronger adaptive immune responses. (II)
   (ii) Female sex, exposure group (sexual transmission vs. IVDU), HBsAg-positivity, jaundice and higher peak ALT (II)
   (iii) Early decline of HCV-RNA 4–8 weeks after presentation (III)

Selection for early antiviral therapy

Ideally only those who will not clear HCV spontaneously would be candidates for early antiviral treatment. However, delays in treatment could reduce efficacy. A positive HCV RNA 12 weeks into acute hepatitis is associated with transition to chronic infection. Thus, treatment has been recommended in those with persistent HCV RNA reactivity 12 weeks after onset of symptoms or 12 weeks after putative exposure, though there may be as much as 8 weeks difference between these time points. Low level viraemia and viral load fluctuations are common in acute HCV and are incorporated in standard diagnostic criteria [11]. The definition of 12 weeks HCV-RNA reactivity as a predictor of chronicity is supported by Gerlach JT et al [64]. In this study in HIV-negative patients, 2 of 24 cases which resolved still had HCV-RNA detectable 12 weeks after diagnosis and none after 16 weeks. A limitation of this study was that the HCV-RNA assay used (Amplicor Monitor) had a sensitivity of 600 IU/ml, more than a log higher than currently available tests. In a recent study of acute post-transfusion hepatitis C [65] utilizing a more sensitive HCV-RNA assay (TMA, transcription-mediated amplification) 48% with resolved infection had HCV-RNA detectable at 12 weeks and 32% at 16 weeks after ALT elevation. However 16% of patients progressing to chronic HCV had a negative HCV-RNA assay result 12 and 16 weeks after occurrence of hypertransaminasemia.

In a European cohort of 92 HIV-positive patients with acute HCV, the sensitivity and specificity of HCV RNA determination at 4 and 12 weeks to predict the outcome of acute HCV was similarly strong [66]. 85% who did not reduce HCV-RNA by more than 2 log, 4 weeks after

diagnosis, progressed to chronic hepatitis C defined as a positive HCV-RNA 24 weeks after the first positive HCV-RNA. 92 % who were HCV-RNA positive 12 weeks after diagnosis developed chronic hepatitis C. The observational setting and high cut-off of HCV-RNA assay used limits generalization of this data. The studies are summarized in Table 4. A robust study utilizing highly sensitive nucleic acid test (NAT) assays is required to provide stronger conclusions on the predictive value of HCV-RNA measurements during acute hepatitis C.

Optimum time interval between the onset of hepatitis and treatment initiation

If initiation of anti-HCV treatment is delayed for more than 1 year after onset, rates of sustained virological response (SVR) in HIV uninfected persons are halved [67]. A shorter delay (12 weeks) did not impair outcome in the HEPNET III cohort [68]. In studies of acute HCV treatment in the HIV infected most initiated treatment between 12 and 24 weeks into acute hepatitis and the length of time between the start of acute hepatitis and treatment initiation did not influence treatment response. This is exemplified in the Australian Trial in Acute HCV (ATAHC) where SVR of greater than 75% was achieved in co-infected individuals with 24 weeks of combination therapy, with a median estimated duration of HCV infection before the start of therapy of 30 weeks, and greater than 24 weeks in over 80% [3].

Consensus recommendation on the monitoring and initiation of treatment in the course of acute hepatitis C infection

(1) HCV RNA levels should be measured at initial presentation and 4 weeks later. (BII)
(2) Treatment should be offered to
    (i) Patients without a decrease of 2 $\log_{10}$ of HCV RNA at 4 weeks compared with initial HCV RNA. (BII)
    (ii) Patients with persistent serum HCV RNA 12 weeks after diagnosis of acute HCV. (AII)

(3) Patients showing spontaneous HCV RNA clearance before and after 12 weeks should undergo serial HCV RNA measurement for 48 weeks to confirm resolution. (AIII)

Testing of retrospective samples may be useful to assess duration of viral infection. In cases of persistent HCV infection of duration greater than 12 weeks, initiation of treatment is recommended.

Management of acute hepatitis C in HIV infected patients

In mono-infected acute hepatitis C, early therapy with standard interferon-alpha or pegylated interferon-alpha alone for up to 24 weeks is sufficient to obtain high rates of SVR (ranging from 71–98%) [64,69,70]. HIV-infected

Table 4. Predictability of week 4 and 12 HCV RNA in determining spontaneous viral clearance.

Author (yr)	Setting	Time point	Endpoint/HCVRNA cut-off	Positive cases/ resolved	Negative cases/ chronic
Gerlach [64]	Acute hepatitis C (clinical Dx) in HIV-negative 54 pts: 24 self limited	12 weeks after onset	Negative HCV-RNA/600 IU/mL	2/24 (8%)	3/17 (18%)
Mosley [65]	Post transfusion hepatitis 94 cases 25 probably resolved (HIV-status not determined)	17 weeks	Negative HCV-RNA/600 IU/mL	0/24	
		12 weeks after Alt > 90 IU/mL	Negative HCV-RNA/5–10 UI/mL	12/25 (48%)	11/69 (16%)
		16 weeks after ALT > 90 IU/mL	Negative HCV-RNA/5–10 IU/mL	8/25 (32%)	11/69 (16%)
Vogel [66]	Acute hepatitis C in HIV-infected patients 92 untreated cases	4 weeks after diagnosis	>2 log decay compared to HCV-RNA at diagnosis	4/26 (15%)	3/26 (12%)
		12 weeks after diagnosis	Negative HCV-RNA/615 IU/ml*	2/34 (6%)	4/27 (15%)

*multiple assays, assay with the least sensitivity used was bDNA assay (lower cut-off 615 IU/ml).

Table 5. Acute HCV treatment in HIV-infected patients.

Place	Number treated (n)	Genotype	Rx Regimen	Rx length (weeks)	SVR n (%)	Predictors of SVR
London [62]	27	23 G1 4 non-1	Peg-IFN 2a RBV 800–1200mg	24	16 (59)	All G non-1
Germany [71]	36	25 G1 7 G2/3 2 G4	Peg-IFN 2a/2b RBV 800–1200 mg (22/36)	24-48	22 (61)	Longer duration G2/3 Complete EVR >80/80/80
New York [72]	15	All G1	Peg-IFN 2a RBV 1000–1200mg	24-48	8 (80)	NA
Paris [48]	20	5 G1 14 G4 1 G3	Peg-IFN 2a RBV 800mg	24-36	13 (65)	NA
Australia [3]	22	16 G1 9 G2/3	Peg-IFN 2a RBV dose unspecified	24	16 (73)	G2/3 RVR >80/80/80
Paris [73]	14	3 G1 5 G3 5 G4 1G+4	Peg-IFN 2a RBV 800mg	24	10 (71)	Complete EVR G3
Moscow [74]	17	5 G1/4 12 G2/3	Peg-IFN 2b RBV 800–100mg	24	9 (53)	G3
Paris [63]	10	10 G4	Std IFN 9/10 RBV 2/10	24	0 (0)	NA
San Francisco [75]	4	3 G1 1 G2	Peg-IFN 2a RBV 1000mg	24-48	2/3 (67)	NA

R = ribavirin, G = genotype, >80/80/80 = more than 80% of planned Rx duration, more than 80% of IFN doses, more than 80% of ribavirin doses.

patients may be different due to a number of factors including high HCV viral loads, the proportion of genotype 1/4 infection, and possible adverse impact of HIV-associated immune suppression.

There are several reports of cohorts studying treatment of acute hepatitis C in HIV-infected persons (Table 5).

In these studies patients were treated with pegylated interferons at standard doses (alpha-2b, 1.5 mcg/Kg/week and alpha-2a, 180 mcg /week). Ribavirin was used in 145 of 170 subjects: weight-adjusted dosing in 122 and fixed dose in 23 (800 mg/d in 19 and 1000 mg/d in 4). Twelve of 25 (48%) treated with pegylated interferon monotherapy showed an SVR compared to 96 of 159 (60%) with combination therapy ($p > 0.05$). Although the cumulative results of these studies do not establish the role of ribavirin, other evidence of breakthrough and non-response in patients treated with pegylated interferon alone are also suggestive [3,76]. In a report of a study of acute hepatitis C genotype 1 and 4, in HIV-infected patients, 6 of 12 (50%) stopped therapy due to lack of early virological response (EVR - fall in HCV-RNA of more than 2 log or undetectability by 12 weeks after start of antiviral therapy) when treated with pegylated interferon alone [77]. The role of ribavirin in improving viral kinetic response has been demonstrated in the ATAHC study where greater reductions in HCV-RNA were seen between weeks 8–12 of treatment in HIV/HCV co-infected patients receiving combination therapy compared to pegylated interferon alone in mono-infected patients [78]. This translated into comparable rapid virological response (RVR - undetectable HCV-RNA 4 weeks after start of therapy) and SVR (undetectable HCV-RNA 24 weeks after the end of antiviral therapy) rates.

Another treatment strategy suggested for acute hepatitis C is to start pegylated interferon and ribavirin, but then discontinue the ribavirin in those with an EVR; no SVR data are yet available [79]. Although 48 weeks of therapy for acute HCV in HIV-infected patients appeared more efficacious than 24 weeks in a single study [71], a preliminary report [80] in mostly genotype 1/4 acute infections showed SVR rates of greater than 70% with no statistically significant difference by length of therapy. Furthermore, as seen in Table 5, 24 weeks of therapy is associated with SVR rates of over 60% overall.

A lack of RVR predicting relapse is apparent from a study in mono-infected patients [81]. Evidence for the use of viral kinetics in determining the chance of SVR and potentially the optimal length of therapy comes from the European Collaborative Cohort Study [82] where 150 HIV-infected men with acute HCV achieved an overall SVR of 62%. 93% of those with an RVR achieved a SVR, whilst only 9% not achieving complete EVR reached a SVR. Response rates were defined by an HCV-RNA below 615 IU/ml. It would be reasonable to aim for 24 weeks of therapy, with a longer duration of therapy reserved for those without RVR but having EVR.

Consensus recommendation on treatment of acute hepatitis C infection

(1) Pegylated-interferon and weight-based ribavirin is recommended for the treatment of acute hepatitis C in HIV-infected patients. (Grade A, Level II)
(2) Duration of treatment should be based on RVR (negative HCV RNA at week 4*), regardless of HCV genotype.
   (i) In patients with RVR, treatment duration should be 24 weeks. (AII)
   (ii) In patients without RVR, treatment duration of 48 weeks should be considered. (BIII)
   (iii) In non-RVR patients not achieving a $2\log_{10}$ drop in HCV RNA at week 12, treatment can be discontinued. (BIII)

* evidence based on using a 615 IU/ml cut-off to define negative HCV-RNA

When and which antiretroviral therapy to use in HIV infected patients with acute HCV

For information on CD4-strata for commencement of therapy and which antiretroviral components to use in HIV-patients with acute hepatitis C commencing pegylated interferon and ribavirin therapy, the EACS guidelines should be consulted [83].

Consensus recommendation on the use of antiretroviral therapy in the setting of acute HCV infection

In those with acute HCV and CD4-cell count $> 350/\mu l$ HCV therapy can be commenced before starting HIV therapy (BIII)

Panel members and conflict of interest

The development of guidelines demanded commercial independence and avoidance of potential conflict of interests, which could influence statements and recommendations made. The organization and related expenses of the conference were therefore solely funded through NEAT. NEAT is a project funded by the European Union under the 6th Framework programme, contract "acronym: NEAT, number: LSHP-CT-2006-037570". All conference participants were asked to declare any conflict of interest of themselves or their families.

The NEAT AHC panelists who were able to participate at the conference and vote on the statements / recommendations were:

Matthieu Albert, no conflict of interest

Jose Benito, no conflict of interest

Sanjay Bhagani ***Group leader "Management"*** (EACS), no conflict of interest

Christoph Boesecke, no conflict of interest

Katja Deterding (EASL), no conflict of interest

Stephanie Dominguez, no conflict of interest

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Emma Page Group leader "Case definition and diagnosis", no conflict of interest

Lars Peters Group leader "Natural history and pathogenesis" (EACS), no conflict of interest

Anton Pozniak, no conflict of interest

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Andri Rauch, no conflict of interest

Alison Rodger, no conflict of interest

Jürgen K. Rockstroh (EACS) ***Co-chair***, advisor of Essex and Roche pharmaceuticals

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Stephane de Wit, no conflict of interest

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Brigitte Autran, no conflict of interest

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Mark Danta, no conflict of interest

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