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Acute Hepatitis C in HIV-Positive Individuals

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Abstract

Due to the asymptomatic nature of acute hepatitis C it can be difficult to diagnose in the early stage of infection, but with the higher treatment success rates and reduced treatment duration at this stage, it is imperative that diagnoses are made. Therefore, physicians should routinely screen at-risk individuals and investigate abnormal liver function tests. Serum HCV RNA should be considered in any HCV-antibody-negative individual in whom acute HCV is clinically suspected, or annually in those high-risk individuals with previous infection. Acute hepatitis C transmission may be facilitated by the presence of an erosive genital lesion, such as syphilis or lymphogranuloma venereum, and thus testing at this time should be encouraged. Reinfection with HCV does occur and patients need to be informed of the sexual and other high-risk behaviors that put them at risk of reinfection. Public awareness of the possibility of HCV infection, and subsequent reinfection, in high-risk groups should be increased. The question of the optimal treatment regimen is still disputed. However, ongoing trials and the proposed randomized controlled trial from the European AIDS Treatment Network should answer many of our questions. In the meantime, units faced with HIV/acute hepatitis C coinfection should follow recommendations from the HCV-HIV International Panel. **(AIDS Rev. 2008;10:245-53)**

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Key words

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Introduction

Due to shared routes of transmission, HIV/hepatitis C virus (HIV/HCV) coinfection is common. Of the 33 million people living with HIV worldwide, 4-5 million are coinfected with HCV. Highly active antiretroviral therapy (HAART) has led to a marked decline in most opportunistic infections and, as a consequence, HCV has emerged as an important cause of morbidity and mortality in HIV-positive individuals. Much is known about the epidemiology, pathogenesis, diagnosis, and management of chronic HIV/HCV coinfection, but in comparison, knowledge about acute hepatitis C (AHC) infection in HIV-positive individuals is limited. Acute hepatitis refers to the presence of symptoms or clinical signs of hepatitis for a period of six months or less after the presumed time of exposure to HCV. The lack of a universally agreed upon diagnostic criteria, the asymptomatic nature of AHC, and a lack of screening programs all result in the vast majority of diagnoses being made when the infection is in the chronic state, resulting in relatively few numbers of AHC diagnoses. Recently, there has appeared to be an increased incidence of AHC in HIV-positive individuals, either due to a true increase in new infections or due to better screening and diagnostic intelligence. Either way, there has been considerable interest in HIV/AHC coinfection from the international community, galvanizing HIV physicians into new areas of research.

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Epidemiology

Globally, 170 million people (3% of the world's population) are chronically infected with HCV and 3-4 million are newly infected each year[1]. There is a large degree of geographic variability in its distribution. The highest

prevalence is reported from Egypt (22%)[2] and the lowest from the Netherlands (< 0.5%)[3].

A precise estimation of the incidence of HCV infection is difficult to determine because most acute infections are asymptomatic and available assays do not distinguish between acute and chronic infection. Surveillance and reporting systems are inadequate in many countries and can underestimate the incidence of AHC[4]. In England and Wales, new diagnoses are reported to the Health Protection Agency, which produces annual reports showing trends in the identification of anti-HCV-positive sera[5]. The European Centre for Disease Prevention and Control (ECDC) has produced its first Annual Epidemiological Report on Communicable Diseases in Europe[6]. However, these data do not distinguish between acute and chronic infections, and it is likely that the vast majority of the reported cases are from patients with chronic infection. Recently, the Health Protection Agency assessed the strategy to detect HCV RNA in the absence of antibody for diagnosis of AHC. They revealed an estimated incidence of 12.9 per 100 person-years in injecting drug users (IDU) and 3.7 per 100 person-years among drug/alcohol service attendees and prison inmates[7].

In the USA, there is a reporting scheme for acute viral hepatitis. Reporting is voluntary, and the U.S. Centers for Disease Control and Prevention produces annual reports[8]. The incidence of AHC has declined among the general population from 130 per 100,000 in the 1980s to 0.3 per 100,000 in 2006. The decline in the incidence of AHC is attributed to improved blood donor screening, needle exchange programs, and education among IDU. A recent study to estimate HCV incidence observed rates of 0.0028 per 100 person-years among blood donors and 33.4 per 100 person-years in young IDU[9].

In HIV-positive men who have sex with men (MSM) there has been a recent increase in the incidence of AHC in a number of European cities. In London, the incidence increased from 0.6% in 1997 to 9.3% in 2003[10] and in Amsterdam from 0.08 per 100 person-years in the 15 years before 2000 to 0.87 per 100 person-years[11]. A recent study looking at the incidence of AHC in individuals diagnosed with primary HIV in the UK found that it had increased from 0% in 2002, to 2.5% in 2003, 3.1% in 2004, and 3.9% in 2005[12].

Routes of transmission

The risk factors accounting for the bulk of HCV transmission worldwide are injection drug use in developed countries and blood transfusions from unscreened blood donors, unsafe therapeutic injections, and other iatrogenic routes in developing countries. Injecting drug users account for about 25-54% of AHC cases in Europe and the USA[13,14]. In HIV-positive individuals who acquired HIV via injection drug use, HCV prevalence reaches 90%[15]. The WHO estimated that unsafe injections accounted for two million new HCV infections in 2000[16] and that 43% of donated blood in the developing world is not screened adequately for transfusion-transmitted infections, including HCV[17].

Transmission of HCV infection through occupational and perinatal exposures occurs with much less efficiency. The risk of HCV transmission via contaminated needlestick injury is as low as 0.3%[18]. Acquisition of HCV infection through perinatal transmission is estimated to occur in 6.5% of infants born to HCV-infected mothers and 13.6% of infants born to HIV/HCV-coinfected mothers[19].

The role of sexual transmission of HCV remains controversial. The possibility of sexual transmission has been supported by the detection of HCV RNA in body fluids such as semen and saliva[20]. A number of seroprevalence studies in America, Asia, and Europe in long-term heterosexual couples estimate the prevalence of HCV in sexual partners to be between 2.5 to 24%[21]. In a study from Japan, looking at the frequency of HCV infection in spouses of individuals with known HCV, no spouses married for less than 10 years were infected with HCV, whereas 60% of spouses were infected after more than 50 years of marriage (< 10 years 0%, < 30 years 9%, 30 years 24%, 50 years 60%; $p < 0.05$)[22]. More recent prospective studies from Europe and Asia report an incidence of HCV transmission in serodiscordant couples of 0.23%[23] and 1%[24] per year in two studies and 0% per year in three other studies[25-27]. In MSM, the Omega Cohort Study found lack of evidence for the sexual transmission of HCV[28]. However, two recent studies in France and the USA have shown that in 15% of individuals diagnosed with AHC, sexual transmission is the only identifiable risk factor[29,30], and the figure was 22% in The German Competence Network for Viral Hepatitis (HEP-NET) AHC Cohort[31].

All this data suggests that sexual transmission of HCV occurs at most with very low frequency. However, HIV/HCV coinfection is common. One-third of the HIV-positive population in Europe is coinfected with HCV. It has been shown that in subjects with no parenteral risk factors, HCV infection is more prevalent in those with HIV than those without[32]. Researchers from the Royal Sussex County Hospital in the UK have shown that HIV-negative MSM are contracting AHC, albeit 13-times less commonly than their HIV-positive cohorts[33]; these findings suggest that HIV enhances the transmission of HCV. This may be explained by the increased HCV viral loads seen in HIV-positive individuals[34], the prolonged viral half-life[35], and the higher rates of HCV RNA in semen in HIV-positive MSM[36]. More recently, several outbreaks of AHC in HIV-positive MSM have been reported in London[37], Paris[38,39], Rotterdam[40], and Amsterdam[41]. These outbreaks appear to be fuelled by sexual transmission, with the majority of individuals denying parenteral risk factors. The presence of concomitant sexually transmitted infections (syphilis and lymphogranuloma venereum) adds weight to the possibility of

sexual transmission. These findings were supported by the Swiss HIV Cohort Study who reported an association between unsafe sexual behavior and the acquisition of HCV among MSM[42].

How HCV is transmitted sexually remains controversial. However, a number of studies have highlighted high-risk sexual behaviors associated with the acquisition of AHC. A cross-sectional study by the Sex, Health and Anti-Retrovirals Project (SHARP) in the UK showed that fisting was associated with the acquisition of HCV. There was no difference in reporting of injection drug use in those who became HCV positive and those who did not. They postulated that the mechanism of sexual transmission was via mucosal trauma as a consequence of receptive fisting, followed by receptive unprotected anal intercourse[43]. In a case-control study from Germany, multivariate analysis revealed that frequent rectal bleeding as well as intranasal administration of recreational drugs was associated with the acquisition of HCV[44]. In London, a case-control study was performed to investigate which factors were associated with the acquisition of AHC[45]. Results showed that individuals diagnosed with AHC had three-times as many sexual partners in the preceding 12 months. Unprotected receptive and insertive anal intercourse, fisting, the use of sex toys, group sex, and sexual activity under the influence of recreational drugs were all independently associated with the acquisition of AHC. In a multivariate analysis, participation in group-sex activities was the only independent predictor of HCV status. Those involved in two of these sexual practices were nine-times more likely to contract HCV and those involved in three, 23-times more likely. Phylogenetic analysis of the viruses revealed multiple monophyletic clades, signifying that several independent HCV lineages are co-circulating. The largest clade involved 43 patients. These results were supported by a similar study in Amsterdam[46].

Diagnosis

Acute hepatitis C is defined as the first six months of infection with HCV. Diagnosing AHC with certainty can be difficult, primarily because of the high proportion of asymptomatic cases, the absence of a reliable and specific IgM-based serologic test[47], and potential overlapping laboratory findings with acute and chronic hepatitis C infection (elevated alanine aminotransferase levels, positive serum HCV RNA, and anti-HCV antibodies). The majority of literature regarding diagnosis of HCV infection refers to the diagnosis of chronic HCV rather than AHC. As yet there is no universally agreed upon diagnostic criteria for AHC.

However, AHC can be diagnosed with a high level of certainty when the following three criteria are met: (i) the patient reports recent risk factors for acquiring HCV; (ii) laboratory studies show positive HCV RNA levels and an elevated alanine aminotransferase (ALT) level; and (iii) laboratory studies obtained within the prior six months demonstrate negative HCV viremia, normal serum hepatic aminotransferase levels, and negative HCV antibodies. In the clinical setting, however, most patients do not have a recent retrospective laboratory sample available for comparison. In the absence of historical data, several studies of acute HCV have relied on a stricter biochemical criterion of an ALT level greater than 10-times or 20-times normal, along with the caveat that the investigators could not find an alternate explanation for the patient's liver disease[48-50]. The presence of HCV RNA without detectable antibody response may also suggest AHC, but some individuals with chronic hepatitis C, especially those who are immunocompromised, may never seroconvert[51].

Definite proof of recent acquisition of HCV infection may be possible with IgG avidity (or antigen binding force). Immunoglobulin G avidity increases over time following antigen challenge. Thus, virus-specific IgG in the weeks following an acute infection will be of low avidity, while that associated with a chronic infection will have matured into high avidity. Assays can distinguish between low and high avidity antibody, based on the extent to which antigen-antibody binding is disrupted by the presence of a chaotropic agent. Results are expressed as an avidity index (AI) and provide clear cutoff values, which distinguish samples taken within 20-100 days of infection and those taken from patients with chronic infection[52]. However, there is no current standardized, agreed methodology for these assays.

Natural history

A recent study from Georgia followed up 16 individuals identified with AHC and gives supporting evidence to what we already know about the natural history[53]. Anti-HCV negative blood donors (n = 7,000) and IDU (n = 3,000) were screened for HCV RNA. Sixteen individuals were identified with AHC; seven from blood donors, nine from IDU. Four (25%) were symptomatic, with jaundice being the most common symptom. In those who were asymptomatic, eight (66%) had an elevated ALT. In all patients, viremia reached a peak at four weeks and, in those with spontaneous clearance, HCV RNA was undetectable by weeks 16-18. Four (25%) spontaneously cleared HCV; 50% of those who were symptomatic and only 16% of those who were asymptomatic.

Onset of AHC is usually insidious, with lack of appetite, vague abdominal discomfort, nausea, and jaundice. The incubation period is 10-14 weeks. Of those who develop it, only 20% have symptoms and it is rarely fulminant. This is even lower in the HIV-positive population, with only about 7% developing jaundice[54]. Elevation in serum ALT is its most characteristic feature. Mean peak ALT values have tended to range between 400-1000 IU/ml. Overall,

ALT values exceed 1000 IU/ml in only about 20% of cases. Serum bilirubin levels may also be elevated, but they do not typically exceed 12 mg/dl. The first marker of HCV infection is serum HCV RNA detected by PCR as early as one week after infection[55]. Seroconversion is detected after 2-6 months or later in certain risk groups, making anti-HCV testing less reliable than HCV RNA assessments for early diagnosis of AHC. A recent study by the German HEP-NET AHC Study Group has looked at the impact of viral and host factors on the initial presentation of AHC in over 250 patients. They found that disease severity was independent from the mode of infection, age, sex, body mass index, and HCV genotype[56].

In many patients, HCV infection is self-limiting and spontaneously resolves before proceeding beyond the acute phase. Spontaneous clearance has been shown to occur in up to as many as 42% of HIV-negative IDU[57]. Spontaneous resolution is most likely during the first 3-4 months of infection; after six months it rarely occurs. Several clinical features can serve as useful predictors of spontaneous resolution in patients with AHC. Robust and multi-specific CD4 and CD8 T-cell responses are closely associated with recovery and therefore it is unsurprising that in HIV coinfection, spontaneous clearance is not as common, ranging from 4-25%[58-61]. This may also explain why those presenting symptomatically are also more likely to clear the virus independently of treatment, with jaundice being an indicator of an effective host immune response. Patients younger than 40 years of age are more likely to spontaneously clear the virus[62] and 75-100% of infants undergo spontaneous resolution[63]. It has also been noted that women are more likely to clear HCV than men (40 vs. 19%), possibly due to facilitated clearance by an estrogen-dependent mechanism[64]. A recent study looking at factors associated with spontaneous clearance of AHC in an HIV-positive population demonstrated that HBV coinfection and acquisition via heterosexual (but not homosexual) exposure were associated with higher rates of clearance[65]. It is felt that viral interference may explain the increased clearance in HBV coinfection and a smaller viral inoculum in heterosexual transmission compared to IDU and mucosal-traumatic sexual practices in MSM.

Immune response

Immune response in hepatitis C virus infection

It has been noted that three different outcomes occur after acute infection. Firstly, spontaneous sustained viral clearance, secondly, transient viral clearance followed by resurgence of HCV RNA levels with development of chronic infection, and lastly, no viral clearance with persistent HCV RNA levels and development of chronic infection[66]. The immune response to AHC involves the coordinated function of both the innate and adaptive immune systems.

The HCV RNA contains pathogen-associated molecular pattern motifs that could bind toll-like receptor 3 at the cell surface and intracellularly to induce type 1 interferons (IFNα, IFNβ) in hepatocytes[67]. Interferon production results in synthesis of transcription factors, cell-surface glycoproteins, cytokines, and chemokines. Only a minority of hepatocytes is infected with HCV[68], but the gene products secreted by this small number of infected cells can produce, via paracrine effects, a transient antiviral state in neighboring uninfected cells. However, HCV RNA levels do not decrease in this early phase due to the ability of HCV to antagonize these antiviral responses. Several HCV proteins, including core[69], E2[70], nonstructural 3/4A[71], and nonstructural 5A[72], disturb the interferon response at multiple levels.

Natural killer (NK) cells are the major effector cells of the innate immune system and play an important role in the activation and maintenance of subsequent adaptive immune responses. Activated NK cells secrete inflammatory cytokines (INFγ, TNFα, IL-3), have cytotoxic activity against infected cells, and activate dendritic cells (professional antigen-presenting cells that bridge the innate and adaptive immune response). The HCV is able to directly block NK cell function. The HCV E2 protein binds the human cell surface molecule CD81 with high affinity. The binding of HCV E2 to CD81 on NK cells directly blocks the cell function[73]. It has also been shown that there is enhanced expression of inhibitory receptors (CD94-NK-G2A) on NK cells in hepatitis C[74]. Whether this is transforming growth factor-beta (TGFβ) or HCV driven is unknown[75], but results in reduced cytotoxic activity against hepatocytes and modified cytokine response with secretion of IL-10 and TGFβ, which impair dendritic cell activation and may enhance fibrosis progression.

The importance of HCV-specific $CD4^+$ T-cell responses in viral clearance was demonstrated when two chimpanzees depleted of $CD4^+$ T-cells were reinfected with HCV and developed persistent, low-level viremia despite functional intrahepatic memory $CD8^+$ T-cell responses[76]. In acutely HCV-infected patients without sufficient HCV-specific $CD4^+$ T-cell help, HCV-specific $CD8^+$ T-cell and heterologous neutralizing antibody responses may develop but fail to clear viremia[77]. Clearance of HCV is associated with a strong, sustained and broadly directed HCV-specific $CD4^+$ T-cell response[78,79]. It has been suggested that a T-helper cell-1 (Th1: IFNγ, TNFα) dominated $CD4^+$ T-cell response, rather than Th2 (IL-10, TGFβ) dominated $CD4^+$ T-cell response, is observed in those who clear AHC[80,81]. The $CD4^+$ T-cell response is maintained indefinitely after recovery from HCV infection[82]. In those who progress to chronic hepatitis, $CD4^+$ T-cell responses are weak, short lived, and barely detectable in the periphery[83].

Clearance of HCV is associated with a strong, broad and IFNγ-producing, HCV-specific $CD8^+$ T-cell response[84].

Most HCV-specific CD8+ T-cells express the inhibitory receptor programmed death 1 (PD-1) at the time of acute infection, but receptor levels decline in those who resolve infection and remain high in persistent infection[85]. Expression of PD-1 is associated with dysfunctional CD8+ T-cells. If viremia persists after acute infection, CD8+ T-cell frequencies may be normal, but responses wane rapidly[86].

Effect of HIV on immune responses to hepatitis C virus

The HIV establishes a chronic and latent infection that induces extensive damage of the immune system through virus-related and indirect pathogenic mechanisms. Individuals infected with HIV show a quantitative depletion of CD4+ T-cells and an overall immune dysfunction that includes dysregulation of the cytokine network, reduced functional capacity of CD8+ T-cells, and an aberrant activation of immune cells with functional alterations. The HIV infection significantly affects the immune system's ability to control HCV replication.

Cytokine dysregulation may contribute to the weakened HCV-specific adaptive immune responses during HIV coinfection[87]. Intrahepatic cytokines TNFα, IL-8 and IL-10 are lower among HCV/HIV-coinfected individuals compared to those with HCV monoinfection, whereas the profibrogenic cytokine TGFβ was found to be increased. Coinfection with HIV may induce TGFβ expression, resulting in accelerated liver fibrosis and reduced IFNγ response of CD8+ T-cells to viral infection, promoting HCV persistence. The enhancement of peripheral HCV-specific T-cell responses with functional blockade of TGFβ secretion is attenuated in individuals with HCV/HIV coinfection[88].

At a number of levels, HIV is likely to affect CD4+ T-cell responses through alterations in CD4+ T-cell survival, antigen-presenting cell function, and disruption of lymphoid architecture. Peripheral CD4+ T-cell responses to HCV antigens are virtually nonexistent in HCV/HIV-coinfected individuals[89], with a much narrower response to HCV in the coinfected population[90]. This defect in cell-mediated immunity occurs early during the course of HCV infection and probably explains the increased HCV persistence and higher HCV RNA levels during acute infection in HIV-infected individuals[91].

Management

Management of acute hepatitis C monoinfection

The 2004 guidelines from the American Association for the Study of Liver Disease[92] state that treatment of AHC should be considered, while delaying this for 2-4 months after acute onset to allow spontaneous resolution would be reasonable, and due to its improved ease of administration, the use of peginterferon (PEG-IFN) should be considered. However, no recommendation was made about either treatment length or the addition of ribavirin.

Interest in treating AHC came from a seminal study by Jaeckel, et al., which demonstrated that a sustained virologic response (SVR) of 98% was possible with 24 weeks of standard interferon-alpha (IFNα) monotherapy (5 MU/day for four weeks and 5 MU three-times a week for 20 weeks)[93]. This was at a time when average SVR rates in treatment for chronic hepatitis C with IFN and ribavirin were 50%. Owing to the large morbidity caused by the sequelae of chronic hepatitis C, these SVR rates for AHC made it a highly desirable alternative. The effectiveness of standard IFNα monotherapy has been confirmed in a number of other studies, obtaining SVR rates of 100 and 75%[94,95]. With the introduction of PEG-IFN, a preferred medication due to the once-weekly dosing and reduced side-effects, studies were carried out to see if a comparable SVR could be achieved. Monotherapy with PEG-IFNα-2b (1.5 μg/kg/wk) for a duration of 24 weeks was shown to have SVR rates of 71-94%; if patients were adherent, SVR of 89-94% were achieved[96-98].

The optimum duration of therapy is still under debate. A recent study compared treatment durations of 8, 12, and 24 weeks using PEG-IFNα-2b (1.5 μg/kg/wk) monotherapy[99]. Overall SVR rates were 67.6, 82.4, and 91.2%, respectively. Stratification by genotype led to relatively small subsets (13-16 per arm for genotypes 1 and 4, 2-3 per arm for genotypes 2 and 3), but gave interesting results. Patients with genotype 2 or 3 achieved an SVR of 100% irrespective of duration of therapy, suggesting that as little as eight weeks would be sufficient in these patients. However, individuals with genotype 1 achieved an SVR of 38, 60, and 88% with 8, 12, and 24 weeks of therapy, respectively ($p < 0.05$ for comparison between all groups), and in those with genotype 4, 12 and 24 weeks of therapy achieved significantly higher SVR rates than eight weeks. The possibility of a shorter treatment duration has been supported by several other recent trials that have evaluated the efficacy of 12 weeks PEG-IFN, with SVR rates of 72-74%[100-102]. An ongoing randomized, multicentre trial in Italy is comparing 12 or 24 weeks of therapy with PEG-IFN and may give definitive answers to the question of treatment duration[103].

The justification for investigating delayed therapy of AHC came from the results of a study by Gerlach, et al.[104]. Only patients who did not achieve spontaneous clearance were treated, achieving an SVR of 81%. If those who spontaneously cleared the virus were included in the response rate, this increased to 91%. Kamal, et al. demonstrated that delaying treatment onset by 8, 12, and 20 weeks resulted in SVR rates of 95, 92, and 76%, respectively, when using PEG-IFNα-2b (1.5 μg/kg/wk) for a duration of 12 weeks. It is important to note that treatment should not be delayed for too long. A Japanese study demonstrated that delaying treatment for a year compared

to eight weeks reduced SVR rates from 86 to 40%[105]. The HEP-NET group is at present conducting a randomized controlled trial to compare immediate treatment versus a 12-week delay[106].

Pegylated interferon in combination with ribavirin has become the mainstay of treatment in chronic hepatitis C. It is unlikely that with such high rates of SVR in monotherapy, combination with ribavirin (a medication with numerous side-effects) will improve results, as suggested in few studies[107,108].

The above literature would suggest that compared with chronic hepatitis C, intervention during AHC is associated with improved viral eradication, and a monotherapy regimen that is better tolerated, less expensive, and shorter than the currently approved combination therapies for chronic hepatitis C.

Management of acute hepatitis C virus/HIV coinfection

Experience in managing chronic HCV has taught us that HIV coinfection can alter treatment outcome, with much lower SVR rates seen in coinfected compared with monoinfected patients. The improved response to treatment in the acute phase of hepatitis C in monoinfected individuals therefore makes treating AHC in the HIV-coinfected population an exciting treatment alternative. This, along with the recent outbreak of AHC in HIV-positive individuals, has allowed a number of small, open, nonrandomized trials to be performed in a number of treatment centers. The evidence, however, remains limited.

Gilleece, et al. performed an open-label, prospective study to evaluate the efficacy of a 24-week course of PEG-IFN (1.5 µg/kg/week) plus weight-based ribavirin (800-1,200 mg/day) in HIV-positive homosexual men[109]. A wait-and-see approach was adopted, with spontaneous clearance in 24% of patients by week 12. The remaining patients were offered treatment, achieving an SVR of 59%. Although treatment success appeared more likely in HCV genotype non-1 than genotype 1 (4/4 vs. 11/20; p = 0.285), this did not reach significance.

Dominguez, et al. performed a similar study[110]. Spontaneous clearance was seen in only one out of 25 patients (4%). The remaining patients who accepted treatment had PEG-IFN (180 µg/week) and ribavirin (800 mg/day) for 24 weeks. At the time of publishing, early virologic response and SVR data were still being collected for five patients. However, initial results showed that 71% (10/14) of patients achieved SVR. A possible reason for the discrepancy in results between these two studies may be explained by the varying prevalence of genotype 1 (74 vs. 28%, Gilleece, et al. vs. Dominguez, et al.).

Vogel, et al. have presented data on 47 individuals enrolled in a prospective study[111]. Spontaneous seroconversion occurred in 25% of patients. Of the remaining patients, 27 were treated for 24 weeks, 11 with PEG-IFN (180 µg/week) monotherapy and 16 in combination with ribavirin. Nine were treated for 48 weeks, four with PEG-IFN (180 µg/week) monotherapy and five in combination with ribavirin. The results demonstrated better success rates with monotherapy compared with combination therapy at 24 weeks (73 vs. 38%) and with longer duration of therapy compared with shorter duration (89 vs. 52%). The lower response in the ribavirin-treated cohorts seems surprising; it does not appear that toxicity resulted in early discontinuation of treatment. However, the majority (11 of 14) of patients who failed were genotypes 1 and 4 (genotypes known to be less responsive to therapy in chronic HCV infection), and it may have been genotype rather than treatment composition that determined outcome. It is possible that a longer duration of therapy (48 weeks) results in higher success rates, but relatively small numbers were included.

The updated recommendations from the HCV-HIV International Panel published in 2007 state that early therapeutic intervention in AHC infection is particularly indicated in patients with HIV disease[112]. It advocates waiting 12 weeks from the estimated date of exposure prior to commencing treatment to allow spontaneous clearance, but discourages any further delay to prevent reduced treatment response. The recommended treatment is 24 weeks of PEG-IFN plus weight-based ribavirin. As these recommendations cannot be based on randomized controlled trials but on the available evidence and expert opinion, queries have been raised about the need for combination therapy with ribavirin[113]. Reasons given to withhold ribavirin are twofold. Firstly, it is believed that monotherapy with PEG-IFN would result in fewer side effects (anemia and thrombocytopenia), less interaction with antiretroviral agents, and lower pill burden, possibly leading to better compliance and higher chances of completing therapy. Secondly, some experts recommend PEG-IFN alone as currently no strong evidence suggests a superior treatment response if combination therapy is used. Moreover re-treatment in the case of failure may be easier if the patient is still naive to ribavirin. On the other hand, substantial data on the treatment of chronic HCV infection in HIV-coinfected individuals has shown that more aggressive treatment in coinfected patients is needed in order to obtain SVR rates that are comparable to HCV-monoinfected patients. By shortening the course of treatment to 24 weeks in the case of an acute infection, already a substantial decrease in drug exposure has been reached for coinfected patients. Therefore, from a conservative point of view, a combination therapy from the start may be just prudent in order not to sacrifice the opportunity to maximally treat the HCV infection in the acute phase of infection. The debate continues and in order to attempt to answer these questions the European AIDS Treatment Network (NEAT) is carrying out a randomized controlled trial to compare monotherapy with combination therapy and 24 weeks duration versus 48 weeks.

In chronic HCV/HIV coinfection, SVR to PEG-IFN and ribavirin varies according to well-known response predictors. These include genotype, HCV RNA level, rapid virologic response, and early virologic response. If we were able to identify response predictors in AHC, this might allow a better selection of candidates for treatment, with improved SVR rates. Nattermann, et al. have identified two host genetic factors which appear to influence response to AHC therapy. The AHC/HIV-positive individuals carrying IL-6 high-producer genotype have higher treatment response rates (74 vs. 33%; $p < 0.05$)[119], as do those carrying TGFβ high-producer (75 vs. 41.7%)[120].

Hepatitis C virus reinfection

Unlike hepatitis A and B, previous HCV infection does not protect against reinfection[114]. Attempts to develop a vaccine have highlighted the inability of the immune system to develop humoral or cellular protective immunity to HCV[115]. It is well described that the immunologic response evoked following HCV infection is not sufficient to protect against reinfection. Most of the data we have on reinfection with HCV has been retrieved from IDU populations with ongoing risk behaviors[116,117]. There are little data detailing HCV reinfection following sexual exposure and, in populations where there is a high prevalence of a single genotype, differentiating reinfection from late relapses can be difficult.

A recent study from two large, UK teaching centers describes a group of HIV-positive MSM with previous AHC re-presenting with a second HCV viremia following further sexual exposure[118]. Of 227 HIV-infected individuals under follow-up for AHC infection, 22 cases were identified as having had two or more defined episodes of HCV viremia. All were MSM and none had a history of injection drug use. All were treated with PEG-IFN and ribavirin for at least 24 weeks during their first episode. The mean length of virologic response was 21 months (range 3-54 months). Phylogenetic analysis and genotyping indicated likely reinfection with a distinct strain in 10 cases. Reinfection was likely to be related to ongoing high-risk sexual activity as evidenced by the prevalence of concurrent sexually transmitted infection. In two individuals, late relapse is possible, although in view of the increase in ALT, common source reinfection remains a possibility. In the remaining 10 individuals, the source of re-emergent virus was not determined due to lack of amplification of the samples, prohibiting phylogenetic analysis.

It has been postulated that these individuals may have been infected with a multitude of HCV quasispecies during initial infection and the second episodes of viremia represent re-emergence of latent virus. This theory seems less biologically plausible than reinfection as all individuals received treatment with PEG-IFN and ribavirin during the first episode, achieving a degree of virologic response for at least three months on cessation of treatment. This theory would also require the identification of an HCV sanctuary site.

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