Diagnosis and Treatment of Acute Hepatitis C Virus Infection

Christoph Boesecke, MD[a], Heiner Wedemeyer, MD[b], Jürgen Kurt Rockstroh, MD[a,*]

KEYWORDS

• Hepatitis C virus • HIV • Injection drug use • Monoinfection • Coinfection
• Acute hepatitis C

KEY POINTS

- The first 6 months after exposure to hepatitis C virus (HCV) are regarded as acute hepatitis C.
- Two patient populations worldwide share the highest prevalence of acute HCV infection: injection drug users and HIV-positive men who have sex with men.
- Diagnosis of acute HCV is often difficult in both patient populations because the acute inflammatory phase can be asymptomatic and patients at highest risk for acquiring acute HCV (injection drug users) tend to evade regular medical care.

INTRODUCTION

The first 6 months after exposure to hepatitis C virus (HCV) are regarded as acute hepatitis C (AHC).[1,2] Two patient populations worldwide share the highest prevalence of AHC virus infection: injection drug users and HIV-positive men who have sex with men (MSM). Within the latter a substantial increase in AHC cases has been observed over the past decade. Diagnosis of AHC is often difficult in both patient populations because the acute inflammatory phase can be clinically asymptomatic and patients at highest risk for acquiring AHC (injection drug users) tend to evade regular medical care. Type and duration of treatment vary depending on the presence of an auxiliary HIV infection. This article addresses similarities and differences in the epidemiology, diagnosis, and management of AHC monoinfection and coinfection.

[a] Department of Internal Medicine I, Bonn University Hospital, Sigmund-Freud-Straße 25, 53105 Bonn, Germany; [b] Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover, Germany
* Corresponding author.
E-mail address: juergen.rockstroh@ukb.uni-bonn.de

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EPIDEMIOLOGY

The highest prevalence and incidence of AHC monoinfection in developed countries can be found in injection drug users.[3–12] Other risk factors include blood transfusion from unscreened donors, unsafe therapeutic injections, and other health care–related procedures (**Table 1**).[13–16] Mother-to-child transmission of HCV has also been reported but on a very infrequent basis (see **Table 1**).[14]

Sexual intercourse with HCV-positive partners or promiscuity has been reported as a likely risk factor for acquiring HCV infection in 22% of cases in the German Hep-Net Acute HCV Studies I–III including more than 250 patients.[17] However, overall sexual transmission of HCV in serodiscordant heterosexual couples has been rare, with a lifetime risk less than 1% (see **Table 1**).[18,19] Still, reported sexual transmissions of HCV have been increasing in a U.S. report on acute HCV.[15] Although a history of intravenous drug abuse was still the most frequent cause for HCV infection in 48% of cases, 42% of the participants reported more than one sex partner and 10% revealed their sexual preference as MSM. The broader availability of lifestyle drugs, such as sildenafil, and use of noninjecting drugs has influenced sexual culture and has been shown to significantly increase the risk for HIV and other sexually transmitted diseases, not only in MSM but also in other populations.[20–23]

Nevertheless, most sexually transmitted acute HCV infections worldwide have been reported among HIV-positive MSM (**Fig. 1**).[16,24–51] These cases of AHC seemed to be linked to unsafe sex and recreational drug use, particularly sexual practices with high risk for blood–blood contact, including fisting, unprotected anal sex, and nasal snorting of drugs, which were previously considered rare and inefficient transmission routes.[52] This overlapping of risk factors may also be an important aspect in transmitting AHC infection via the sexual route. Within the German behavioral study,[52] 30% of patients with sexually transmitted AHC infection reported 2 or 3 risk factors, compared with 6% of controls.

Furthermore, transmission seems to occur via social networks separate from intravenous drug use. Phylogenetic analyses identified MSM-specific clustering of HCV strains, with almost three-quarters of HCV strains found in Europe circulating in more than one country. Viral sequences from injection drug users or endemic HCV strains were not part of any of these clusters.[53,54] Additionally, phylogenetic analyses of the Australian Trial in Acute Hepatitis C (ATAHC), in which a significant proportion of MSM self-reported intravenous drug abuse was the most likely route of hepatitis C

Table 1
Average estimated risk of transmission for HIV, HCV, and HIV/HCV coinfection

Mode of Transmission	HIV	HCV	HIV/HCV
Perinatal	10%–20%	<2%–7%	10%–20%
Sexual contact	<1%	<1%	<1%–3%[a]
Needle stick injury with cannula	0.3%	0.4%	Unknown

[a] Values are based from data from HCV serodiscordant heterosexual couples. It has to be speculated that, within the current outbreak of HCV in MSM, traumatic mucosal damage through unprotected anal sex or fisting with high risk of blood–blood contacts, the risk for acquisition of HCV is much higher.

Modified from Lacombe K, Rockstroh JK. HIV and viral hepatitis co-infections: advances and challenges. Gut 2012;61(Suppl 1):i48.

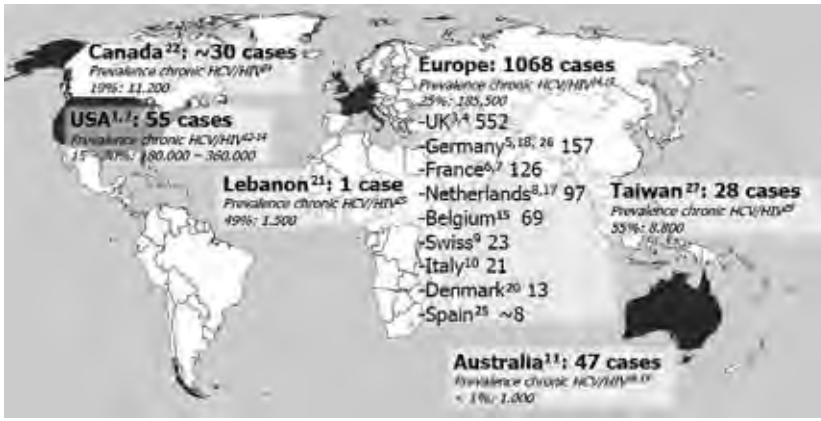

Fig. 1. Prevalence of acute hepatitis C in HIV-positive MSM.

transmission, revealed MSM-specific clustering regardless of the underlying mode of transmission.[36]

DIAGNOSIS

The AHC period is defined as the first 6 months after infection with HCV. Because the exact time point of infection is often difficult to determine, distinguishing between a true AHC and early chronic infection is frequently difficult.[1,2] Seroconversion from anti-HCV negativity to anti-HCV positivity, reflecting the development of antibodies, can be regarded as a definite diagnosis. However, because observable seroconversion is uncommon in clinical care, HCV RNA testing via polymerase chain reaction must be performed if AHC is suspected and anti-HCV antibodies are still negative. However, anti-HCV positivity does not necessarily imply a long-lasting chronic infection, but can also be observed in the acute phase. If prior serologic testing is not available (in injection drug users), viral load fluctuations and low-level viremia can be useful in distinguishing acute from chronic phase HCV infection.[55]

In addition, elevated aminotransferases can be a helpful indicator of AHC, although definitions vary from study to study. In contrast to HIV-positive patients who are seen every 3 to 6 months for routine control of HIV infection, those who are HIV-negative may consult with their general practitioner on a less frequent basis, and therefore acute liver transaminase elevations may possibly be missed in the HIV-negative population and thus only symptomatic patients are diagnosed. In addition, timely diagnosis is problematic because most individuals with acute HCV infection are asymptomatic. Only around one-third to a half of individuals with acute HCV infection show signs of an acute illness, such as lethargy and myalgia, and less frequently jaundice.[16,33] In the German Hep-Net AHC cohort, disease severity was not associated with HCV genotype, viral load, age, sex, and body mass index.[17] HIV-positive patients are less likely to experience a clinically apparent AHC infection.[16,33] In addition, anti-HCV seroconversion may be significantly delayed in HIV-positive patients, with 5% of cases still anti-HCV–negative despite ongoing viral replication for 1 year.[56] However, at least annual anti-HCV antibody and 6-monthly alanine aminotransferase (ALT)

measurements followed by HCV RNA testing in cases of suspected AHC seems to be a reasonable approach for AHC screening in HIV-positive individuals.[57] This recommendation derives from findings from the British St Mary's Acute Hepatitis C Cohort (SMACC), in which 88% of patients experienced elevated ALT within 3 months of infection, with peak ALT levels greater than 5 times the upper limit of normal in 55%.[56] In the absence of consensus recommendations, screening for clinically asymptomatic AHC in other at-risk populations, such as HIV-negative MSM and injection drug users, should consist of at least annual anti-HCV antibody testing. HCV RNA testing may be performed after defined high-risk exposures or clinical suspicion, which would be similar to recommendations after occupational exposure, wherein HCV RNA should be tested after 2 to 4 weeks.[58]

Clinicians worldwide are beginning to notice a second wave of AHC in HIV-infected individuals who had been successfully treated for or had spontaneously cleared their first episode of AHC previously.[59–61] This area clearly needs further study to identify risk factors for reinfection.

Natural Course

Rates of spontaneous HCV clearance have been estimated as high as 25% of cases in AHC monoinfection.[62] In some special cohorts, such young women, even up to 50% of patients may clear the virus without any antiviral treatment.[63] In contrast, chronicity rates are high in HIV-coinfected individuals, with around 85% of patients experiencing progression to chronic hepatitis C.[35,56,64–67] Scientific interest is still high in identifying predictors of viral clearance, because this would allow clinicians to expose to antiviral therapy only those patients who would not clear HCV spontaneously. Unfortunately, most of these studies lack power because of the number of patients evaluated is too small to accurately distinguish between predictive factors. So far, factors associated with spontaneous HCV clearance include symptomatic disease, female gender, nonblack ethnicity, clearance of HCV RNA within 4 weeks after onset of clinical symptoms, presence of neutralizing antibodies, T-cell responses, natural killer (NK) cell activities and the presence of distinct NK cell receptor and HLA ligands, hepatitis B surface antigen (HBsAg) positivity, and geographic region (other European regions vs southern Europe/Argentina).[68–84] Additionally, 2 studies have described high ALT and CD4 cell count as predictors for spontaneous clearance in HIV coinfection.[66,85]

In recent years, genome-wide association studies in HCV monoinfection identified single nucleotide polymorphisms (SNP) near the IL28B gene encoding for interferon lambda that constitute a crucial part of the host's innate immune defense against HCV.[66,84–89] Individuals with the CC genotype of the SNP rs12979860 were more than 3 times as likely to clear HCV RNA as individuals with CT and TT genotypes.[64,87,88,90] The IL28B genotype seems to be less important in patients with jaundice.[91] Similar observations regarding the influence of IL28B on spontaneous clearance rates have been made in HIV/HCV coinfected individuals.[37,48] These SNPs could explain differences in spontaneous clearance rates between races, because the frequency of the protective allele varies across ethnic groups, with a lower frequency in those of African origin compared with European patients.[87] The role of different SNPs in the IL28B region is currently a matter of debate. A positive impact of 4 SNPs, rs8099917 TT, rs8105790 TT, rs12980275 AA, and rs10853728 CC, on spontaneous clearance of HCV was shown in an Asian cohort infection.[92] In this cohort no link was seen between the rs12979860 SNP and spontaneous clearance of HCV infection. Further studies are needed to clarify the value of IL28b genotyping in AHC and whether treatment decisions can be based on distinct SNPs in the Il28b gene.[93]

To date, inconclusive data exist on liver fibrosis progression after AHC in HIV coinfection. Cohort data from the United States showed moderately advanced fibrosis on liver biopsy of 82% of patients (n = 11) with higher age, longer duration of HIV infection, and longer exposure to antiretroviral therapy.[94] Additionally, recent data from the European AHC Cohort should reassure patients and clinicians about the risk of liver cirrhosis after AHC, because the investigators found no evidence of a fastened fibrosis progression rate, assessed mainly with transelastography, in 45 patients over a median follow-up of 6 months after diagnosis of AHC.[95]

To further investigate into the epidemiology, natural history, and treatment outcomes of acute HCV infection in a more meaningful setting, the European AIDS Treatment Network (NEAT) group recently opened a multicenter prospective cohort study for recruitment, in which 600 HIV-positive and HIV-negative patients with documented AHC infection will be followed prospectively over an initial period of 3 years after diagnosis of AHC infection (PROBE-C study; ClinicalTrials.gov identifier: NCT01289652).

START OF TREATMENT

Also of high clinical significance is the determination of the point in time until which spontaneous clearance can be expected and subsequent treatment can be postponed without impeding its efficacy. In AHC monoinfection, early treatment is usually advisable, but so far no consensus exists. In patients who do not seem to be spontaneous clearers 2 to 4 months after onset of AHC, antiviral treatment should be considered, because 80% to 90% of patients may respond to interferon monotherapy.[1] Researchers have also suggested following these patients with HCV RNA quantification every 4 weeks and treating only those still positive at 12 weeks after initial presentation.[93] Data from a small cohort in HIV-negative patients support the definition of 12 weeks' HCV RNA negativity as a predictor of chronicity.[96] In this study, only 2 of 24 cases with spontaneous clearance had HCV RNA detectable 12 weeks after diagnosis, and none did after 16 weeks. However, some clinicians may prefer to start treatment earlier if the HCV RNA is persistently high.[1] Recent data from the German Hep-Net Acute HCV III study, to date the largest and first randomized European trial on AHC, confirm that early immediate treatment with pegylated interferon α-2b (PEG-IFNα-2b) is highly effective in both symptomatic and asymptomatic patients, and that delayed PEG-IFNα-2b plus ribavirin treatment may result in lower overall response rates in symptomatic patients in the absence of good adherence.[97] An economic evaluation in this patient population showed that early monotherapy was more cost-effective.[98] An algorithm for the treatment of AHC monoinfection is shown in **Fig. 2**.

In HIV/AHC coinfection, several cohort data have provided useful answers to the question of whether progression to chronicity of AHC infection can be predicted by looking at the course of HCV RNA after diagnosis. In a European cohort of 92 HIV-positive patients with acute HCV who did not receive HCV-specific antiviral therapy, the sensitivity and specificity of HCV RNA determination for predicting the outcome of AHC were similarly strong 4 and 12 weeks after diagnosis.[99,100] Nine of 10 patients showing spontaneous regression of HCV RNA of at least 2 log 4 weeks after diagnosis subsequently cleared HCV, whereas 92% of patients who were HCV RNA–positive 12 weeks after diagnosis developed chronic HCV. Further support comes again from the SMACC cohort, in which a rapid decline in HCV RNA (>2 log within 100 days of infection) in 112 HIV-infected patients was also identified as a predictor for spontaneous clearance, along with high CD4 T-cell count and elevated bilirubin and ALT levels.[66]

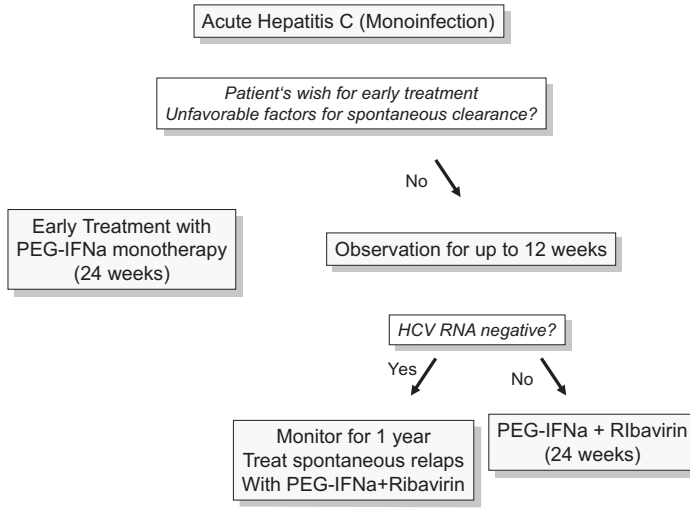

Fig. 2. Algorithm for the treatment of AHC monoinfection.

Comfortingly, a delay of 12 weeks in starting antiviral therapy has been shown to not impair the virologic outcome; the ATAHC cohort showed that treatment response rates seemed similar in AHC or early chronic HCV infection in both HIV-negative and HIV-positive patients.[101]

In the light of the given data, experts such as the European AIDS Treatment Network (NEAT) acute HCV consensus panel recommend that treatment be offered to all HIV patients who do not spontaneously show a drop in HCV RNA of more than 2 log at week 4 or who are still HCV RNA–positive at week 12 after diagnosis (**Fig. 3**).[57]

Type of Treatment

Over the years, reports of cohorts studying treatment of AHC in HIV-negative and HIV-positive individuals have accumulated.

In AHC monoinfection, high sustained virologic response (SVR; undetectable HCV RNA 24 weeks after end of treatment) rates up to 90% or even higher regardless of HCV genotype have been reported with PEG-IFNα monotherapy.[96,102–104] The study by Wiegand and colleagues[96] also highlights the importance of adherence to therapy for successful treatment responses in populations with mediocre compliance. The low overall SVR rate of 71% could be explained as reflecting a substantial proportion of nonadherent patients. Among those adherent to therapy, the SVR rate was 89%. The usual treatment of AHC should therefore be based on PEG-IFNα monotherapy (ie, either PEG-IFNα-2a, 180 μg/wk, or PEG-IFNα-2b, 1.5 μg/kg/wk).[1] Combination therapy with ribavirin does not significantly increase the SVR rate but may be considered in those patients in whom the differential diagnosis of acute versus chronic hepatitis is uncertain.[1] In the German Hep-Net Acute HCV III study, delayed PEG-IFNα-2b plus ribavirin treatment in symptomatic patients fully adherent to therapy led to response rates similar to those seen with early immediate treatment with PEG-IFNα-2b monotherapy.[97] To date, data supporting the addition of ribavirin to PEG-IFN in the treatment of early AHC monoinfection are still inconclusive.[105] In clinical practice, starting monotherapy with PEG-IFN and monitoring HCV RNA may be reasonable. If

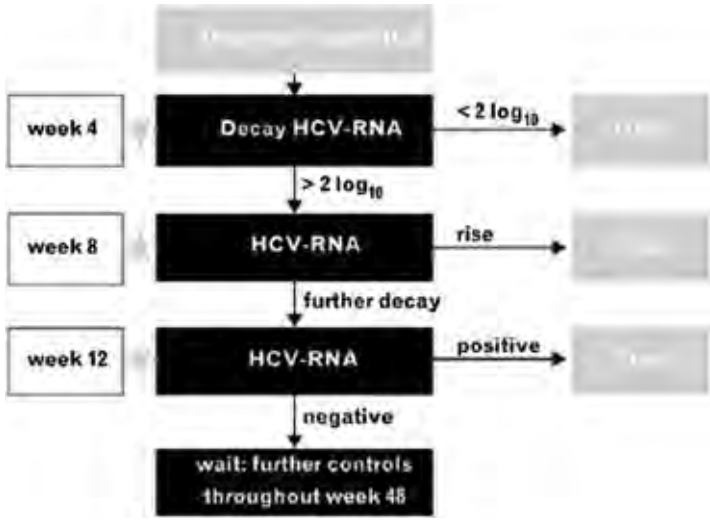

Fig. 3. Starting antiviral therapy according to the course of HCV RNA in HIV coinfection. (*Reproduced from* Deterding K, Gruner NH, Buggisch P, et al. Early versus delayed treatment of acute hepatitis C: the German HEP-NET Acute HCV-III study - a randomized controlled trial. Presented at the 47th Annual Meeting of the European Association for the Study of the Liver (EASL 2012). Barcelona, Spain, April 18–22, 2012; with permission.)

patients do not become HCV RNA–negative by week 4, the addition of ribavirin should be considered.

In AHC coinfection, SVR rates of 60% to 80% after early antiviral therapy with PEG-IFN and ribavirin have been shown within clinical studies and cohorts, regardless of HCV genotype.[24,49,50,85,106–111] These rates are clearly higher compared with those observed in the setting of chronic HCV infection, wherein rates of around 30% are reached for genotype 1 infection,[112,113] which is the predominant HCV genotype in acute HCV infection. Patients were treated with PEG-IFNs at standard doses (PEG-IFNα-2b, 1.5 μg/kg/wk, and PEG-IFNα-2a, 180 μg/wk), and ribavirin was used in 85% of patients.

The added value of ribavirin is still very much a focus of scientific interest. Ribavirin nonetheless seems to be necessary to reach high response rates in HIV-coinfected patients in light of case reports of inefficient PEG-IFN monotherapy from Germany[106] and a first pilot trial of PEG-IFN monotherapy from the Netherlands.[37] In addition, ribavirin's important contribution to improving viral kinetic response has been shown in early chronic infection in the aforementioned ATAHC study in which greater reductions in HCV RNA were seen between weeks 8 and 12 of treatment in HIV/HCV coinfected patients receiving combination therapy compared with PEG-IFN alone in monoinfected patients.[114,115]

With regard to IL28B's influence on treatment outcome, published data from a German cohort showed that, in contrast to HIV-infected patients with chronic HCV, the IL28B genotype was not significantly associated with treatment response rates in patients with AHC,[38,116] which is in line with known data on the effect of IL28B in the treatment of AHC in HIV-negative individuals.[64,93]

To date, no data exist on the efficacy and safety of specifically targeted antiviral therapy for HCV genotype 1 with the novel HCV protease inhibitors in the setting of acute HCV monoinfection or coinfection.

Duration of Treatment

The usual duration of treatment in AHC monoinfection is 24 weeks.[1,117] A small number of studies have evaluated different short-course therapies (8, 12 weeks) but failed to show similar SVR rates, as seen after 24 weeks of treatment.[118–124] The only independent factor associated with SVR was a rapid virologic response (RVR; undetectable HCV RNA at week 4 of treatment).

Analogous to using viral kinetics in predicting spontaneous viral clearance, evidence for the use of viral kinetics in determining the chance of SVR and potentially the optimal length of therapy in AHC coinfection comes from the European multicenter cohort study.[119] In this observational cohort, patients who were able to achieve a viral load of less than 600 IU/mL at week 4 had a very high chance of reaching SVR. In contrast, therapy was likely to fail in patients who did not reach a viral load of less than 600 IU/mL at week 12. An additional subanalysis showed that German patients who were treated for at least 20 weeks or longer after a first HCV RNA level of less than 600 IU/mL had a 96% chance of cure (SVR), compared with only 20% of patients reached SVR if they were treated less than 20 weeks after a first HCV RNA level of less than 600 IU/mL.[119] Although 48 weeks of therapy for acute HCV in HIV-infected patients seemed more efficacious than 24 weeks in another single study,[120] other reports in AHC coinfection showed SVR rates of greater than 70%, with no statistically significant difference by length of therapy.[101,106,121] Most recent data from the United Kingdom support the RVR-driven treatment duration, as recommended by the NEAT consensus panel.[57,122,125]

Modern commercial assays have reached lower limits of HCV RNA detection of 10 or 15 IU/mL. Although the value of more sensitive assays for defining virologic response have not yet been explored in the setting of acute HCV infection, residual viremia less than 600 IU/mL at week 4 of treatment has been associated with decreased odds for achieving SVR in the setting of chronic HCV infection.[123]

In summary, experts recommend using PEG-IFN and weight-based ribavirin for all HIV-positive patients with AHC infection. Stopping ribavirin after week 12 in patients who have achieved a negative HCV RNA level at week 8 or 12 may be an option for those experiencing ribavirin-associated toxicity. Viral decay may be slowed in HIV-positive compared with HIV-negative patients, and groups of patients may benefit from prolonged duration of treatment. The NEAT Acute Hepatitis C Infection Consensus Panel therefore recommends considering 24 weeks of therapy sufficient if patients reach RVR; in patients who do not reach RVR, 48 weeks may be considered (**Fig. 4**).[57]

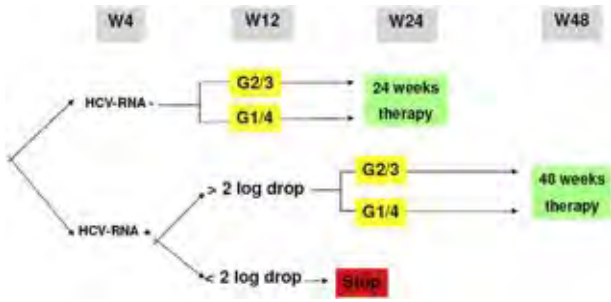

Fig. 4. Duration of antiviral therapy according to the course of HCV RNA in HIV coinfection.

SUMMARY

Transmission of HCV mainly occurs in injection drugs users and HIV-positive individuals, especially MSM, in whom AHC has been increasing over the past decade. The rates of spontaneous viral clearance are estimated at around 15% for HIV-positive and 25% for HIV-negative individuals. Early antiviral therapy is recommended in patients who do not reach a significant decay of HCV RNA 4 weeks after diagnosis or who still have detectable HCV RNA 12 weeks after diagnosis. The current standard regimen for treating acute HCV infection is PEG-IFN for 24 weeks in HIV-negative individuals regardless of HCV genotype, and PEG-IFN in combination with weight-based ribavirin in HIV-positive individuals. Duration of treatment should be adjusted based on the initial virologic response to antiviral therapy. Randomized controlled trials are urgently needed to help develop guidelines on best clinical management of AHC, including topics such as use of newly developed protease inhibitors, added value of ribavirin, and influence of HCV genotype and IL28B genotype polymorphism on treatment duration.

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