Hepatitis C Virus (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations
• Testing for hepatitis C virus (HCV) infection should be performed on any child whose mother is known to have the infection **(AIII)**. All HIV-infected adults and adolescents should be tested for HCV infection **(AIII)**.
• Recommendations for route of delivery and infant feeding for HIV/HCV-coinfected women and their infants are the same as those for HIV-monoinfected women and their infants **(AII)**.
• Diagnostic evaluation for HCV infection in the first 18 months of life after HCV exposure: 2 negative HCV RNA tests at or after age 2 months, including one at or after age 12 months, definitively excludes HCV infection **(BIII)**. Two positive HCV RNA results before age 18 months are required for definitive diagnosis of HCV infection **(BIII)**.
• Diagnosis of HCV infection in the child older than age 18 months: Screen with anti-HCV antibody test and confirm active viral infection with HCV RNA polymerase chain reaction testing **(AIII)**.
• Adolescents should be counseled to avoid injection drug use; if using drugs, they need HCV (and HIV and HBV testing), and appropriate referral and therapy, including drug treatment. Other exposures, such as through unprotected sex, (commercial) tattooing and body-piercing, represent a much lower risk of transmission but should also be avoided **(BIII)**.
• All children (regardless of HIV and HCV infection status) should receive standard vaccination with hepatitis A and B vaccines **(AIII)**.
• Treatment of children aged <3 years who have HCV infection usually is not recommended **(BIII)**.
• Treatment should be considered for all HIV/HCV-coinfected children aged ≥3 years who have no contraindications to treatment **(BIII)**.
• A liver biopsy to stage disease is recommended before deciding whether to initiate therapy for chronic HCV genotype 1 infection **(BIII)**. However, some specialists would treat children infected with HCV genotypes 2 or 3 without first obtaining a liver biopsy **(BIII)**.
• Treatment of HCV-infected children, regardless of HIV status, should include interferon alfa (IFN-α) plus ribavirin combination therapy **(AI)**. Duration of treatment for HIV/HCV-coinfected children should be 48 weeks, regardless of HCV genotype **(BIII)**.
• Ribavirin and didanosine should not be used together **(AIII)**.
• When possible, ribavirin and zidovudine should not be administered simultaneously because both are associated with anemia **(BII*)**.
• IFN-α therapy is contraindicated for children with decompensated liver disease, substantial cytopenias, renal failure, severe cardiac or neuropsychiatric disorders, and non-HCV-related autoimmune disease **(AII*)**.
• Use of erythropoietin can be used to manage clinically significant anemia during HCV treatment **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials in children[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion
[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

In the United States, the prevalence of hepatitis C virus (HCV) infection is 0.2% among children aged 1 to 11 years and 0.4% among adolescents aged 12 to 19 years.[1,2] Modeling based on a recent U.S. census predicts that ~7,200 new cases of pediatric HCV infection occur annually.[3] At least six HCV genotypes are known (genotypes 1–6), with genotype 1 occurring most commonly in the United States.[4] The prevalence of HCV infection among HIV-infected children may be higher. In a serostudy of 535 HIV-infected children followed in pediatric HIV clinical trials, the prevalence of HCV infection by HCV antibody and RNA testing was 1.5%.[5] In a more recent study of 228 HIV-infected children at an inner-city hospital in the Bronx, seven HIV-infected children had chronic HCV infection (3.1% [95% CI, 1.4%–6.5%]), defined as a reactive HCV

antibody and positive HCV real-time polymerase chain reaction (PCR).[6] The mean age of HIV/HCV-coinfected children was 16 years, and 57% had mild elevation (up to twofold above upper limit of normal) in serum transaminase levels.

Mother-to-child transmission (MTCT) is the predominant mode of HCV acquisition in children.[7,8] Other potential sources of HCV infection in older children, as for adults, include injection-drug use and, to a lesser extent, non-commercial body piercing or tattoos, unintentional needle stick injury, household contact, and sexual exposure.[9,10] Before 1992, blood transfusion was a source of HCV infection in children. A recent retrospective study found that 3% of infants who had received blood transfusions in a neonatal intensive-care unit between 1975 and 1992 were anti-HCV-antibody positive.[11] However, the incidence of HCV infection from transfusion has dramatically declined since 1992, when second-generation HCV enzyme-linked immunosorbent assay (EIA) screening was implemented. With the current additional use of nucleic acid amplification testing, the risk of HCV infection through transfusion is approximately 1 in 2 million.[12]

The overall risk for MTCT of HCV from a woman infected with HCV alone ranges from 4% to 10%.[7,13-21] The primary risk factor for perinatal HCV transmission is maternal HCV viremia at delivery, although an absolute threshold for HCV transmission has not been identified.[14,22-27] Data do not indicate that HCV genotype is related to risk of perinatal HCV transmission.[14,20] Although a few studies have suggested that vaginal delivery increases risk of HCV transmission[13,15,17,22] and that HCV can be transmitted during the intrapartum period,[28] most studies have found that mode of delivery does not appear to influence perinatal HCV transmission.[8,15,16,18,29-33] In addition, even though HCV RNA can be detected in breast milk, studies of infants born to HCV-infected women have not demonstrated a higher risk of HCV transmission in breastfed infants than in those who are formula-fed.[8,13-16,18,25,28,29,34]

Maternal HIV coinfection increases the risk of perinatal transmission, with perinatal HCV transmission rates of 6% to 23% reported for infants born to women who are HIV/HCV-coinfected[7,13-15,19,26,30-32,35-41] Furthermore, a few studies suggest that children who are infected with HIV during the perinatal period may be more likely than HIV-uninfected children to acquire HCV infection from mothers who are HIV/HCV-coinfected.[30,31,38,40] Dual virus transmission has been reported in 4% to 10% of children born to HIV/HCV-coinfected mothers.[13,30,36,38,39] HCV RNA levels are hypothesized to be higher among women coinfected with HIV than in those infected with HCV alone, which could account, in part, for the increased risk of MTCT of HCV from HIV/HCV-coinfected women; however, not all studies have found higher levels of HCV viremia among HIV-infected mothers.[24,31,35] One European study suggested that perinatal transmission of HCV may be reduced in HIV-infected women receiving combination antiretroviral therapy (cART).[32]

Acute HCV infection appears to spontaneously resolve in 15% to 25% of adults.[4] Findings from a limited number of longitudinal studies suggest that HCV infection resolves spontaneously in 17% to 59% of children with perinatal HCV infection.[42-47] Spontaneous viral clearance in perinatal HCV infection was more common with HCV genotype 3 and usually occurred by age 3 years.[46,48] Spontaneous viral clearance also has been associated with the presence of CC interleukin-28 (IL28B) host genotype in perinatally HCV-infected infants.[49]

Chronic HCV infection is defined as the presence of HCV RNA for >6 months. A study from Italy reported on long-term outcome in more than 350 children with chronic, untreated HCV infection (mean follow up 5.9±3.8 years), encompassing both perinatal and parenteral modes of transmission. The overall proportion of children who had spontaneous viral clearance was 7.5%. The rate of spontaneous viral clearance in the vertically acquired cases was 11.5%: half of these cases were genotype 3 and clearance occurred within the first 3 years of life. Evidence of chronic liver disease and cirrhosis was present in 1.8% of HCV-infected children. The average time from diagnosis of HCV infection to development of cirrhosis was 9.87±5.9 years.[50] In a study comparing children with perinatal HIV/HCV coinfection with those with perinatal HCV infection alone, spontaneous clearance of HCV infection occurred in 10 (17.5%) of 57 with HCV monoinfection but none of the 13 children with HIV/HCV coinfection.[51]

Clinical Manifestations

Children with perinatal HCV infection appear to have a more benign clinical course than do adults with newly acquired HCV infection.[9,52,53] Most HCV-infected children are asymptomatic, with minor abnormalities such as hepatomegaly, or mild nonspecific symptoms such as fatigue, myalgias, and poor weight gain;[9,53,54] however, intermittent asymptomatic elevations in transaminase levels are common during the first 2 years of life.[45,54-56] In a large European cohort of HCV-infected children, about 20% of children had apparent clearance of HCV viremia; 50% had chronic asymptomatic infection, characterized by intermittent viremia, rare hepatomegaly, and usually normal liver transaminase levels; and 30% had chronic active infection with persistent viremia and abnormal transaminase levels.[46]

Histopathologic inflammatory changes of chronic hepatitis may be present in patients with chronic HCV infection despite lack of symptoms, normal serum transaminase levels, and low HCV RNA levels.[54] Analysis of liver histology in 121 treatment-naive pediatric patients showed some degree of inflammation in all samples, mild fibrosis (Ishak stage 1–2) in 80% and cirrhosis in only 2% of patients.[57] Most children with chronic HCV infection who have undergone liver biopsy and are included in published studies typically have mild-to-moderate liver disease as determined by signs of structural alterations, inflammatory activity, and necrosis.[9,24,53,55] Similar proportions of vertically and parenterally HCV-infected children have signs of chronic hepatitis on liver biopsy.[56] A small subset of children may develop severe liver disease. In a study of 60 children with perinatally acquired or transfusion-acquired HCV infection who were infected for a mean duration of 13 years, 12% had significant fibrosis on liver biopsy.[53] Older age at time of infection and elevated serum gamma-glutamyltranspeptidase correlated with fibrosis; serum transaminase levels correlated with inflammation.[53]

In HIV/ HCV-coinfected adults, the natural history of HCV infection appears to be accelerated, with more rapid progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC), and death.[58,59] In HIV/HCV-coinfected adults, there are conflicting reports about the effect of cART and immune reconstitution on liver-related mortality, with some studies showing decreases and others little difference in liver-related mortality.[60,61] Data are minimal on the effect of HIV/HCV-coinfection on the natural history of HCV infection in children and insufficient to draw conclusions about HCV disease progression in coinfected children.[7]

Data are conflicting on the impact of HCV infection on HIV disease progression in adults; some studies suggest higher rates of HIV progression and others do not.[7] The effect of pediatric coinfection on HIV disease progression also is unclear because the number of coinfected children is small, and few studies have evaluated this. Two studies of children with perinatal HIV/HCV coinfection found no increase in HIV progression. On the other hand, in a study from Spain comparing children with perinatal HIV/HCV coinfection with those with perinatal HCV infection alone, HCV viremia and maximum transaminase levels were higher in the coinfected children than in those with HCV infection alone.[51] In a study of older children with thalassemia who were infected through transfusion, disease progression was more rapid and mortality higher in those with HIV/HCV-coinfection than in those with HIV monoinfection.[30,39,62]

Making the Diagnosis

Testing for HCV infection should be performed on any child whose mother is known to have HCV infection **(AIII)**. All HIV-infected adults and adolescents should be tested for HCV infection **(AIII)**.

Serologic and nucleic acid tests are used to diagnose HCV infection. HCV RNA first becomes detectable 1 to 3 weeks after HCV infection and precedes serologic response to HCV.[4] A third-generation EIA is available for detecting antibody to HCV (anti-HCV). Passively transferred maternal anti-HCV can be detected for up to 18 months in infants born to HCV-infected mothers. In a large cohort of HCV-exposed but -uninfected children, anti-HCV was present in 15% of children at 12 months, 5% at 15 months, and 2% at 18 months.[24] Therefore, only the presence of persistent HCV viremia can be used to reliably verify HCV infection in at-risk children aged <18 months.[63] HCV infection can be diagnosed in such children using a nucleic acid test to detect HCV RNA after age 1 month; the sensitivity of the HCV RNA testing is low at birth (22%), but

increases to 85% at 6 months.[64] Most children with perinatal HCV infection will have a positive HCV RNA test by age 12 months. However, because of intermittent viremia, a single negative HCV RNA test is not conclusive evidence of lack of infection. Thus, two negative HCV RNA results obtained at or after age 2 months, including at least one test at or after age 12 months, definitively excludes HCV infection in an HCV-exposed infant **(BIII)**. Two positive HCV RNA results before age 18 months are required for definitive diagnosis of HCV infection **(BIII)**.[64]

A positive anti-HCV antibody test in a child aged >18 months indicates prior HCV infection. Supplemental testing with a more specific assay, such as HCV RNA testing, is recommended to clarify whether the positive antibody test indicates a chronic active or a resolved infection **(AIII)**. A positive HCV RNA test confirms current HCV infection, and if positive for >6 months, indicates chronic infection. HCV RNA can be measured qualitatively or quantitatively. Qualitative nucleic acid tests include qualitative PCR and transcription-mediated amplification. Quantitative tests include branched-chain DNA amplification, quantitative PCR, and real-time PCR and are most useful for monitoring response to anti-HCV therapy. Quantitative HCV RNA level (i.e., HCV viral load) does not correlate with degree of liver damage and does not serve as a surrogate for measuring disease severity, but it does provide important information about response to antiviral therapy. Assays vary substantially, and if serial values are required to monitor treatment, continued use of the same quantitative assay for all assessments is strongly recommended.

Liver biopsy is the most accurate test to assess the severity of hepatic disease and measure the amount of hepatic fibrosis present. The degree of liver injury found on biopsy can be used to determine the need for treatment. A liver biopsy is recommended before initiating therapy for chronic HCV genotype 1 infection, but is often used for other genotype infections (2, 3 or 4) as well.[65,66] Virus eradication from anti-HCV therapy is much more likely in HCV genotypes 2 and 3 (~80%), compared with genotype 1 (<50%). Thus, the need for liver biopsy before treatment of HCV genotypes 2 or 3 is debatable.[67]

Prevention Recommendations

Preventing Exposure

All HIV-infected patients should be screened for HCV. No reliable strategy exists to prevent perinatal HCV transmission. Cesarean delivery is not associated with reduced perinatal transmission of HCV infection and is not recommended for this purpose for women with chronic HCV infection **(AII)**. The presence of maternal HCV coinfection does not alter the current recommendation for scheduled cesarean delivery for HIV-infected women who have HIV RNA levels >1,000 copies/mL near delivery to prevent perinatal HIV transmission. Limited data suggest that breastfeeding does not transmit HCV; maternal HCV infection is not a reason to avoid breastfeeding. The presence of maternal HCV coinfection does not alter the current recommendation that HIV-infected women in the United States should not breastfeed their infants (see *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*).

No vaccines are available to prevent HCV infection. Adolescents considering tattooing or body-piercing should be informed about potential risks of acquiring HCV, which could be transmitted if equipment is not sterile or if proper infection-control procedures are not followed, and to avoid injection-drug use and unprotected sex **(BIII)**.[68] HCV-infected persons should be advised not to share toothbrushes, razors, tweezers, nail clippers and other personal-care articles that might be contaminated with blood to prevent transmission of HCV.

Preventing First Episode of Disease

Patients with chronic liver disease can develop fulminant hepatitis from hepatitis A (HAV) or B (HAB) infection; all children (regardless of HIV and HCV infection status) should receive standard vaccination with HAV and HAB vaccines **(AIII)**.[68-70] Patients with advanced HCV-related liver disease and/or HIV infection may not mount an appropriate immune response to vaccines.[71] Therefore, measurement of HBV antibody titers 3 months after completion of the vaccination series is recommended.[72]

Treatment Recommendations

Treating Disease

The standard of care for treatment of chronic HCV infection in children, in the absence of HIV infection, is combination therapy with pegylated interferon-alfa (Peg-IFN-α) administered as a subcutaneous (SQ) injection once a week and twice-daily oral ribavirin.[73] For HIV-uninfected individuals, the length of therapy is 48 weeks for treating HCV genotype 1, and 24 weeks for genotypes 2 or 3. Recent studies demonstrate improved response rates in adults with the addition of protease inhibitors (PIs) (telaprevir or boceprevir) to pegylated-IFN-α and ribavirin in adults with HCV genotype 1 infection.[74,75] A recently completed randomized, double-blind, placebo-controlled trial of peg-IFN-α with and without ribavirin in HCV-infected children has shown superior efficacy with combination therapy.[76] Improved viral eradication was previously noted with combination therapy in a non-randomized European study as well.[67] There is a paucity of studies on the treatment of HIV/HCV-coinfected children. Consultation with experts in treating chronic HCV infection in children is recommended.

The PIs telaprevir and boceprevir have been approved for use in adults for treatment of HCV genotype 1, in concert with peg-IFN-α and ribavirin therapy.[77] This "triple therapy" was associated with markedly improved viral clearance, with sustained virologic responses demonstrated in up to 68% of treated patients.[75]

HIV/HCV-coinfected Adults and Adolescents

Regardless of HIV coinfection status, treatment should be considered in all non-pregnant, HCV-infected adults or adolescents who have abnormal serum transaminase levels and liver biopsies that show chronic hepatitis with inflammation, fibrosis, and compensated liver disease.[78] Because of the high rate of HCV eradication with treatment for HCV genotypes 2 or 3, a liver biopsy is optional before initiating therapy. Treatment should be considered for HIV/HCV-coinfected adults and adolescents for whom potential benefits of treatment are judged to outweigh potential risks, including those infected with HCV genotypes 2 or 3, those with stable HIV infection not requiring cART, and those with HCV-related cryoglobulinemic vasculitis or glomerulonephritis.[65,79] Baseline serum HCV RNA level and HCV genotype are the primary predictors of response to treatment. Younger age, higher CD4 T lymphocyte (CD4 cell) count, elevated transaminase levels, lack of liver fibrosis, low body mass index, lack of insulin resistance, and white race are other variables associated with better treatment response.[79] The recommended treatment for HCV genotypes 2 and 3 is combined peg-IFN-α2a (or 2b) plus ribavirin for 48 weeks, while telaprevir is added to that regimen for the first 12 weeks in most adults with HCV genotype 1 infection (see _Adult OI Guidelines_). In HIV/HCV-coinfected adults, rates of sustained virologic response to treatment with peg-IFN-α plus ribavirin range from 44% to 73% for treatment of HCV genotypes 2 and 3 infection and from 14% to 29% for HCV genotype 1 infection.[73,80,81] Response to anti-HCV treatment improves in HIV/HCV-coinfected adults with CD4 cell counts >200 cells/mm^3; therefore, cART should be considered before anti-HCV therapy is initiated in HIV/HCV-coinfected patients with CD4 cell counts <200 cells/mm^3. Anti-HCV treatment is not recommended during pregnancy for HCV-infected women because ribavirin is teratogenic.

HCV-Infected, HIV-Uninfected Children

Treatment usually is not recommended for HIV-uninfected children aged <3 years who have HCV infection because spontaneous HCV clearance can occur in this age group **(BIII)**. All decisions about treatment of HCV infection in children should be individualized because HCV usually causes mild disease in this population and few data exist to identify risk factors differentiating those at greater risk for progression of liver disease.[80,82]

HCV-infected, HIV-uninfected children ≥3 years old who are chosen for treatment should receive combination therapy with peg-IFN-α and ribavirin for 48 weeks for genotype 1 and 24 weeks for genotypes 2 or 3 **(AI)**. This recommendation is based on the results of a recently completed pediatric trial in the United States on the efficacy of peg-IFN-α with or without ribavirin.[76] In this trial, children aged 5 to 17 years were defined as having chronic HCV infection based on at least 2 positive HCV RNA blood tests for >6 months

duration and liver histology consistent with HCV infection. The primary outcome measured was a sustained virologic response (SVR) defined as non-detectable HCV RNA in plasma at 24 weeks after treatment completion. The overall SVR was 53% with combination therapy and 21% with peg-IFN-α monotherapy. Combination therapy resulted in SVR in 47% of patients with genotype 1 HCV and 80% of patients with genotypes 2-6 HCV. A non-randomized trial using peg-IFN-α and ribavirin for pediatric HCV infection in Europe found similar efficacy for combination therapy. SVR was achieved in 48% of patients with genotype 1 and 100% of patients with genotypes 2 or 3.[67]

Previous studies on the use of combination therapy with standard IFN-α (SQ injections 3 times weekly) and ribavirin reported overall rates of SVR ranging from 46% to 65%.[66,83-87] In these studies, children infected with genotype 1 were less likely to have a SVR (36%) than those infected with genotypes 2 or 3 (SVR 84%).[83] Other factors associated with favorable response to anti-HCV treatment in children include lower pretreatment HCV RNA levels, white race, and possibly younger age.[66]

HIV/HCV-coinfected Children

No specific studies have been done of treatment of children with HIV/HCV-coinfection, and recommendations are based primarily on data from adults. Because therapy for HCV infection is more likely to be effective in younger patients and in those without advanced disease or immunodeficiency, treatment should be considered for all HIV/HCV-coinfected children aged ≥3 years who have no contraindications to treatment **(BIII)** (see Dosing Table for contraindications to anti-HCV drugs). Treatment of HIV/HCV-coinfected children aged <3 years usually is not recommended **(BIII)**, even though spontaneous HCV clearance in HIV/HCV-coinfected children may occur at lower rates than in HIV-uninfected children.[51]

In HIV/HCV-coinfected adults, the recommended duration of combination treatment is 48 weeks for infections with all HCV genotypes, including 2 and 3, because coinfected adults may not respond as well as those who are HIV-uninfected and they may have higher rates of relapse. Moreover, the efficacy of shorter treatment has not been adequately evaluated in HIV-infected individuals.[79] By extrapolation, 48 weeks of therapy also are recommended for HIV/HCV-coinfected children, regardless of genotype **(BIII)**. Potential drug interactions complicate the concomitant use of cART and anti-HCV therapy. Ribavirin enhances phosphorylation of didanosine, which could increase the risk of toxicity; therefore, these drugs should not be used together **(AIII)**. Ribavirin and zidovudine both are associated with anemia and should not be administered together **(BII*)**.[79]

The PIs telaprevir and boceprevir are approved only for use in adults with genotype 1 HCV infection. These agents may be tested and approved for use in children in the near future. No recommendations for use of these agents in children can be made at this time. See *Adult OI Guidelines* for important warnings about drug interactions between HCV PIs and HIV PIs and other antiretroviral drugs.

Monitoring and Adverse Events (Including IRIS)

Monitoring in Children Not Receiving Anti-HCV Therapy

Although no evidence-based long-term monitoring guidelines exist for children with perinatally acquired HCV, many experts monitor HCV RNA levels and serum transaminase levels every 6 to 12 months and complete blood counts (CBC) and serum alpha fetoprotein levels annually.[82] Serum transaminase levels can fluctuate and do not necessarily correlate with histologic liver damage because significant liver disease can be present in patients with normal serum transaminase levels. In HCV-infected persons who are HIV-uninfected, HCC rarely is seen in the absence of cirrhosis. The benefits of serum alpha-fetoprotein (AFP) and abdominal sonography as screening tools for HCC have not been studied in children. Some experts perform periodic sonographic screening at defined intervals (every 2-5 years) in children with chronic HCV infection; others do these tests only in those with advanced liver disease and/or rising serum AFP concentrations.[82] The risk of HCC in HCV-infected children, with or without HIV infection, is unknown.

As with HIV/HBV-coinfection, use of cART in HIV/HCV-coinfected patients can worsen hepatitis, with increases in serum transaminase levels and clinical signs of liver disease, including hepatomegaly and

jaundice (also called "hepatic flare"). This does not represent a failure of ART, but rather, is a sign of immune reconstitution. Immune reconstitution inflammatory syndrome (IRIS) manifests by an increase in serum transaminase levels as the CD4 cell count increases during the first 6 to 12 weeks of cART. Thus, serum transaminase levels should be monitored closely after introduction of cART in HIV/HCV-coinfected children. The prognosis for most patients with IRIS is favorable. Consultation with a hepatologist should be sought if elevated aminotransferases are associated with clinical jaundice or other evidence of liver dysfunction, in other words, low serum albumin.

Monitoring During Combination Therapy (Interferon and Ribavirin)

HCV RNA quantitation is used to monitor response to antiviral therapy. HCV RNA levels should be performed at baseline; after 5, 12, and 24 weeks of antiviral therapy; at treatment completion (48 weeks); and 6 months after treatment cessation. Some experts continue to perform serial HCV RNA testing at 6- to 12-month intervals for an additional 1 to 5 years to exclude late virologic relapse.

The following are outcomes measured during the treatment of HCV:

- **Rapid Virological Response (RVR):** Non-detectable plasma HCV RNA after 4 weeks of therapy;

- **Early Virologic Response (EVR):** Decrease in HCV RNA $\geq 2 \log_{10}$ IU/mL below baseline after 12 weeks of therapy;

- **End Of Treatment Virologic Response:** Non-detectable HCV RNA at time of treatment completion;

- **Sustained Virologic Response (SVR):** Non-detectable HCV RNA at 24 weeks after treatment completion;

- **Virologic Relapse:** Achievement of end of treatment response followed by return of HCV RNA positivity after treatment completion;

- **Nonresponse:** Failure to suppress HCV RNA below detection at any time during treatment; and

- **Breakthrough Response:** Reemergence of detectable HCV RNA from non-detectable status despite the continuation of therapy.[4]

In the absence of specific data for HIV/HCV-coinfected children, the criteria for determining response to therapy in HCV-monoinfected children and HIV/HCV-coinfected adults are used. Failure to achieve EVR with treatment with peg-IFN-α and ribavirin correlates with a low chance (<3%) of achieving SVR (based on adult data) and treatment can be discontinued after 12 weeks. Treatment should be discontinued in patients who achieve an EVR but still have detectable HCV RNA at 24 weeks of therapy. For all other HIV/HCV-coinfected children, treatment should be given for 48 weeks, regardless of genotype **(BIII)**. In addition to HCV RNA quantification, patients receiving antiviral therapy for HCV infection should be closely monitored for medication side effects with CBC, measurement of serum transaminase levels, thyroid function tests, ophthalmologic exams, and assessment of mental status/mood disorders. Some experts would monitor transaminase levels more frequently during the first few months of therapy, such as monthly for 3 months, in HIV/HCV-coinfected children who are also starting cART because of the risk of IRIS.

Side effects of IFN-α in children are common but usually not severe; approximately 5% of children need to discontinue treatment because of side effects. The most common side effects include influenza-like symptoms (e.g., fever, chills, headache, myalgias, arthralgias, abdominal pain, nausea, vomiting) in 80% of patients during the first month of treatment. However, these symptoms usually resolve over time and usually are not treatment-limiting; pre-medication with acetaminophen or ibuprofen may reduce the incidence of side effects. In 42% of children subtle personality changes that resolve when therapy is discontinued have been reported.[88] Depression and suicidal ideation also have been reported in clinical trials of children treated with IFN-α.[83] Neutropenia, which usually improves with dose-reduction, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Abnormalities in thyroid function (hypothyroidism or hyperthyroidism) have been reported with IFN-α therapy.[89] Loss of appetite, with transient weight loss and

impaired height growth, can occur but usually resolves after completion of therapy.[90]

Less commonly observed side effects of IFN-α include epistaxis and transient mild alopecia. Some children develop antinuclear autoantibodies. The incidence of interferon-associated ophthalmologic complications in HCV-infected children on combination therapy was recently reported.[91] Three of 114 patients developed significant eye disease, including ischemic retinopathy with cotton wool spots, uveitis, and transient monocular blindness. Despite the low incidence of disease, the severity of the ophthalmologic findings warrants follow-up with eye exams at 24 and 48 weeks of therapy. IFN-α therapy is contraindicated in children with decompensated liver disease, substantial cytopenias, renal failure, severe cardiac or neuropsychiatric disorders, and non-HCV-related autoimmune disease **(AII*)**.[92]

Side effects of ribavirin include hemolytic anemia and lymphopenia. Ribavirin-induced hemolytic anemia is dose-dependent and usually presents with a substantial decrease in hemoglobin within 1 to 2 weeks after ribavirin initiation, but the hemoglobin usually stabilizes. Significant anemia (hemoglobin <10 g/dL) occurs in about 10% of ribavirin-treated children.[82] Erythropoietin can be used to manage clinically significant anemia during HCV treatment **(BIII)**. Coadministration of didanosine is contraindicated in children receiving ribavirin because this combination can increase the risk of mitochondrial toxicity and hepatic decompensation **(AIII)**. Children receiving concomitant zidovudine may be more likely to experience bone marrow suppression; if possible, zidovudine should be avoided in children receiving ribavirin **(BII*)**. Children who are receiving zidovudine and ribavirin together should be monitored closely for neutropenia and anemia. Ribavirin is teratogenic and should not be used by pregnant women. Sexually active adolescent girls or those likely to become sexually active who are receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy.

In patients on HCV therapy who start cART and experience hepatic flares, differentiating between IRIS and drug-induced liver toxicity may be difficult, and no reliable clinical or laboratory predictors exist to distinguish between the two. Close interaction of the HIV specialist with a specialist in hepatic disease—usually a hepatologist—is recommended for such patients; prompt consultation with a hepatologist should be sought if elevated aminotransferases are associated with clinical jaundice or other evidence of liver dysfunction (such as low serum albumin).

Managing Treatment Failure

No data exist on which to base recommendations for treatment of HIV/HCV-coinfected children in whom initial HCV treatment fails. In HIV/HCV-coinfected adults, a second course of treatment has a limited chance of resulting in sustained virologic response in nonresponders (those who do not achieve early virologic response by week 12 or undetectable HCV load at week 24) or patients whose HCV relapses. Therapeutic interventions for such adults need to be individualized according to prior response, tolerance, and adherence to therapy; severity of liver disease; viral genotype; and other underlying factors that might influence response. Some experts might extend the duration of treatment (e.g., to 72 weeks) in adults who experience a virologic response followed by relapse after adequate HCV therapy or in patients with advanced fibrosis. In the setting of treatment failure, the addition of PIs (telaprevir or boceprevir) to peg-IFN-α and ribavirin may increase rates of eradication.[74,75] In a clinical trial, the addition of boceprevir to peg-IFN-ribavirin resulted in significantly higher rates of sustained virologic response (up to 66%) in previously treated adults with chronic HCV genotype 1 infection, as compared with peg-interferon-ribavirin alone.[93] HIV/HCV-coinfected adults with prior suboptimal treatment of HCV genotypes 2 or 3 infection may benefit from optimized retreatment; coinfected adults with treatment failure for HCV genotype 1 infection may benefit from retreatment with a combination regimen that includes boceprevir or telaprevir (see *Adult OI Guidelines*). See *Adult OI Guidelines* for important warnings about drug interactions between HCV PIs and HIV PIs and other antiretroviral drugs. No data exist on which to base a recommendation for management of HCV treatment failure in HIV/HCV-coinfected children, and pediatric trials of triple therapy are warranted.

Preventing Recurrence

Not applicable.

Discontinuing Secondary Prophylaxis

Not applicable.

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Dosing Recommendations for Prevention and Treatment of Hepatitis C Virus (HCV)

Preventive Regimen			
Indication	**First Choice**	**Alternative**	**Comments/Special Issues**
Primary Prophylaxis	None	N/A	N/A
Secondary Prophylaxis	None	N/A	N/A

Treatment	IFN-α Plus Ribavirin Combination Therapy:
	• Pegylated IFN-α: Peg-IFN 2a 180 μg/1.73 m^2 body surface area subcutaneously once per week (maximum dose 180 μg) OR Peg-IFN 2b 60 μg/m^2 body surface area once per week
	
	PLUS
	
	• Ribavirin (oral) 7.5 mg/kg body weight twice daily (fixed dose by weight recommended):
	  • 25–36 kg: 200 mg a.m. and p.m.
	  • >36 to 49 kg: 200 mg a.m. and 400 mg p.m.
	  • >49 to 61 kg: 400 mg a.m. and p.m.
	  • >61 to 75 kg: 400 mg a.m. and 600 mg p.m.
	  • >75 kg: 600 mg a.m. and p.m.
	
	Treatment Duration:
	• 48 weeks, regardless of HCV genotype
		None	Optimal duration of treatment for HIV/HCV-coinfected children is unknown and based on recommendations for HIV/HCV-coinfected adults
			
			Treatment of HCV in children <3 years generally is not recommended.
			
			Indications for treatment are based on recommendations in HIV/HCV-coinfected adults; because HCV therapy is more likely to be effective in younger patients and in those without advanced disease or immunodeficiency, treatment should be considered for all HIV/HCV-coinfected children aged >3 years in whom there are no contraindications to treatment
			
			For recommendations related to use of telaprevir or boceprevir in adults, including warnings about drug interactions between HCV protease inhibitors and HIV protease inhibitors and other antiretroviral drugs, see *Adult OI guidelines*.
			
			IRIS may be manifested by dramatic increase in transaminases as CD4 cell counts rise within the first 6–12 weeks of cART. It may be difficult to distinguish between IRIS and drug-induced hepatotoxicity or other causes of hepatitis.
			
			IFN-α is contraindicated in children with decompensated liver disease, significant cytopenias, renal failure, severe cardiac disorders and non-HCV-related autoimmune disease.
			
			Ribavirin is contraindicated in children with unstable cardiopulmonary disease, severe pre-existing anemia or hemoglobinopathy.
			
			Didanosine combined with ribavirin may lead to increased mitochondrial toxicities; concomitant use is contraindicated.
			
			Ribavirin and zidovudine both are associated with anemia, and when possible, should not be administered together

Key to Acronyms: cART = combined antiretroviral therapy; HCV = hepatitis C virus; IFN = interferon; IRIS = immune reconstitution inflammatory syndrome; Peg-IFN = pegylated interferon; SQ = subcutaneous