Treatment and prevention of hepatitis D virus infection

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INTRODUCTION

Hepatitis D virus (HDV) is a defective virus requiring the simultaneous presence of hepatitis B virus (HBV) to fully express its pathogenicity; thus, hepatitis D always occurs in the presence of HBV. In most cases of HDV infection, HBV replication is suppressed to low levels by HDV [1,2]. Liver damage in these patients is essentially due to HDV only. However, HBV and HDV may replicate simultaneously on occasion, each virus contributing to the liver damage, thereby resulting in more severe liver disease [3]. The clinical course is influenced by several factors, including the HDV genotype [4]. The predominant genotype in the Western world is genotype 1.

Once chronic HDV infection is established, it usually exacerbates the pre-existing liver disease due to HBV. Thus, progression towards cirrhosis and its sequelae is often faster than among patients with HBV monoinfection [5].

This topic will review the treatment and prevention of HDV infection. The pathogenesis, epidemiology, clinical manifestations, and diagnosis of HDV are discussed in separate topic reviews. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection".)

TREATMENT OF ACUTE HEPATITIS D

Treatment of acute hepatitis D is mostly supportive. There are no specific antiviral treatments for acute hepatitis D. However, patients with severe acute hepatitis D should be referred for liver

transplant evaluation, and hepatitis B virus (HBV) antiviral should be administered, particularly in those with detectable HBV DNA, as prevention of recurrent HBV is key to preventing recurrent HDV post-transplant. (See "Liver transplantation in adults: Hepatitis D virus reinfection in liver transplant recipients" and "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients" and "Hepatitis B virus: Overview of management", section on 'Acute infection'.)

TREATMENT OF CHRONIC HEPATITIS D

Pretreatment evaluation — To help determine the approach to treatment in patients with chronic HDV infection, patients should have laboratory testing for HDV RNA and transaminase levels. In addition, noninvasive test for fibrosis or a liver biopsy should be performed to assess for the presence of fibrosis and cirrhosis. More detailed information on the pretreatment evaluation for hepatitis B virus infection is presented separately. (See "Hepatitis B virus: Overview of management", section on 'Initial evaluation'.)

Active liver disease without advanced fibrosis or cirrhosis — Patients with active liver disease without advanced fibrosis or cirrhosis include those with elevated serum aminotransferase (ALT) levels and no evidence of cirrhosis or advanced fibrosis on histology or noninvasive testing such as imaging or elastography.

Whom to treat — For patients with chronic HDV infection without advanced fibrosis or cirrhosis, we suggest treatment for those with:

- Elevated ALT levels and/or chronic hepatitis on liver biopsy

AND

- Detectable HDV RNA

Patients should be treated as soon as possible, particularly if there is fibrosis. Virologic suppression with pegylated interferon alfa-2a (Peg-IFNa-2a) is more likely to be attained in patients with a shorter duration of infection [6]. Although the effect of antiviral therapy is modest, successful treatment is associated with amelioration of necroinflammatory activity and clearance of HDV RNA from serum. (See 'Efficacy' below.)

Considerations for patients with advanced fibrosis or cirrhosis are discussed below. (See 'Patients with advanced fibrosis or cirrhosis' below.)

Pegylated Interferon alfa-2a as preferred therapy — If antiviral therapy is indicated, pegylated interferon alfa-2a (Peg-IFNa-2a) is the only available option in most countries, even though it is not officially approved for this indication. Bulevirtide, an entry inhibitor, has been conditionally approved in parts of Europe for treatment of persons with compensated chronic liver disease due to HDV but is not available in the United States. More detailed information on this agent is found below. (See 'Bulevirtide' below.)

The mechanism of action of IFNa for treatment of hepatitis D is unclear since IFNa does not have any antiviral activity against HDV when tested in vitro [7,8]. The efficacy of IFNa in patients with chronic hepatitis D may depend upon its immunomodulatory effects or the antiviral effects on the helper virus, hepatitis B virus (HBV). (See "Pegylated interferon for treatment of chronic hepatitis B virus infection".)

Dosage and administration — Peg-IFNa-2a (180 mcg subcutaneously once weekly) should be administered for 48 weeks [9]. Peg-IFNa-2b, which had been used in the past, is no longer available.

Several studies have tried to evaluate the appropriate duration of treatment with Peg-IFNa using HDV RNA suppression as the end point. In one study of 18 patients with chronic HDV infection who were randomly assigned to receive 12 versus 24 months of Peg-IFNa-2b, extending the treatment duration to 24 months did not increase the likelihood of achieving HDV RNA suppression [10].

Monitoring on therapy — Patients receiving Peg-IFNa-2a should be assessed for virologic and biochemical responses both during treatment and after therapy has been completed. They should also be monitored for evidence of toxicity. We monitor patients at weeks 4, 12, 24, and 48 during treatment and weeks 12 and 24 post treatment (table 1).

- **HDV viral load** – The commonly accepted primary endpoint for finite treatment of chronic HDV is an undetectable serum HDV RNA 24 weeks **after** completing therapy, accompanied by normalization of the ALT level. Approximately one third of patients achieve an undetectable HDV RNA at some point after treatment. Virologic suppression is associated with improved clinical outcomes if maintained over time [11,12]. (See 'Efficacy' below.)

  Relapses occurring more than 24 weeks after the end of therapy have been reported [13], although the majority of these may be due to low-level residual HDV RNA at the end of the treatment that was not detected by insensitive assays [14]. However, in the absence of cirrhosis, clinical outcomes are improved even in patients with transient relapses [15].

Although the ideal endpoint of treatment would be the clearance of hepatitis B surface antigen (HBsAg), which is associated with improved survival [11], this is rarely achieved [16]. In addition, patients would require prolonged treatment (eg, up to four years) or repeated cycles to achieve a negative HBsAg value, and this would only be feasible in a minority of highly selected patients [12].

More recently, a 2 log reduction of serum HDV RNA level (either alone [17] or combined with ALT normalization [18]) has been proposed for patients on treatment. However, this endpoint is not routinely used in clinical practice as data are based on the findings of a single study that followed 36 patients with chronic HDV [19]. In this report, patients who reached an average 2 log reduction of serum HDV RNA at the end of a standard 48-week course of high-dose (9 million units three times per week), standard IFNa had further reductions in HDV RNA after the end of therapy and improved survival over the course of 12 years. This endpoint has also been used in patients receiving bulevirtide [20].

- **HBV** – We also monitor the efficacy of interferon on HBV (table 2). HBsAg loss with development of hepatitis B surface antibody (anti-HBs) will protect the individual from reinfection with HBV as well as HDV. Patients who have cleared HDV but who remain positive for HBsAg are at risk of reinfection with HDV. This phenomenon has been observed in the chimpanzee experimental animal model. However, re-exposure to HDV appears to cause only a mild and self-limiting hepatitis [21].

- **Adverse reactions** – Adverse events associated with Peg-IFNa-2a can be severe and may require dose reduction or discontinuation of treatment.

  - The major side effects of Peg-IFNa-2a include flu-like symptoms, which occur in approximately 90 percent of patients [22].

  - Other side effects include fatigue, anorexia and nausea, diarrhea, weight loss, hair loss, emotional lability and depression, and bone marrow suppression.

  - Induction of autoantibodies can also occur, and this may result in thyroid abnormalities in up to 30 percent of patients or enhancement of autoimmune diseases [23,24].

  To evaluate for adverse reactions, we evaluate the patient clinically and obtain a complete blood count with differential at all assessment visits (table 1). In addition, thyroid-stimulating hormone should be obtained at baseline; weeks 12, 24, and 48 on treatment; and week 12 post-treatment.

Efficacy — Patients treated with IFNa have modest reductions in their HDV RNA levels [25-27]. In a meta-analysis of Peg-IFNa (2a or 2b) monotherapy that included 13 studies with 475 patients, 29 percent cleared HDV RNA from serum 24 weeks after the end of therapy (95% CI 24 to 34 percent) [16]. Higher virologic response rates (43 percent) have been seen in patients without cirrhosis [26].

IFNa therapy is also associated with improvement in clinical endpoints. In one observational report, complications such as hepatic decompensation (ascites, encephalopathy, and variceal bleeding), hepatocellular carcinoma, liver transplantation, and liver-related death occurred less frequently in those who were treated with IFNa-based therapies compared with those who received no therapy (hazard ratio 2.2; 95% CI, 1.0-5.0) [11]. In another observational study of 99 patients with chronic HDV who were treated with IFN, those who had an undetectable HDV RNA two years after treatment was discontinued were significantly less likely to die from liver disease or develop complications compared to patients without this response [12]. However, persons with cirrhosis at baseline did worse than those without cirrhosis.

The addition of ribavirin does not improve the response. One published study included 38 patients who were treated with Peg-IFNa-2b (1.5 mcg/kg per week) alone or in combination with ribavirin for 48 weeks [25]. Most patients had previously failed treatment with standard IFNa. All patients were maintained on Peg-IFNa-2b for an additional 24 weeks and then followed off therapy for 24 weeks. At the end of follow-up, HDV RNA was undetectable in eight patients (21 percent). Treatment had to be discontinued in 25 percent of patients while 58 percent required dose modification. The response rate was similar in the monotherapy and combination therapy groups, suggesting that ribavirin had no effect on the viral clearance rate.

Similarly, there is no role for the routine use of nucleos(t)ide analogs, as discussed below. (See 'Role of nucleos(t)ide analogs' below.)

Role of nucleos(t)ide analogs — For patients with chronic HDV, we suggest against the routine use of nucleos(t)ide analogs. Although it may seem logical to target HBV in its capacity as an HDV helper virus, most of the available data do not support their use in this setting [28-35]. Nucleos(t)ide analogs should only be used if the patient has an indication based on the management of their chronic HBV. (See "Hepatitis B virus: Overview of management".)

A study from the Swiss HIV Cohort found nucleos(t)ide analog monotherapy had only a minimal effect on HDV in patients with HIV/HBV/HDV infection [29]. Only 14 percent of patients achieved an undetectable HDV RNA after five years of treatment with tenofovir-containing antiretroviral therapy, and this may have been due to host immune reconstitution rather than to an antiviral effect on HBV. In another study of patients with dual HBV/HDV infection from Italy, HBV

suppression induced by nucleoside analogs did not prevent liver-related events like hepatocellular carcinoma or liver-related mortality [30].

A large, controlled trial evaluated 90 patients with compensated chronic hepatitis D who were randomly assigned to Peg-IFNa-2a alone or in combination with adefovir dipivoxil or adefovir monotherapy [31]. After 48 weeks, HDV RNA was negative in approximately 25 percent of patients in both Peg-IFNa-2a arms and none in the adefovir monotherapy arm. The response was sustained up to 24 weeks after stopping therapy. A significant decline in HBsAg levels was observed in patients receiving Peg-IFNa-2a (especially when combined with adefovir) but not in patients treated with adefovir monotherapy.

In another trial, 120 HDV RNA-positive patients received Peg-IFNa-2a 180 mcg subcutaneously once weekly plus either tenofovir disoproxil fumarate (TDF; 300 mg orally once daily; n = 59) or placebo (n = 61) for 96 weeks [36]. Fifty-four patients had cirrhosis. Twenty-four weeks after the end of therapy, overall virologic response (undetectable HDV RNA) was observed in 32 out of 120 patients (27 percent) without significant difference between the two arms, demonstrating that prolonged therapy does not offer additional benefit and that 48 weeks of Peg-IFNa remain the standard of care.

Bulevirtide — The HDV entry inhibitor, bulevirtide, acts upon the sodium taurocholate cotransporting polypeptide (NTCP), which is a receptor shared by HBV and HDV [37,38]. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Virology'.)

On July 31, 2020, the European Medicines Agencies (EMA) provided a conditional marketing authorization to bulevirtide for chronic hepatitis D, at the dose of 2 mg subcutaneously once daily, alone or in combination with a nucleoside or nucleotide analog for the treatment of the underlying hepatitis B. This approval is only for patients with compensated liver disease. There are no data on the use bulevirtide in persons with decompensated cirrhosis or liver transplant.

Neither the United States Food and Drug Administration nor regulatory authorities in other countries have authorized the use of bulevirtide.

In a randomized, open-label phase 2 trial of 120 patients with chronic HDV (59 with cirrhosis), patients received bulevirtide at various doses (2 mg, 5 mg, or 10 mg subcutaneous once per day) with TDF or TDF alone for 24 weeks [39]. Although patients receiving bulevirtide achieved undetectable hepatitis D virus RNA levels or a >2 $\log_{10}$ international units/mL decline in hepatitis D virus RNA by 24 weeks, levels rebounded when therapy was stopped. Bulevirtide was well tolerated overall, but modest, asymptomatic dose-dependent increases in bile acid levels were observed in some patients.

Bulevirtide has also been evaluated in combination with Peg-IFNa-2a [20,40,41]. In one phase 2 trial, 60 patients with chronic HDV were randomized to receive 48 weeks of monotherapy with Peg-IFNa-2a (180 mcg subcutaneously once weekly) or bulevirtide (2 mg subcutaneously once daily) or combination therapy with Peg-IFNa-2a plus bulevirtide (2 mg or 5 mg daily) [41]. An undetectable HDV RNA was achieved in eight and four of the patients who received combination therapy with the 2 and 5 mg doses of bulevirtide, respectively. In addition, HBsAg also became undetectable in 4 of 15 patients receiving the combination regimen using 2 mg of bulevirtide.

Other clinical trials have also evaluated bulevirtide in combination with Peg-IFNa. Combination therapy was synergistic with regards to HDV RNA declines on treatment, but off-treatment HDV RNA responses were only observed in patients who became HBsAg negative [20].

Patients with advanced fibrosis or cirrhosis — Patients with HBV/HDV and advanced fibrosis (bridging fibrosis) or cirrhosis (≥F3) (table 3) should be managed in consultation with a specialist in liver disease.

Such patients should receive nucleos(t)ide analogs for HBV regardless of HBV DNA, HDV RNA, or ALT level. In addition, this group needs surveillance for hepatocellular carcinoma. (See "Hepatitis B virus: Overview of management".)

The use of other antiviral agents depends on whether the patient has complications related to cirrhosis (ie, decompensated cirrhosis) (see "Cirrhosis in adults: Overview of complications, general management, and prognosis"):

- Patients **without** decompensated cirrhosis should be considered for Peg-IFN. Bulevertide can also be considered in countries where it is available. (See 'Bulevirtide' above.)

  For those who initiate Peg-IFN, nucleos(t)ide analogs can be held since Peg-IFN also has activity against HBV. However, they should be restarted after completing Peg-IFN. (See "Hepatitis B virus: Overview of management", section on 'Nucleos(t)ide analogs'.)

- Patients with HDV-related decompensated liver disease are not candidates for Peg-IFN or bulevirtide. They should receive nucleos(t)ide analogs for HBV and be referred for liver transplant evaluation. (See "Liver transplantation in adults: Hepatitis D virus reinfection in liver transplant recipients" and "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

No active liver disease — Treatment is generally not warranted for persons with HDV who have no or very mild fibrosis (ie, F0/F1) (table 3) and persistently normal ALT levels.

However, clinical and laboratory monitoring (eg, ALT levels and HDV RNA) should be performed every 6 to 12 months to assess for signs of disease progression, which would indicate the need for treatment.

Additional considerations — For all patients with chronic HDV, management should include counseling regarding the safe consumption of alcohol, healthy lifestyle to prevent concomitant fatty liver, and control of other significant comorbidities potentially affecting the liver (eg, diabetes). Patients with chronic HDV should also be vaccinated against hepatitis A virus if they are not already immune. (See "Hepatitis A virus infection: Treatment and prevention".)

EXPERIMENTAL THERAPIES

Several drugs have been evaluated as alternatives to Peg-IFNa. Agents that have novel mechanisms of action and show more promise include:

Interferon lambda – Interferon (IFN) lambda has activity against hepatitis B and D viruses with fewer side effects than IFNa due to the preferential expression of its receptor at the level of hepatocytes. In one randomized, open-label study (LIMT HDV Study), 33 patients received IFN lambda dosed at 120 (n = 19) or 180 mcg (n = 14) subcutaneously once weekly for 48 weeks [42]. In the patients that received 180 mcg dose of IFN lambda, 36 percent achieved an undetectable HDV RNA at 24 weeks after the end of therapy, which compared favorably with historic rates following Peg-IFNa-2a, which have been reported to be about 29 percent [16]. Patients previously treated with IFNa reported significantly fewer side effects while receiving IFN lambda. This agent has also been evaluated in combination with lonafarnib, as discussed below.

Specific inhibitors of HDV prenylation − Prenylation involves the covalent addition of a farnesyl or geranylgeranyl isoprenoid molecule to a conserved cysteine residue at or near the C-terminus of a protein [43]. This link promotes membrane interactions with the prenylated protein since the isoprenoid chain is hydrophobic.

> Lonafarnib, a farnesyltransferase inhibitor used to treat other diseases (eg, progeria), was evaluated in a phase 2a study of 14 patients with HDV [44]. Eight patients received 100 mg of lonafarnib orally twice daily, and six patients received 200 mg of lonafarnib orally twice daily. Treatment was administered for 28 days and, when compared with placebo, resulted in a greater decline in HDV RNA (average serum HDV RNA decline of 0.73 log and 1.54 log international units/mL for the lower and higher doses, respectively). Although all patients experienced adverse events (nausea, diarrhea, abdominal bloating, and weight loss), no

patients had to discontinue treatment due to these effects. Lonafarnib serum concentrations correlated with changes in HDV RNA.

A subsequent study that included 15 patients with chronic hepatitis D infection evaluated several different treatment regimens (lonafarnib at varying doses, lonafarnib plus ritonavir, lonafarnib plus Peg-IFNa) [45]. In this study, adding the cytochrome P450 3A4 inhibitor ritonavir (100 mg once daily) allowed for a reduction in the lonafarnib dose to 100 mg twice daily and yielded a better antiviral response than higher lonafarnib doses with fewer side effects. A similar improvement was observed when lonafarnib 100 mg twice daily was combined with Peg-IFNa-2a 180 mcg once weekly. The mean HDV RNA decrease in the ritonavir and Peg-IFN-2a group at the end of eight weeks of treatment was -2.4 log and -1.8 log, respectively. Six patients were treated with 12 weeks of lonafarnib monotherapy at varying doses, and two underwent a transient post-treatment elevation of serum alanine aminotransferase (ALT), followed by HDV RNA negativity and ALT normalization. The authors speculated that the ALT flares may have reflected restoration of a favorable immune response, although this needs to be confirmed.

Lonafarnib (50 mg twice daily, combined with ritonavir 100 mg twice daily) has also been evaluated in association with IFN lambda 180 mcg once weekly for 24 weeks (LIFT HDV Study). In an analysis of data from 26 patients, 24 patients (92 percent) achieved a >2 log decline and 20 patients (77 percent) achieved either undetectable HDV RNA levels or levels below the lower limit of quantification [46]. Five of 22 patients had undetectable HDV RNA, decrease in ALT, and improved liver histology 24 weeks after completion of treatment. However, side effects, especially gastrointestinal, were prominent and led to treatment discontinuation in four patients. Preliminary results of a phase 3 trial showed promise [47].

Inhibitors of virion secretion – REP 2139 is a nucleic acid polymer that has been shown to clear hepatitis B surface antigen (HBsAg) by blocking the release of subviral particles. This agent was evaluated for the treatment of HDV infection in an uncontrolled phase 2 study in 12 patients with chronic HDV who received 500 mg of REP 2139 intravenously (IV) once per week for 15 weeks, followed by combination therapy with 250 mg of IV REP 2139 and 180 mcg of subcutaneous Peg-IFNa-2a once per week for 15 weeks, and finally, monotherapy with 180 mcg Peg-IFNa-2a once per week for 33 weeks [48,49]. Response was mostly maintained during the Peg-IFNa-2a phase of the study, although five patients rebounded after cessation of REP 2139 during post-treatment follow-up. Thus, at the end of the one-year post-treatment follow-up, eight patients had suppressed hepatitis B virus (HBV) DNA levels, seven were HDV RNA negative, and five had seroconverted from HBsAg to hepatitis B surface antibody (anti-HBs). ALT flares have been reported in studies using REP 2139 and REP 2165. Although the flares have not

resulted in liver failure, further studies are needed to establish the safety and efficacy of these compounds.

MONITORING FOR HEPATOCELLULAR CARCINOMA

Patients with chronic HDV should also be monitored at least yearly with ultrasound or elastography for evidence of hepatocellular carcinoma. Such patients have an increased risk of hepatocellular carcinoma, even compared to those with chronic hepatitis B virus (HBV) monoinfection [50]. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Chronic HDV infection'.)

PREVENTION OF HDV INFECTION

General approach — The mainstay of prevention of HDV infection is vaccination against hepatitis B virus (HBV; its helper virus). Chimpanzees who are positive for hepatitis B surface antibody (anti-HBs) are protected against experimental HDV infection [51]. A detailed discussion of HBV immunization is presented elsewhere. (See "Hepatitis B virus immunization in adults" and "Hepatitis B virus immunization in infants, children, and adolescents".)

For HBV carriers, it is important to counsel patients on ways to reduce the risk of HDV transmission (eg, reducing high-risk drug use and sexual behaviors). (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Epidemiology'.)

Experimental vaccines — There are no available vaccines to prevent HDV infection; however, animal studies suggest that vaccine strategies to prevent superinfection in patients with chronic HBV may be feasible. Chimpanzees rechallenged with HDV many years after recovery from the initial HDV infection were partially protected [21], which suggests that a protective immune response is present.

Woodchucks have served as a useful animal model for evaluating HDV vaccines. Early attempts to vaccinate woodchuck hepatitis virus (WHV) carrier woodchucks with liver-derived hepatitis D antigen (HDAg) [52] or the N-terminal portion of recombinant HDAg that contain a major immunogenic epitope [53] were unsuccessful. However, a later experiment suggested that partial protection against HDV superinfection could be achieved by active immunization [54]. In this study, six WHV carrier woodchucks were repeatedly immunized with the full-size, recombinant, yeast-derived small form of HDAg. Upon challenge with HDV, two woodchucks were not infected, as serum HDV RNA was never detected by polymerase chain reaction; two

showed a transient, low-level HDV viremia; and only two had a typical acute HDV infection. All control animals developed acute hepatitis D.

A similar study used the short form of HDAg expressed by recombinant baculovirus or vaccinia virus as immunogen [55]. Again, after challenge of the woodchucks with HDV, partial protection was observed even though anti-HDV was not detected. It is possible that the protection was related to induction of cytotoxic T-cell response.

However, these encouraging results were not confirmed by other investigators who used live recombinant vaccinia virus expressing either the small or the large form of HDAg [56]. The explanations for the different outcomes using vaccines that are manufactured by very similar approaches are unknown.

In another approach, three synthetic HDAg peptides were administered to four woodchucks, resulting in the production of specific antibodies. These woodchucks developed transient, low-level viremia after inoculation with HDV but none developed chronic HDV infection [57].

Vaccination against HBV remains the most cost-effective means to prevent HDV infection, except for individuals who are already infected with HBV.

SUMMARY AND RECOMMENDATIONS

- **Virology** – Hepatitis D virus (HDV) is a defective virus requiring the simultaneous presence of hepatitis B virus (HBV) to fully express its pathogenicity; thus, hepatitis D always occurs in the presence of HBV. In most cases of HDV infection, HBV replication is suppressed to low levels by HDV. (See 'Introduction' above.)

- **Treatment of acute HDV** – Treatment of acute hepatitis D is mostly supportive. There are no specific antiviral treatments for acute hepatitis D. (See 'Treatment of acute hepatitis D' above.)

- **Treatment of chronic HDV** – The approach to treatment of chronic HDV depends largely on the presence of active liver disease, which includes elevated serum aminotransferase (ALT) levels, fibrosis, and/or chronic hepatitis on liver biopsy. (See 'Treatment of chronic hepatitis D' above.)

    - **Patients with active liver disease without advanced fibrosis or cirrhosis** – For most patients with chronic HDV who have active liver disease and a detectable HDV RNA, we suggest treatment with pegylated interferon alfa-2a (Peg-IFNa-2a) (**Grade 2C**). (See 'Whom to treat' above.)

Peg-IFNa-2a (180 mcg subcutaneously once weekly) should be administered for 48 weeks. Patients should be treated as soon as possible, since virologic suppression with Peg-IFNa-2a is more likely to be attained in patients with a shorter duration of infection. (See 'Pegylated Interferon alfa-2a as preferred therapy' above.)

In most countries, pegylated interferon alfa-2a is the only available treatment. Bulevirtide, an entry inhibitor, has been conditionally approved in Europe for treatment of patients with compensated liver disease due to HDV but is not available in the United States and most countries in the world. (See 'Bulevirtide' above.)

We suggest against the routine use of nucleos(t)ide analogs if they don't otherwise have an indication for management of HBV (**Grade 2C**). There is only a minimal benefit of these agents for treatment of HDV when used alone or in combination with Peg-IFNa. (See 'Role of nucleos(t)ide analogs' above.)

- **Patients with cirrhosis** – For patients with chronic HDV/HBV cirrhosis, HBV nucleos(t)ide therapy should be administered. In addition, surveillance for hepatocellular carcinoma should be performed. Such patients should also be considered for Peg-IFN if they have a detectable HDV RNA, compensated cirrhosis, and no contraindications to use of Peg-IFN. For patients with decompensated cirrhosis, Peg-IFN should not be used and safety of bulevirtide is not established in these patients. These patients should be referred for liver transplant evaluation. (See 'Patients with advanced fibrosis or cirrhosis' above.)

- **Patients without active liver disease** – Treatment is generally not needed for persons with chronic HDV who have persistently normal ALT levels and no or very mild fibrosis (ie, F0/F1). However, close clinical and laboratory monitoring (eg, ALT levels) should be performed to assess for signs of disease progression. (See 'No active liver disease' above.)

- **Prevention** – The best way to prevent HDV infection is vaccination against HBV (its helper virus). For persons who already have chronic hepatitis B infection, it is important to educate patients about ways to reduce the risk of HDV transmission (eg, reducing high-risk drug use and sexual behaviors). (See 'Prevention of HDV infection' above.)

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Topic 3664 Version 21.0

GRAPHICS

Monitoring of patients receiving interferon therapy for the treatment of hepatitis D virus infection

Assessment point	Laboratory tests
Baseline*	▪ CBC with differential (including platelet count) ▪ Hepatic panel¶, creatinine, glucose ▪ INR ▪ TSH ▪ Serum HDV RNA ▪ Serum HBV DNA ▪ Serum HBeAg and anti-HBeΔ ▪ Serum HBsAg◇ ▪ Pregnancy test§
Week 4	▪ CBC with differential (including platelet count) ▪ Hepatic panel¶ ▪ INR
Week 12	▪ CBC with differential (including platelet count) ▪ Hepatic panel¶ ▪ INR ▪ Pregnancy test§ ▪ Serum HDV RNA (optional) ▪ Serum HBV DNA (optional)
Week 24	▪ CBC with differential (including platelet count) ▪ Hepatic panel¶, creatinine, glucose ▪ INR ▪ Serum HDV RNA ▪ Serum HBV DNA ▪ Serum HBeAg and anti-HBeΔ ▪ Serum HBsAg (quantitative), if available¥ ▪ TSH ▪ Pregnancy test§
Week 48	▪ CBC with differential (including platelet count) ▪ Hepatic panel¶, creatinine, glucose ▪ Serum HDV RNA ▪ Serum HBV DNA ▪ Serum HBeAg and anti-HBeΔ

	▪ Serum HBsAg◇ ▪ TSH ▪ Pregnancy test§
Week 12 post-treatment	▪ CBC with differential (including platelet count) ▪ Hepatic panel¶ ▪ INR ▪ Serum HDV RNA (optional) ▪ Serum HBV DNA (optional)
Week 24 post-treatment	▪ CBC with differential (including platelet count) ▪ Hepatic panel¶, creatinine, glucose ▪ Serum HDV RNA ▪ Serum HBV DNA ▪ Serum HBeAg and anti-HBeΔ ▪ TSH ▪ Pregnancy test§
Week 48 post-treatment	▪ CBC with differential (including platelet count) ▪ Hepatic panel¶, creatinine, glucose ▪ Serum HDV RNA ▪ Serum HBV DNA ▪ Serum HBeAg and anti-HBeΔ ▪ Serum HBsAg◇ ▪ TSH ▪ Pregnancy test§

This table focuses on monitoring patients who are receiving interferon treatment for HDV. More detailed information on monitoring response to treatment for HBV is presented separately.

CBC: complete blood count; INR: international normalized ratio; TSH: thyroid-stimulating hormone; HDV: hepatitis D virus; HBV: hepatitis B virus; HBeAg: hepatitis B e antigen; anti-HBe: hepatitis B e antibody; HBsAg: hepatitis B surface antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

* Prior to initiating therapy, noninvasive test for liver stiffness or a liver biopsy should be performed to assess for the presence of fibrosis and cirrhosis. In persons with advanced fibrosis or cirrhosis, liver ultrasound should be repeated at week 24 and every 6 months thereafter to evaluate for hepatocellular carcinoma. Elastography may be repeated every 2-3 years to assess for progression/regression.

¶ Hepatic panel includes: ALT, AST, albumin, bilirubin, and alkaline phosphatase.

Δ Only for patients who are HBeAg-positive at baseline.

◇ Quantitative HBsAg should be performed, if available. Quantitative HBsAg should be performed at baseline, week 24 and 48 of treatment, and week 48 post-treatment. If only qualitative HBsAg testing is available, it should be performed at baseline and then repeated at week 48 of treatment and week 48 post-treatment if HBV DNA becomes undetectable.

§ Only for persons of childbearing potential.

¥ This can be used to assess utility of continued therapy.

Graphic 141098 Version 1.0

Endpoints for assessing efficacy of IFNa in chronic HBV infection

Suppression of HBV replication
Clearance of HBV DNA from serum
Clearance of HBeAg with or without the development anti-HBe antibodies
Improvement in liver disease
Normalization in ALT level
Decrease in necroinflammatory activity on liver biopsies
Eradication of HBV (which is seldom achieved)
Clearance of HBsAg with or without the development of anti-HBs antibodies
Clearance of HBV DNA from serum (by PCR); rare in patients who remain HBsAg positive
Disappearance of HBV DNA from liver
Prevention of cirrhosis and hepatocellular carcinoma and improvement in survival
Scanty data

Graphic 63634 Version 2.0

METAVIR fibrosis and activity score

METAVIR fibrosis score		METAVIR activity score	
No fibrosis	F0	No activity	A0
Portal fibrosis without septa	F1	Mild activity	A1
Portal fibrosis with few septa	F2	Moderate activity	A2
Portal fibrosis with numerous septa without cirrhosis	F3	Severe activity	A3
Cirrhosis	F4		

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Graphic 98097 Version 1.0

Contributor Disclosures

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