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Clinical management of **coinfection** with **HIV-HBV-HDV**

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Clinical management of **HIV-HBV-HDV coinfection**

Executive summary

- In persons with HIV infection (*Persons Living With HIV, PLWH*), hepatitis Delta virus infection (*Hepatitis Delta Virus, HDV*) is an important determinant of progression to hepatic cirrhosis and hepatocarcinoma, worsening the prognosis of HBsAg positive individuals or those with triple infection with HCV/HBV/HIV
- The prevalence of anti HDV antibodies in HBsAg positive PLWH belonging to the ICONA cohort is estimated to be around 18,8%; most of the anti HDV positive PLWH show also reactivity for anti HCV. Most of these subjects have acquired these infections through intravenous drug addiction.
- PLWH suffering from chronic hepatitis Delta have to be followed in collaboration with
  - Clinicians with documented experience in clinical management of persons with viral hepatitis
  - Laboratories able to undergo first and second level diagnoses
  - Close relationship with liver transplantation centers.

Diagnosis of HDV infection

- HBsAg, HBcAb and HBsAb detection have to be performed in all PLWH irrespective of year of birth and vaccination status. In HBsAg-positive subjects it is mandatory to test for total (IgG + IgM) anti HDV.
- It is conceivable to negotiate with lab the determination of HBsAg 'reflex' test upon specific request.
- HBsAg positive subjects should be evaluated to ensure that they have been tested for HDV.
  The test should be repeated yearly in HBsAg positive subjects with risk factors for HDV superinfection.
- In the presence of "hepatitis flare" or suspected HDV superinfection or coinfection in HBsAg positive persons, IgM anti HDV and IgM anti HBc should be determined.
- In subjects with anti HDV reactivity the determination of HD -RNA in serum with standardised reliable quantitative methods should be performed.
- In subjects negative for HDV-RNA the test should be repeated in case of HCV Ab reactivity, expecially after HCV-RNA negativization occurring after anti HCV therapy.
- In persons coming from Asian or African countries HDV-RNA determination should be repeated with alternative methods.
- In persons with CD4 <200 in case of reactivity for HBsAg and not otherwise unexplained liver damage, it could be advisable to test for HDV-RNA in serum also with negative HDV antibodies.
- In persons with hepatitis Delta it is important to define HBV infection by determining HBeAg, anti HBe, quantitative HBV-DNA and HBsAg.
- HBV and HDV genotype testing at present are a research topic and is not yet to be implemented in the daily clinical practice.

Counselling

- It is mandatory to recommend testing for HBsAg, anti HBc and anti HBs in all the cohabitants and sexual partners of HBV and HDV carriers if not vaccinated, and testing for anti HDV if HBsAg positive.
- PLWH with hepatitis Delta infection should be advised:
  - To use condom in sexual intercourses with partners not vaccinated for HBV and with vaccinated individuals up to 2-3 months after the last dose of vaccine
  - not to share with other subjects commonly used objects (razors and nail scissors, toothbrushes, syringes) and other objects used to prepare and inject drugs
  - to avoid alcoholic drinks
  - to mantain a BMI < 25 with adequate diet and physical activity.
- Total (IgG and IgM) anti HAV antibodies should be determined, and, in absence of these, anti HAV vaccination should be proposed.

Characterization and staging of liver disease

- Reactivity for anti HCV should be sought. In anti HCV positive subjects the test for the quantification of HCV-RNA will have to be performed. In the presence of positive HCV-RNA, anti HCV treatment will be carried out.
- Concomitant causes of liver disease should be evaluated:
  - autoimmune
  - from accumulation
  - fatty liver disease.
- Overweight and obesity and glucose and lipid metabolism abnormal values should be evaluated and treated.
- To evaluate the activity and stage of liver disease, it is necessary to perform:
  - laboratory tests
  - abdomen ultrasound
  - FibroScan.
- Elevated liver stiffness values on elastography (FibroScan) are indicative of the severity of chronic hepatitis Delta. The following cutoffs are recommended:
  - <8-10 kPa to exclude the presence of advanced fibrosis
  - >12-15 kPa for the diagnosis of advanced fibrosis.
- Based on the above parameters the disease can be staged into:
  - Compensated chronic liver disease:
    - with non-advanced fibrosis
    - with possible advanced fibrosis
    - with advanced fibrosis:
      - without clinically significant portal hypertension
      - with clinically significant portal hypertension
        - without esophageal varices
        - with esophageal varices.
  - Decompensated chronic liver disease:
    - in class B according to Child-Pugh
    - in class C according to Child Pugh
- Liver biopsy is not necessary, however it may be indicated in special cases.

Monitoring of liver disease

Virological hepatitis monitoring includes quantitative HDV-RNA every 6-12 months or in case of liver *flares*.

- In anti HCV positive PLWH who are treated and with exposure to risk factors for reinfection, it is mandatory to control HCV-RNA every 6-12 months or in case of hepatitis *flares*.
- Liver enzymes, INR, reflex bilirubine, albumin, Na and creatinine should be tested at least every 6 months.
- Liver ultrasound should be performed every 6 months in PLWH with even possible advanced fibrosis, in those born in Asia or Africa and in those with a family history of hepatocellular carcinoma.
- Digestive endoscopy should be performed every 2 years in PLWH with portal hypertension. In the absence of varices it will have to be repeated every 2 years and after 1 year in the presence of small varices not at risk for bleeding.
- In decompensated chronic liver disease, complications will be identified, classified and treated according to the latest guidelines and with the collaboration of a specialist centre.
- All subjects with MELD > 12 and/or decompensated liver disease should be evaluated for liver transplant, in collaboration with a transplant center. All persons with HCC should be evaluated by a multidisciplinary team in collaboration with a transplant center.

Antiretroviral therapy in PLWHs with hepatitis Delta

- In all individuals therapy should preferentially include tenofovir disoproxil (TDF) or tenofovir alafenamide (TAF). In cases where it is not possible to administer these drugs as anti HIV therapy, entecavir 0.5 mg should be added to HIV therapy after assessing the presence of HBV resistance to lamivudine. In persons with lamivudine resistance, therapy with TDF/TAF is mandatory.
- Pending *in vivo* drug-drug interaction studies, co-administration of bulevirtide with ritonavir, the protease inhibitors, efavirenz, etravirine and presumably cobicistat should be avoided.

Therapy of hepatitis Delta in PLWHs

Pegylated interferon alpha

- Pegylated interferon alpha therapy:
  - is an "*off label*" therapy with response in less than 25% of persons, with relapse rates as high as 50% at five years
  - is contraindicated in persons with decompensated disease or clinically significant portal hypertension
  - is associated with important side effects.
- Before starting, absolute contraindications should be ruled out and any relative contraindications evaluated.
- During treatment it is necessary to check thyroid function, blood count and neuropsychiatric conditions at least every 3 months in addition to the trend of liver enzymes, INR, albumin and reflex bilirubin, reflex TSH and HDV-RNA levels, always at the same laboratory, every 3-6 months.
- The minimum duration is 48 weeks.

Bulevirtide

- Bulevirtide is the only "on label" therapeutic option whose reimbursed use was authorized in Italy in February 2023 in subjects with compensated chronic hepatitis Delta.
- The drug should be administered subcutaneously at a dose of 2 mg every 24 hours with maximum tolerance of 4 hours by following the instructions given in the "Step-by-step injection guide" attached to the package leaflet of the medicine.
- It has no major side effects, the most frequent being an asymptomatic elevation of bile acids or injection site reactions.
- Bulevirtide therapy is able to induce at 48 weeks after the start of treatment a virological response, i.e. a decrease in HDV-RNA levels by 2 logarithms in 71% of treated people, a biochemical response, i.e. the normalization of aminotransferases in 51% of treated people and a combination of virological and biochemical response in 45% of treated people. Real-life studies in subjects with cirrhosis and clinically significant portal hypertension showed at 72 weeks a virological response in 75%, biochemical in 63% and a combined response in 63% with 38% of people with non quantifiable HDV-RNA and 81% with HDV-RNA <1000 IU/mL.

Drug interactions

- Co-administration of sulfasalazine, irbesartan, ezetimibe, ritonavir, and cyclosporine A is not recommended.
- Co-administration of NTCP substrates such as estrone-3-sulfate, fluvastatin, atorvastatin, pitavastatin, pravastatin, rosuvastatin and thyroid hormones where possible should be avoided.

Who to treat

- Priority consideration should be given to subjects with compensated chronic hepatitis Delta with even possible advanced fibrosis (i.e. with stiffness at FibroScan > 10kPa or platelets < 150,000 or FIB4 > 3.25 or with clear ultrasound signs of cirrhosis). Evidence from real world data supports the decision to treat these people
- In other subjects decision must be individualized taking into account the possible cost-benefit ratio and especially considering the high evolutiveness of chronic hepatitis toward cirrhosis in HBV/HDV/HIV co-infection. In people in whom the decision is made not to start bulevirtide should be considered as alternatives:
  - the possible off-label use of pegylated interferon alpha monotherapy
  - the possible access to experimental therapies
  - the possibility of carefully monitoring the people without immediate antiviral treatment pending new studies, new data and new antiviral strategies.

What to do before treating

- Reassess HIV therapy and concomitant therapies.
- Offer anti HBV therapy with TDF/TAF.
- In the presence of HCV coinfection, this can also be treated concurrently with anti HDV therapy if there is an urgency for both treatments. In these cases, for the reasons explained above, the combination of sofosbuvir and velpatasvir should preferably be used
- Before treatment, the person should be informed of the risks of the evolution of the liver disease and trained by nurses to perform the injections by following the drug administration guidelines included in the package insert.

Monitoring during treatment

- Quantification of HDV-RNA should always be performed in the same laboratory every 2 months for the first 6 months then every 3 months.
- Liver enzymes assay, INR, albumin and reflex bilirubin.
- It may be useful to quantify serum bile acid levels to assess treatment adherence.
- Individuals should be evaluated on an outpatient basis at least every 2 months for the first 6 months then at least every 3 months.

Discontinuation of therapy

- The optimal duration of therapy is not defined.
- Therapy should be discontinued in the presence of HBsAg clearance and occurrence of anti HBs antibodies for at least 6 months.
- In case of significant side effects, it can be hypothesized to discontinue treatment in persons who do not experience HDV-RNA decrease of at least one logarithm and reduction in aminotransferase values after at least 48 weeks of therapy.
- Discontinuation of therapy in persons who are still HBsAg positive can give rise to a hepatitis flare from reactivation of HDV infection.
- Duration of treatment can be better assessed once data from ongoing clinical studies are acquired.

Clinical management of **HIV-HBV-HDV coinfection**

Hepatitis Delta virus (*Hepatitis Delta Virus; HDV*) in HIV-infected people is a major cause of death from liver disease and liver cancer as well as liver transplantation[1]. The availability of new treatments should stimulate clinical practice to reconsider the need for screening and treatment of this co-infection even in people living with Human Immunodeficiency Virus HIV (*Human Immunodeficiency Virus HIV; Persons Living with HIV, PLWH*). For this reason, as part of ICONA cohort educational initiatives, it was decided to draw up a document with the aim of providing practical indications for the screening, diagnosis and management of Delta virus coinfection in PLWHs.

Introduction

Several cross-sectional and longitudinal studies have demonstrated that in **PLWH HDV infection is an important determinant of rapid evolution towards cirrhosis and hepatocellular carcinoma, worsening the prognosis of HBsAg positive persons or those with triple infection with HCV/HBV/HDV[2-5]. The prevalence of anti HDV antibody reactivity in PLWH in HBsAg positive subjects in the ICONA cohort is estimated to be 18.8%,** however among new individuals enrolled in the cohort, a progressive decrease in anti HDV reactivity from 28% of the years between 1997 and 1999 to 12% in subjects enrolled between 2012 and 2013[3]. It should be emphasized that due to the increased efficacy of HDV transmission via blood, **most of the anti HDV positive PLWHs also have anti HCV reactivity[1-5]**.

The management of persons with chronic hepatitis Delta requires precise virological characterization, both for HBV and HDV and for any HCV coinfection, and staging of liver damage, as per national and international recommendations guidelines. Currently, the following treatment options are indicated:

1) Pegylated interferon alpha (pegIFNα), which can have an immunomodulatory antiviral effect on both HBV and HDV but it is off-label in HDV infection
2) Bulevirtide (BLV), a new HDV-specific antiviral able to block the virus entry into hepatocytes and therefore the spread of infection in the liver.

Nucleos(t)ide analogues (NUCs) active on both HIV and HBV and able to block HBV replication have no direct efficacy against HDV.

WHO SHOULD MANAGE CHRONIC HEPATITIS DELTA IN PLWH

Given the rapid progression of HDV disease to advanced cirrhosis, it is believed that PLWHs with chronic hepatitis Delta **should be followed up in collaboration with clinicians with documented experience in the management of persons with viral hepatitis and with laboratories that are able to supply first and second level tests.** Furthermore, it is essential that clinicians who follow these persons must have **a close link with the reference liver transplant centers** at the regional level for the referral of persons with decompensated HDV disease or with hepatocellular carcinoma (HCC). However, HIV treatment centers authorized at a regional level to prescribe anti HCV directed antivirals (DAAs) and with experienced and qualified physicians in the management of persons with liver disease may be considered the ideal setting for referral and management of persons with CHD.

Diagnosis of HDV infection

SCREENING FOR HBV MARKERS IN PLWH AND DOUBLE REFLEX TESTING

Screening for HBsAg, HBcAb and HBsAb must be performed in all PLWHs regardless of year of birth and vaccination status[6]. In HBsAg positive people the determination of total anti HDV (IgG + IgM) must be performed. In people negative for the three markers who do not respond to the vaccine, testing must be repeated annually (follow-up tests). **It is suggested to agree with the referring laboratory** at the first screening or at the follow-up tests in PLWH negative for the three markers, **the execution on specific request of a "reflex" HBsAg test** which involves performing of anti HBeAg HBe, HBV-DNA and anti HDV and the execution of HDV-RNA in the same laboratory or in a reference laboratory in anti HDV positive subjects or a “double reflex testing” recommended by an international consensus document[7].

INITIAL DIAGNOSIS

In published studies, the detection rate of anti HDV in PLWHs with reactivity for HBsAg is markedly unsatisfactory and varies from 39% recorded in PLWHs in ICONA cohort to 56% of the European EUROSIDA cohort[3,8-9]. For this **reason it is recommended that HBsAg positive subjects be re-evaluated to verify that they have been screened for HDV. The test should be repeated annually in HBsAg positive subjects with risk factors for HDV superinfection**. The recommended screening test measures total anti HDV (IgG + IgM).

In the presence of "hepatitis flare" or suspected HDV superinfection or coinfection in HBsAg positive persons, it is also necessary to perform a search for IgM class anti HBc antibodies and IgM class anti HBc antibodies to exclude a recent HBV-HDV coinfection or HDV superinfection on HBV.

In subjects with anti HDV reactivity, serum HDV-RNA detection **must be performed by a standardized and reliable quantitative method, following a standardized pre-analytical procedure**, possibly in a laboratory of the Vironet network following the indications of the same on pre-analytical procedures (containers, transport, etc.).

In subjects with negative reactivity for HDV-RNA, the test should be repeated in the presence of anti HCV reactivity, in particular after HCV-RNA negativization induced by anti HCV therapy. In fact, in the presence of quadruple HIV/HBV/HDV/HCV infection, due to the complex phenomena of viral interference, the replication of one or more of the three viruses can be transiently suppressed[10].

It should be taken into account that:

- **in persons from African or Asian countries**, peculiar HDV genotypes may be present so in case of anti HDV reactivity -and HDV-RNA negativity with liver damage not otherwise explained, **HDV-RNA detection can be repeated** using alternative methods.
- **in persons with significant immunosuppression** (CD4<200) the anti HDV reactivity may fail even in the presence of Delta virus infection[11]. **In case of HBsAg reactivity with unexplained liver damage, it may be appropriate to determine serum HDV-RNA even in the absence of anti HDV reactivity.**

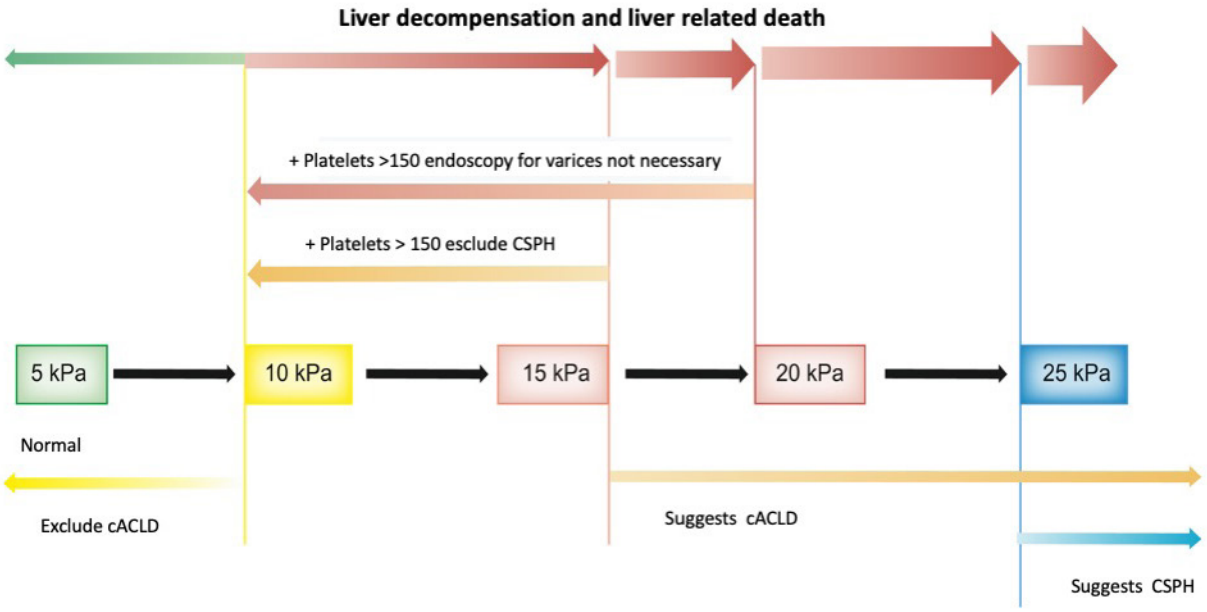
The diagnostic algorithm is summarized in *figure 1*.

As in all HBsAg positive persons, even **in persons with hepatitis Delta it is important to characterize the HBV infection by determining HBeAg, anti HBeAg, the quantification of HBV-DNA and HBsAg**.

In subjects with chronic HBeAg negative HBV infection, the determination of HBV DNA levels must be repeated over time as the partial control of viral replication and the production of viral proteins observed in HBeAg negative infection can be a dynamic and discontinuous process. For this reason, determination of liver enzyme values must also be repeated jointly to differentiate a person with chronic infection from one with HBeAg negative chronic hepatitis. Quantification of HBsAg can be useful in assessing the likehood of response to some therapies, the risk of HCC and both spontaneous and drug-induced short-term HBsAg clearance. Standardized assays aimed at identifying and quantifying additional markers such as circulating HBc related antigen, HBV-RNA and quantification of anti HBc antibodies are being validated. Although such tests have different potential uses. there is not enough data at the moment to recommend their use in the routine clinical practice.

In HBV-DNA positive persons with past lamivudine administration HBV resistance test should be performed.

Figure 1



cACLD: chronic Advanced Compensated Liver Disease
CSPH: Clinical Significant Portal Hypertension

HBV AND HDV GENOTYPING

Hepatitis Delta virus has been classified into 8 genotypes. Genotype 1 in turn divided into at least 5 subtypes identified by the letters from a to e is more represented worldwide and is the predominant genotype in Central-Western Europe and North America; genotype 2 is more prevalent in South-East Asia, genotype 3 in South America, in the Amazon region, while genotypes 4 to 8 are mainly present in Sub-Saharan Africa.

Combining the 8 HDV genotypes with the 8 HBV genotypes can theoretically generate 64 different viral subtypes. Genotypic differences of HDV and HBV envelope proteins are the main determinants of HDV assembly and ability to infect cells de novo; consequently the different viral subtypes could have great relevance both in pathogenetic terms related to the development of disease and on the efficacy of antiviral drugs. **HBV and HDV genotype determination is currently a research topic and is not yet to be implemented in daily clinical practice.**

Counselling

In all cohabitants and sexual partners of subjects with HDV infection, testing for HBsAg, anti HBc and anti HBs if not vaccinated and anti HDV if HBsAg positive should be advised. Condom use during intercourses with unvaccinated sexual partners and with vaccinated subjects should also be recommended until 2-3 months after the last dose of vaccine. The person infected with HBV/HDV should be advised not to share with other subjects commonly used objects (razors and nail scissors, toothbrushes, syringes) and other objects used for the preparation and injection of drugs.

Although an antiretroviral therapy containing TDF or TAF is likely to be able to reduce transmission of HBV infection to an extremely relevant way, there are still no studies that can translate the concept "U = U" from HIV to HBV and consequently to HDV by quantifying the contagiousness of HBV-DNA and HDV-RNA negative subjects in sexual and relationship life.

In all subjects with hepatitis Delta it is necessary to recommend:
- **avoid the consumption of drinks containing alcohol**
- **keep a BMI <25 with adequate diet and physical activity.**

Screening for Total anti HAV antibodies (IgG and IgM) must be done and in the absence of positive tests the anti HAV vaccination must be proposed.

Characterization and staging of liver disease

In all subjects with anti HDV, reactivity for **anti HCV reactivity** will be sought in addition to characterizing the HBV infection. **In anti HCV positive subjects HCV-RNA quantification will be performed. In the presence of positive HCV-RNA, anti HCV treatment will be carried out** in compliance with the most recent guidelines and the presence of sustained virological response will be evaluated with quantification for HCV-RNA at 3, 6 and 12 months after the end of treatment. In the presence of negativity of HDV-RNA detection in HCV-RNA positive subjects, quantification of HDV-RNA will have tobe repeated after HCV-RNA negativity as indicated above.

Concomitant causes of liver disease should be evaluated:
- **autoimmune**, by measuring the autoantibody reactivity by detecting and quantifying the titre of non-organ specific antibodies (antinuclear, anti-mitochondrion, anti LKM)
- **by accumulation of iron**, copper, alpha 1 antitrypsin and fibrinogen by measuring transferrin saturation, copper and ceruloplasmin levels, alpha 1 antitrypsin and fibrinogen
- **hepatic steatosis** by ultrasound and possible evaluation of the CAP by FibroScan.

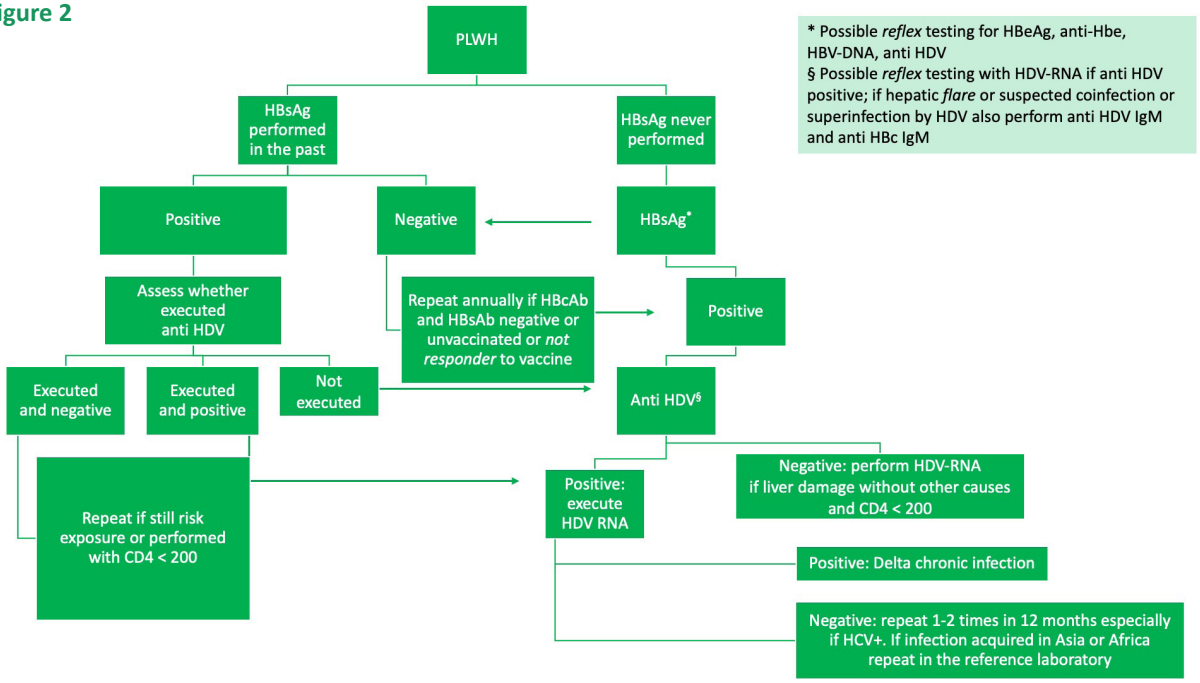
In all subjects with hepatitis Delta, **overweight and obesity and alterations of glucose and lipid metabolism must be evaluated and treated**. Diabetes is an important risk factor for the progression of liver disease to cirrhosis and HCC.

To evaluate the activity and stage of liver disease, it is necessary to perform:
- **laboratory tests:** complete blood count with liver enzymes formula (ALT AST GGT ALP), albumin, reflex bilirubin, total protein and protidogram, INR, creatinine and sodium
- **abdomen ultrasound** with assessment of the liver margin with 7.5 MHz probe and echo color Doppler ultrasound, assessing the presence of focal hepatic lesions and elements indicative of evolution to cirrhosis such as nodularity of the liver margin, hypertrophy of lobe caudate, splenomegaly, signs on color Doppler of portal hypertension and portal thrombosis.
- **FibroScan** with adequate measurement of stiffness (with IQR < 20% of the measured value) and CAP if available. The use of non-invasive tests is not yet fully validated in HDV disease; **high values of liver stiffness on elastography (FibroScan) are indicative of the severity of chronic hepatitis Delta**.

The following cutoffs are recommended:
- **<8-10 kPa to esclude the presence of advanced fibrosis**
- **>12-15 kPa for the diagnosis of advanced fibrosis.**

An elastography value >14kPa in persons with HDV infection has a specificity for liver cirrhosis of 86%. On the basis of the available elements APRI and FIB-4 can be calculated and based o stiffness and platelet count (*figure 2*) **the disease can be staged in**:
- **Chronic compensated liver disease:**
  - with non-advanced fibrosis with stiffness < 8-10 kPa platelets > 150,000/mmc, APRI < 1, FIB-4 < 3.25 and in the absence of ultrasound drawings of advanced disease
  - with possible advanced fibrosis with stiffness 12-15 kPa or platelets < 150,000/mm^3 with no other possible causes or APRI > 1.5-2 or FIB4 > 3.25 or ultrasound signs of cirrhosis
  - with advanced fibrosis with stiffness > 15 or platelets < 150,000 without other causes:
    - without clinically significant portal hypertension with stiffness < 20 kPa and platelets > 150,000/mmc

Figure 2



  - with clinically significant portal hypertension with stiffness > 20 kPa or platelets < 150,000/mm^3 with no other cause
    - without oesophageal varices
    - with oesophageal varices.
- **Chronic decompensated liver disease:**
  - **in class B according to Child-Pugh**
  - **in class C according to Child Pugh.**

Liver biopsy is not necessary; however it may be indicated in cases where:

- clinical acumen and evaluation of non-invasive tests are unable to define a significant staging that is deemed clinically necessary
- it is necessary from the point of view of clinical decisions to evaluate the presence of other causes of liver damage that cannot be inferred from non-invasive tests.

Monitoring of liver disease

Virological monitoring of persons with hepatitis Delta should be carried out by **quantification of HDV-RNA every 6-12 months or in the presence of hepatitis flares** to be performed always in the same laboratory, possibly with the same method. It is also important to evaluate with the same timing also HBV-DNA, quantitative HBsAg and in HBeAg positive persons also HBeAg and anti HBe. In **anti HCV positive persons treated with exposure to risk factors for reinfection, the HCV-RNA should be checked every 6-12 months or in the presence of hepatitis flares.**

Liver enzymes, INR, reflex bilirubin, albumin, sodium, and creatinine should be evaluated at least every 6 months. In persons with possibly evolving and advanced disease, Child-Pugh score and MELD or MELD-Na should be calculated every 6 months.

Persons with **advanced or evolving chronic liver disease, persons born in Asia or Africa and persons with a family history of hepatocellular carcinoma** will undergo liver ultrasound every 6 months to highlight any

focal lesions which will be managed in accordance with international guidelines for diagnosis and HCC therapy. Persons with **clinically significant portal hypertension will undergo GI endoscopy to identify the presence of esophageal varices. In the absence of varices**, endoscopy should be repeated every 2 years in persons with HDV coinfection or other concurrent causes of liver disease. In the presence of small varices with no risk of bleeding, the endoscopy should be repeated **after 1 year** respectively. Varices with bleeding risk should be managed in accordance with current guidelines.
Complications in chronic decompensated liver disease will be identified, classified and treated according to the latest guidelines and with the collaboration of a specialist center: HCC, ascites, hyponatremia, hepatic hydrothorax, acute and chronic kidney damage, hepatorenal syndrome, digestive bleeding, gastropathy and portal hypertension enteropathy, portal thrombosis, acute liver failure in chronic disease, portosystemic encephalopathy, bacterial infections, cirrhotic heart disease, hepatopulmonary syndrome, portopulmonary hypertension. **All persons with MELD > 12 and/or decompensated and complicated liver disease will be evaluated for liver transplantation in collaboration with a transplant center. All persons with HCC will be evaluated by a multidisciplinary team in collaboration with a transplant center.**

Antiretroviral therapy in PLWHs with hepatitis Delta

In all persons, therapy should preferably include TAF or TDF. In cases where these drugs cannot be administered, entecavir 0.5 mg should be added to the antiretroviral therapy after assessing the presence of HBV resistance to lamivudine. In persons with lamivudine resistance, therapy with TDF/TAF is mandatory.
In vitro **ritonavir, protease inhibitors, efavirenz, etravirine and presumably cobicistat** reduce the expression of NTCP (Na Taurocholate Co-Transporting Peptide), the target of the pharmacological action of **bulevirtide**. Although formal drug interaction studies have not been performed, **co-administration of these drugs should be avoided pending in vivo studies**. It must be said that 2 cases of HIV persons treated with darunavir/cobicistat and bulevirtide have been recently reported but no data indicative of the absence or presence of signs of clinically significant drug interaction have been reported.

Therapy of hepatitis Delta in PLWHs

Pegylated interferon alpha

Therapy with interferon alpha, first recombinant and then **pegylated**, has been used in the treatment of HDV infection for the last 40 years. It is an **"off label" therapy** which, even in persons in PLWH, resulted in a **combined response** at least 6 months after discontinuation (enzyme normalization and unquantifiable HDV-RNA) **in less than 25% of persons with recurrence rates that reached 50% at five years. Therapy is contraindicated in persons with decompensated disease or clinically significant portal hypertension and is burdened by important side effects**. Before starting **exclude absolute contraindications** (severe psychopatology, uncontrolled thyroid disease, autoimmune disease, uncontrolled depression) and **evaluate any relative contraindications** (depression, heart disease, minor autoimmune diseases) should be ruled out. The person should be instructed on the management of the flu-like syndrome which may last up to 48 hours after administration and should be warned of side effects (asthenia, fatigability, myalgias, possible neuropsychiatric alterations). diseases, depression of mood) and **during treatment thyroid function, blood crasis and neuropsychiatric conditions of the patient must be monitored at least every 3 months in addition to the trend of liver enzymes, INR, albumin and reflex bilirubin, reflex TSH and HDV-RNA levels always at the same laboratory every 3-6 months.**
Therapy is administered with weekly subcutaneous injections at a dose of 180 mcg of pegylated interferon alpha 2a and 1.5 mcg/kg of pegylated interferon alpha 2b; **the minimum duration is 48 weeks**. Higher response

rates with prolonged therapies of 2 to 6 years have been described in small series, however, poor tolerability makes this approach difficult in most people.

Bulevirtide

Bulevirtide is the only drug approved by the European Medicine Agency; it is, therefore, **the only recenton-label therapeutic option whose reimbursable use was authorized in Italy in February 2023 in subjects with compensated chronic hepatitis Delta**. It is a 47 amino acid lipopeptide that acts as an inhibitor of virus entry into the liver cell by competing with the pre-S1 domain of the HBV surface antigen for the cellular receptor, Na-Taurocolate Co-Transporting Peptide (NTCP).
The drug should be administered subcutaneously at a dose of 2 mg every 24 hours with a maximum tolerance of 4 hours following the directions given in the "Step-by-step injection guide" attached to the insert in the drug package. In case the drug cannot be administered within 28 hours after the previous injection, the dose should be skipped. The dose following the dose administered late should in any case be administered 48 hours after the penultimate dose.
It has no important side effects; the most frequent are asymptomatic elevation of bile acids due to its mechanism of action or injection site reactions which may include swelling, redness, irritation, bruising, itching, infection or pain occurring in less than 10 % of persons. Other side effects described in less than 10% of persons include headache, dizziness, nausea, fatigue, drowsiness, tachycardia, flu-like syndrome, abdominal bloating, itching, joint or muscle pain, excessive sweating, skin rash or other skin rashes.

It has been observed that some drugs can inhibit Na Taurocholate Co-Transporting Peptide (NTCP), the target of bulevirtide. Co-administration of such drugs as sulfasalazine, irbesartan, ezetimibe, ritonavir and cyclosporine A is not recommended.
As a precautionary measure, close clinical monitoring is required when NTCP substrates (e.g. **estrone-3-sulfate, fluvastatin, atorvastatin, pitavastatin, pravastatin, rosuvastatin and thyroid hormones**) are co-administered with bulevirtide. **Where possible, co-administration of these substrates should be avoided**.

In vitro inhibition of OATP1B1/3 transporters by bulevirtide has been observed, although only at a concentration ≥ 0.5 µM, achieved in vivo only after administration of high doses of bulevirtide 5 times higher than those used in therapy (10 mg subcutaneously). The clinical relevance of these findings is unknown. However, a recent study in healthy volunteers showed no clinically significant interactions between bulevirtide administered at 5 times the indicated dose and pravastatin

Randomized clinical trials have shown that **bulevirtide therapy is able to induce at 48 weeks after the start of treatment a virological response, i.e. a decrease in HDV-RNA levels of 2 logarithms in 71% of people treated, a biochemical response or normalization of aminotransferase values in 51% of treated persons and a combination of virological and biochemical response in 45% of treated persons**.

Real-life data in cohorts of people in France and Germany confirmed these results. The data were also confirmed in an Italian cohort: 93 subjects with advanced fibrosis and clinically significant portal hypertension reported **at 72 weeks a virological response in 75%, biochemical in 63% and combined in 63% with 38% of subjects with unquantifiable HDV-RNA and 81% with HDV-RNA <1000 IU/mL.**
Complete recovery from infection was observed in one person followed in Milan after three years of therapy and more than 18 months of HDV-RNA negative.
These real-life cohorts treated with bulevirtide monotherapy included 5 PLWHs in Italy and 14 in France, and responses were observed that overlapped with those observed in people without HIV infection.

Who to treat

The bulevirtide indication admits to treatment all persons with compensated chronic hepatitis Delta with re-activity for HDV-RNA on peripheral blood.

People with compensated chronic hepatitis Delta with even possible advanced fibrosis (i.e., with stiffness at FibroScan > 10 kPa or platelets < 150,000 or FIB4 > 3.25 or with clear ultrasonographic signs of cirrhosis) should be considered with priority for bulevirtide therapy.

As for others, an individualized decision is recommended taking into account the possible risk-benefit ratio. In this regard, it should be considered that HIV infection is a cofactor of disease progression along with elevated HDV-RNA and aminotransferase levels and that incisive counseling is needed to achieve the necessary adherence to a therapy involving daily injection administration. Possible off-label use of pegylated interferon-alpha monotherapy or even possible access to experimental therapies or careful monitoring of the untreated person pending new studies, new data, and new antiviral strategies should be considered as alternatives.

Concurrent administration of bulevirtide 2 mg and pegylated interferon alpha (de novo combination) or use of pegylated interferon alpha as an add-on strategy in people with limited virologic response is not recommended at this time. Specific studies are ongoing.

What to do before treatment

HIV therapy and concomitant therapies should be reevaluated to avoid drug interactions, and anti HBV therapy with TDF/TAF should be offered as previously indicated. In the presence of HCV coinfection, this can also be treated concurrently with anti HDV therapy if there is an urgency for both treatments. In these cases for the reasons outlined above the combination of sofosbuvir and velpatasvir should preferably be used.

Prior to treatment, the person should be informed of the risks of developing liver disease and trained by nurses in performing the injection by following the drug administration guide included in the package insert.

Monitoring during treatment

During the therapy it is suggested to monitor its efficacy through **quantification of HDV-RNA which should always be performed in the same laboratory every 2 months for the first 6 months then every 3 months, and assay of liver enzymes, INR, albumin and reflex bilirubin It may be useful to quantify serum bile acid levels to assess adherence to treatment. Persons should be evaluated on an outpatient basis at least every 2 months**

Therapy discontinuation

Pending the results of ongoing studies, **therapy should be suspended only in presence of HBsAg clearance and positivity for anti HBs for at least 6 months. In case of significant side effects, it can be hypothesized to discontinue the treatment in persons who do not show HDV-RNA decrease in of at least one logarithm and reduction in aminotransferase values after at least 48 weeks of therapy**. It should be kept in mind that **discontinuation of therapy in persons still HBsAg positive may result in a hepatitis flare from reactivation of the HDV infection**.

The duration of treatment can be better assessed once data from ongoing clinical studies are acquired which include discontinuation of treatment after three years of therapy and the post-treatment follow-up.

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