Italian Cohort
I. C O.
N A.
Naive Antiretrovirals

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS
Conceived by Professor Mauro Moroni

Clinical management of HIV-HBV-HDV COINFECTION

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How important is HDV infection in PLWH

In *Persons Living With HIV* (PLWH) *Hepatitis Delta Virus* (HDV) is an important determinant of evolution to hepatic cirrhosis and hepatocarcinoma, worsening the prognosis of HBsAg positive individuals or those with triple infection with HCV/HBV/HIV.

- **In ICONA cohort (Italian cohort naïve antiretrovirals):**
  - HDV Ab prevalence in HBsAg pos PLWH: 18.8%
  - HDV Ab pos/HCV Ab pos: 65.8%
- **PLWH suffering from chronic HDV hepatitis have to be followed in collaboration with:**
  - Clinicians with experience in clinical management of persons with viral hepatitis
  - Laboratories able to undergo second level diagnoses
  - Close relationship with liver transplantation centers

Diagnosis of HDV hepatitis

- **HBsAg, HBcAb and HBsAb:** have to be searched in all PLWH.
- **In HBsAg-positive subjects:** mandatory to test for total (IgG + IgM) anti-HDV, possibly by HBsAg “reflex” test.
- **HBsAg positive PLWH:** mandatory to repeat HDV Ab yearly and in the presence of hepatic flares.
- **All HDV Ab positive:** should be tested for HDV-RNA, to be repeated if HCV-RNA turned negative (possible viral interactions).

Diagnosis of HDV hepatitis

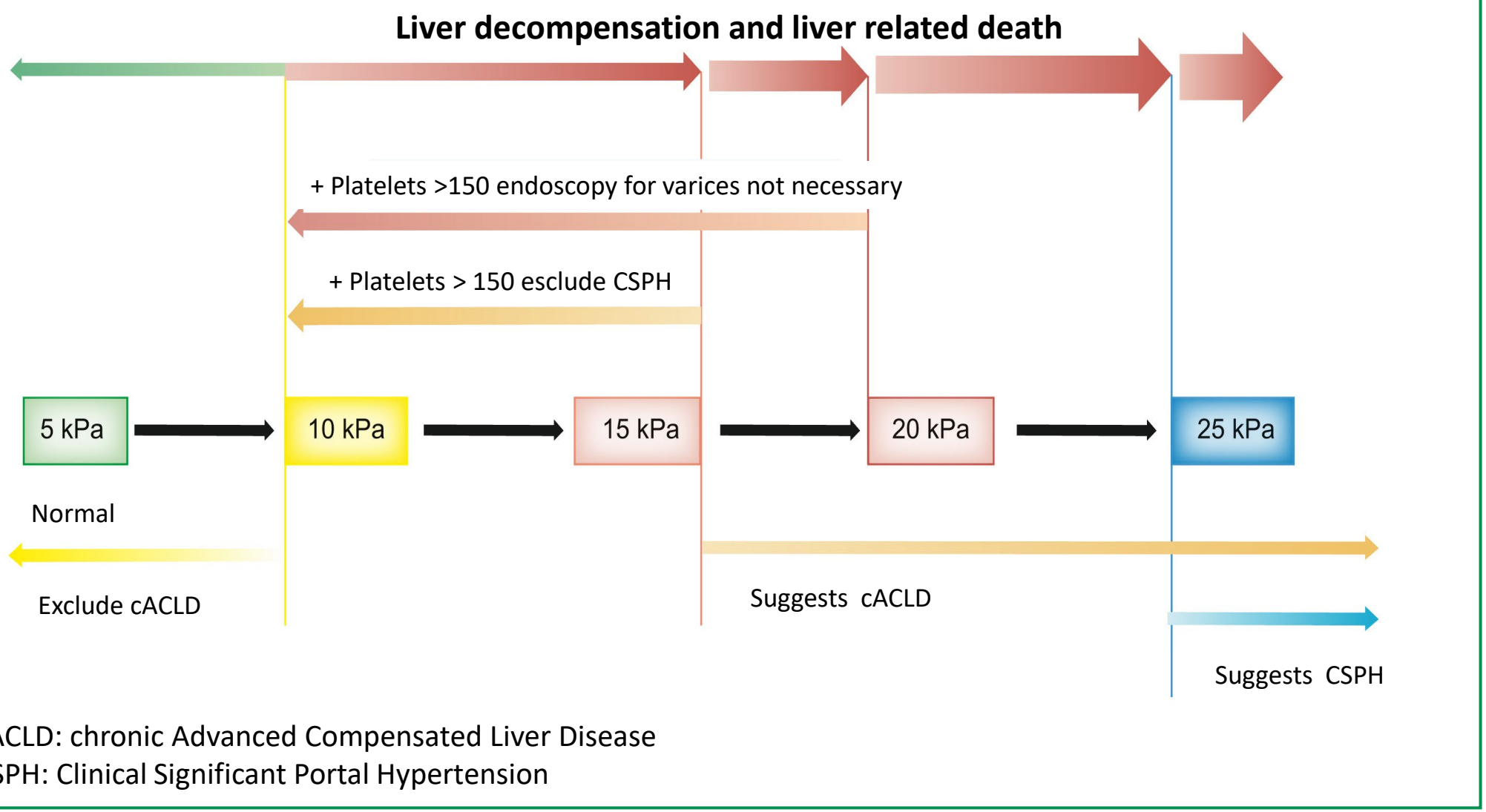
- In persons coming from Asian or African countries HDV-RNA determination should be repeated with alternative methods.
- HBsAg positive PLWH with CD4 <200/cmm and not otherwise explicable liver damage, should be tested for HDV-RNA also with negative HDV antibodies.
- In PLWH with HDV: define HBV infection, testing for: HBeAg, anti HBe, quantitative HBV-DNA and HBsAg.
- HBV and HDV genotype testing not yet implemented in the daily clinical practice.

HBV and HDV genotypes

HDV: 8 genotypes

- **Genotype 1** (at least 5 subtypes): more represented worldwide
  predominant genotype in Central-Western Europe and North America.
- **Genotype 2:** more prevalent in South-East Asia.
- **Genotype 3:** in South America, in the Amazon region.
- **Genotypes 4 to 8:** mainly present in Sub-Saharan Africa.

- At present only epidemiological importance
- Genotype 1 seems to be related to a worse prognosis
- Combination HBV (8 genotypes) and HDV genotypes: 64 subtypes



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

Counselling for cohabitants and partners of persons with HDV hepatitis

- 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.
- Although an anti HIV therapy containing TDF or TAF is likely to be able to reduce the transmission of HBV infection in 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 the HBV-DNA and HDV-RNA negative subjects in sexual and relationship life.

Counselling for the HDV positive PLWH

- 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 others subjects commonly used objects such shaver and nail scissors, toothbrush, syringe and other objects
  - to avoid alcoholic drinks
  - to mantain a BMI < 25 through 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
Virological screening

In all HDV Ab positives:

- 1- characterize the HBV infection,
- 2- test for HCV Ab

  In HCV Ab positive: quantification of HCV-RNA

  - 2a- In HCV-RNA positive: treat HCV with DAA
  - 2b- In SVR (HCV-RNA neg 12 weeks post DAA) quantification of HDV RNA

Characterization and staging of liver disease

Concomitant causes of liver disease should be evaluated

- **autoimmune** — quantification of the titre of non-organ specific antibodies (antinuclear, anti-mitochondrion, anti LKM)
- **By accumulation of iron, copper, alpha 1 antitrypsin and fibrinogen** — transferrin saturation, copper and ceruloplasmin levels, alpha 1 antitrypsin and fibrinogen
- **hepatic steatosis** — ultrasound and possible evaluation of the CAP by FibroScan.

Overweight and obesity, alterations of glucose and lipid metabolism should be evaluated and treated

Diabetes is an important risk factor for the progression of liver disease to cirrhosis and HCC.

Staging of liver disease

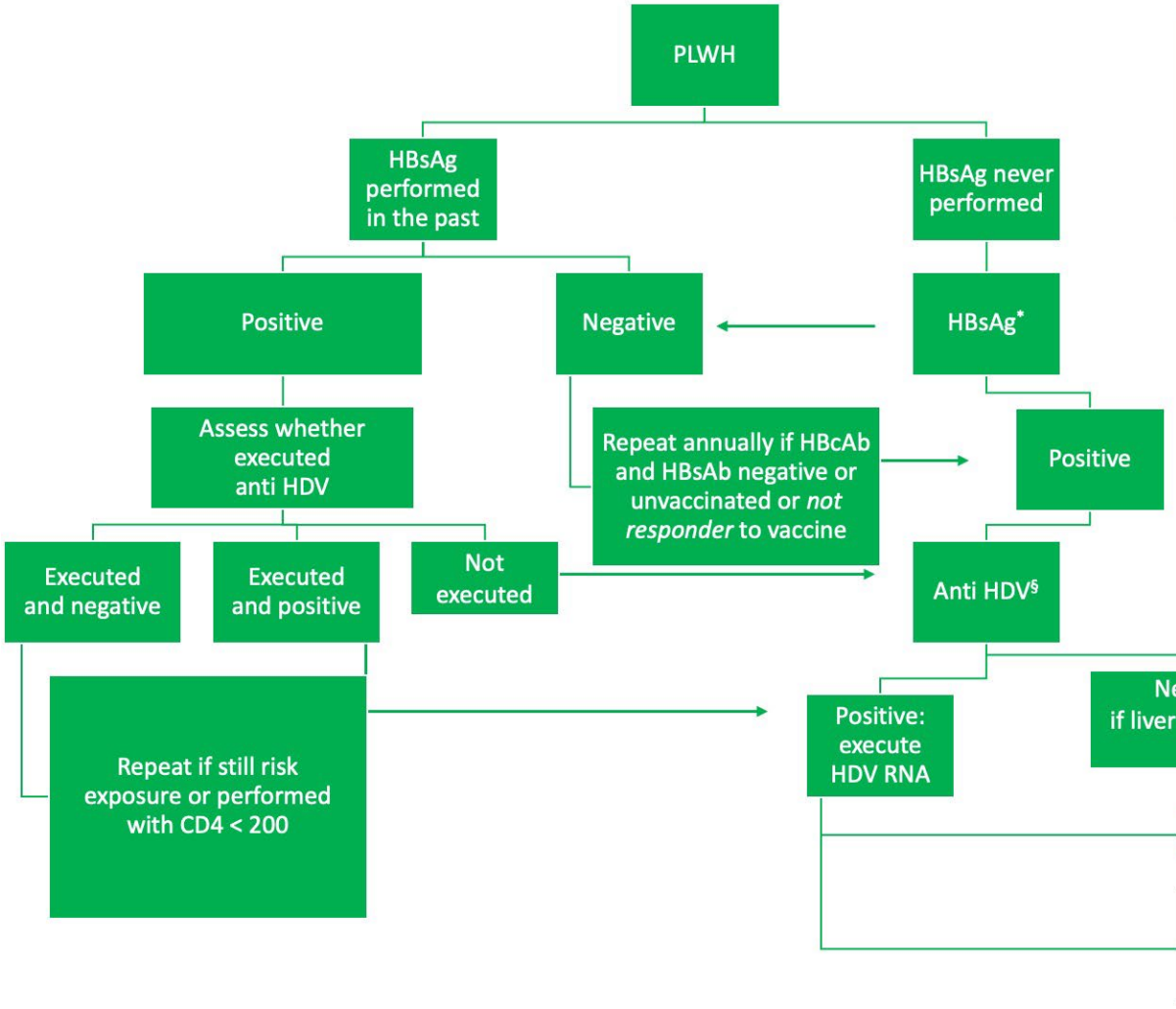
Lab tests and abdomen ultrasound

- **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.

Staging of liver disease
Fibroscan in HDV persons

- **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 exclude the presence of advanced fibrosis
  - >12-15 kPa for the diagnosis of advanced fibrosis
- **>14kPa specificity for liver cirrhosis of 86%.**

Staging of liver disease



* Possible *reflex* testing for HBeAg, anti-Hbe, HBV-DNA, anti HDV
§ Possible *reflex* testing with HDV-RNA if anti HDV positive; if hepatic *flare* or suspected coinfection or superinfection by HDV also perform anti HDV IgM and anti HBc IgM

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Staging of liver disease

On the basis of APRI and FIB-4, stiffness and platelet count, 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
  - **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.**

Always evaluate the presence of other causes of liver injury that cannot be inferred from non-invasive tests

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Monitoring of liver disease

Virological monitoring

- Quantification of HDV-RNA every 6-12 months or in the presence of hepatitis flares (same laboratory, same method)

At the same time:

- HBV-DNA, quantitative HBsAg, HBeAg and anti-HBe (in HBeAg positive persons)
- HCV-RNA every 6-12 months in HCV Ab positive at risk of reinfection or in the presence of hepatitis flares

Lab monitoring

- Liver enzymes, INR, reflex bilirubin, albumin, sodium and creatinine: every 6 months.
- Child-Pugh score and MELD or MELD-Na: every 6 months, in persons with possibily evolving advanced disease

Monitoring of liver disease

Liver ultrasound

- every 6 months (at risk of HCC):
  - persons with advanced or evolving chronic liver disease
  - persons born in Asia or Africa
  - persons with a family history of HCC

GI endoscopy to identify esophageal varices

- persons with significant portal hypertension:
  - absence of varices — every 2 years
  - presence of small varices — every year
  - varices with bleeding — according to guidelines

Monitoring of liver disease

Complications in chronic decompensated liver disease

- *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*. identified, classified and treated according to guidelines and with the collaboration of a specialist center
- **All persons with MELD > 12 and/or decompensated and complicated liver disease: to evaluate for liver transplantation**
- **All persons with HCC: multidisciplinary team in collaboration with a transplant center.**

Antiretroviral therapy in PLWHs with hepatitis delta

- TAF or TDF should be included in all persons
- Entecavir 0.5 mg should be added to the anti-HIV 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: co-administration of these drugs should be avoided pending *in vivo* studies.

Therapy in persons with hepatitis Delta

Pegylated interferon

- "off label" therapy with interferon alpha or pegylated:

  a combined response (enzyme normalization and undetectable HDV-RNA) ≥6 months after suspension: **in less than 25% of persons**

  recurrence rates: **50% at five years.**

- Contraindicated in persons with decompensated disease or clinically significant portal hypertension.

Pegylated interferon

Before starting

- exclude absolute contraindications (severe psychopathology, uncontrolled thyroid disease, autoimmune disease, uncontrolled depression) and evaluate any relative contraindications (depression, heart disease, minor autoimmune diseases).

During treatment

- check the thyroid function, blood counts and neuropsychiatric conditions, liver enzymes, INR, albumin and reflex bilirubin, reflex TSH and HDV-RNA levels, always at the same laboratory every 3-6 months.

Administration

- weekly subcutaneous injections at a dose of 180 mcg of pegylated interferon alfa 2a and 1.5 mcg/kg of pegylated interferon alfa 2b;
- minimum duration is 48 weeks.

Pegylated interferon

Counselling

The patient should be instructed:

- on the management of the flu-like syndrome which can last up to 48 hours after administration (asthenia, fatigability, myalgias, possible neuropsychiatric alterations, depression of mood)
- on way of administration
- on lab tests every 3 months

Therapy in persons with hepatitis Delta

Bulevirtide

- The only drug approved by the European Medicine Agency;
- The only on-label therapeutic option
- It was authorized in Italy in February 2023 in subjects with compensated chronic hepatitis delta under a reimbursement regime

Mechanism of action

- 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, the taurocholate co-transporter peptide Sodium (*Na-Taurocolate Co-Transporting Peptide NTCP*).

Bulevirtide

Way of administration

- subcutaneously at a dose of 2 mg every 24 hours with a maximum tolerance of 4 hours
- if the drug cannot be administered within 28 hours of 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.

Bulevirtide

Side effects

- It has no important side effects
- The most frequent (in less than 10%) are
  - asymptomatic elevation of bile acids due to its mechanism of action
  - injection site reactions which may include swelling, redness, irritation, bruising, itching, infection or pain
  - Others: headache, dizziness, nausea, fatigue, drowsiness, tachycardia, flu-like syndrome, abdominal bloating, itching, joint or muscle pain, excessive sweating, skin rash or other skin rashes.

Bulevirtide

Efficacy

Randomized clinical trials

- virological response (decrease in HDV-RNA levels of 2 log) at 48 weeks after the start of treatment in 71% of treated persons
- biochemical response or normalization of ALT in 51% of treated persons
- combination of virological and biochemical response in 45% of treated persons.

Bulevirtide

Efficacy

Real-life data

- cohorts of people in France and Germany confirmed the RCT
- Italian cohort of 93 subjects with advanced fibrosis and clinically significant portal hypertension
- **at 72 weeks: virological response in 75%, biochemical in 63% and a combined response in 63% with 38% of subjects with unquantifiable HDV-RNA and 81% with HDV-RNA <1000 IU/mL.**
- A complete recovery from the 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.

Bulevirtide

Drug interactions

- *In vitro* some drug can inhibit the sodium taurocholate co-transport polypeptide (NTCP), a target of bulevirtide.
- Not recommended co-administration of: sulfasalazine, irbesartan, ezetimibe, ritonavir and cyclosporine A
  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 (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

Bulevirtide

Who to treat

Priority

- Persons with compensated Delta chronic hepatitis even with possible advanced fibrosis (i.e. with stiffness at FibroScan > 10kPa or platelets < 150,000 or FIB4 > 3.25 or with clear ultrasonographic signs of cirrhosis).
- As for the others, decision must be individualized taking into account the possible cost-benefit ratio.
- Possible off-label use of pegylated interferon alpha monotherapy or even the 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 persons with limited virological response is not currently recommended. Specific studies are on going.

Bulevirtide

What to do before treating

- HIV therapy and concomitant therapies should be reevaluated to avoid drug interactions, 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, combination of sofosbuvir and velpatasvir should preferably be used.
- Prior to treatment, the person should be informed on 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.

Bulevirtide

Monitoring during treatment

- Quantification of HDV-RNA in the same laboratory every 2 months for the first 6 months then every 3 months.
- Dosage of liver enzymes, INR, albumin and reflex bilirubin.
- Quantify serum bile acid levels to assess adherence to treatment.
- Persons should be evaluated on an outpatient basis at least every 2 months.

Bulevirtide

Therapy discontinuation

- Pending the results of ongoing studies, therapy should be discontinued 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 of at least one logarithm and reduction in aminotransferase values after at least 48 weeks of therapy.
- Discontinuation of the therapy in still HBsAg positive people may result in a hepatitis flare due to 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 the treatment after three years of therapy and the post-treatment follow-up.