**VIRAL HEPATITIS B**

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| SEROLOGICAL MARKERS OF HBV SURCE: WHO: first hepatitis B treatment guidelines<http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1> | |
| Hepatitis B surface antigen (HBsAg) | HBV envelope protein and excess coat particles detectable in the blood in acute and chronic hepatitis B infection |
| Hepatitis B core antigen (HBcAg) | HBV core protein. The core protein is coated with HBsAg and therefore not found free in serum |
| Hepatitis B e antigen (HBeAg) | Viral protein found in the high replicative phase of hepatitis B. HBeAg is usually a marker of high levels of replication with wild-type virus but is not essential for viral replication |
| Hepatitis B surface antibody (anti-HBs) | Antibody to HBsAg. Develops in response to HBV vaccination and during recovery from acute hepatitis B, denoting past infection and immunity |
| Anti-HBe | Antibody to HBeAg. Detected in persons with lower levels of HBV replication but also in HBeAg-negative disease (i.e. HBV that does not express HBeAg) |
| Hepatitis B core antibody (anti-HBc) | Antibody to hepatitis B core (capsid) protein. Anti-HBc antibodies are not neutralizing antibodies and are detected in both acute and chronic infection |
| IgM anti-HBc | Subclass of anti-HBc. Detected in acute hepatitis B but can be detected by sensitive assays in active chronic HBV |
| IgG anti-HBc | Subclass of anti-HBc detected in past or current infection |
| Occult HBV infection | Persons who have cleared hepatitis B surface antigen, i.e. they are HBsAg negative but HBV DNA positive, although at very low levels (invariably <200 IU/mL); most are also anti-HBc positive |

**Acute hepatitis B**

# SURCE: WHO: first hepatitis B treatment guidelines

<http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1>

Antiviral therapy is not necessary for uncomplicated symptomatic acute hepatitis B, as >95% of immunocompeten tadults will spontaneously clear HBV infection. Persons with fulminant or severe acute hepatitis may benefit from NA therapy with **entecavir or tenofovir**, to improve survival and reduce the risk of recurrent hepatitis B. The duration of treatment is not established, but continuation of antiviral therapy for at least 3 months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss is generally advised.

Currently available treatments of chronic VHB fail to eradicate the virus in most of those treated, necessitating potentially life long treatment.

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| **WHO TO TREAT AND WHO NOT TO TREAT IN PERSONS WITH CHRONIC HEPATITIS B** SURCE: WHO: first hepatitis B treatment guidelines <http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1> | |
| **Who to treat** | * **As a priority:**   + all adults, adolescents and children with CHB and clinical evidence of:     - compensated cirrhosis or     - decompensated cirrhosis     - (or cirrhosis based on APRI score >2 in adults)     - regardless of ALT levels, HBeAg status or HBV DNA levels. * **Treatment is recommended** **for**:   + adults with CHB who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults):     - **but** are aged more than 30 years (in particular),     - **and** have persistently abnormal ALT levels     - **and have** evidence of high-level HBV replication (HBV DNA >20 000 IU/mL),     - regardless of HBeAg status. * *Where HBV DNA testing is not available*:   + **Treatment may be considered** based on:     - persistently abnormal ALT levels alone,     - regardless of HBeAg status. * In HBV/HIV-coinfected individuals:   + **ART should be initiated:**     - in all those with evidence of severe chronic liver disease,       * regardless of CD4 count;     - in all those with a CD4 count ≤500 cells/mm3,       * regardless of stage of liver disease.   In HBV-monoinfected pregnant women:   * the indications for treatment are the same as for other adults, * tenofovir is recommended. * no recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission |
| **Who not to treat but continue to monitor** | * persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults):   + **and** with persistently normal ALT levels   + **and** low levels of HBV DNA replication (HBV DNA <2000 IU/mL),   + regardless of HBeAg status   + regardless of age. |

All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours,

followed by two or three doses. WHO. Hepatitis B vaccines. Wkly Epidemiol Rec. 2009;84:405–20

**FIRST-LINE ANTIVIRAL THERAPIES FOR CHRONIC HEPATITIS B**

# SURCE: WHO: first hepatitis B treatment guidelines

<http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1>

* In all adults, adolescents and children aged 12 years or older:
  + the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (**tenofovir or entecavir**)
* In children aged 2–11 years:
  + Entecavir

**NAs with a low barrier to resistance** (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended.

* In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older:
  + tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination = the preferred option to initiate ART.
* In persons with confirmed or suspected antiviral resistance to lamivudine, entecavir, adefovir or telbivudine:
  + switch to tenofovir
* All persons **with cirrhosis** based on clinical evidence (or APRI score >2 in adults):
  + require lifelong treatment with nucleos(t)ide analogues (NAs),
  + and should not discontinue antiviral therapy because of the risk of reactivation
* Discontinuation of NA therapy may be considered exceptionally in:
  + persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults);
  + **and** who can be followed carefully long term for reactivation;
  + **and** if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg positive and after completion of at least one additional year of treatment;
  + **and** in association with persistently normal ALT levels **and** persistently undetectable HBV DNA levels *(where HBV DNA testing is available)*.
* Relapse may occur after stopping therapy with NAs.
* Retreatment is recommended if there are consistent signs of reactivation:
  + HBsAg or HBeAg becomes positive,
  + ALT levels increase,
  + HBV DNA becomes detectable again

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| **Phases of chronic hepatitis B** SURCE: WHO: first hepatitis B treatment guidelines <http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1> | | | |
| **Phase** | **HBeAg status** | **Pattern** | **Indications for treatment** |
| **1. “Immune tolerant”** | HBeAg positive | • HBeAg-positive children / young adults, particularly among those infected at birth  • High HBV DNA >200 000 IU/mL  • Persistently normal ALT  • Minimal histological disease | Treatment not generally indicated, but monitoring required |
| **2. “Immune active”**  (HBeAg-positive chronic hepatitis) | HBeAg pos; may develop anti-HBe | • Abnormal or intermittently abnormal ALT  • High or fluctuating levels of HBV replication (HBV DNA >2000 IU/mL)  • Histological necroinflammatory activity present  • HBeAg to anti-HBe seroconversion possible, leading to “immune-control” phase | Treatment may be indicated |
| **3. Inactive chronic hepatitis “Immune control”**  (previously called inactive carrier) | HBeAg negative, anti-HBe positive | • Persistently normal ALT  • Low or undetectable HBV DNA ( HBV DNA levels <2000 IU/mL)  • Risk of cirrhosis and HCC reduced  • May develop HBeAg-negative disease | Treatment not generally indicated, but monitoring required for reactivation and HCC |
| **4. “Immune escape”**  (HBeAg-negative chronic hepatitis) | HBeAg negative, with or without being anti-HBe positive | • HBeAg negative and anti-HBe positive  • Abnormal ALT (persistent or intermittently)  • Moderate to high levels of HBV replication (HBV DNA levels >20 000 IU/mL)  • Older persons especially at risk for progressive disease (fibrosis/cirrhosis) | Treatment may be indicated |
| **5.“Reactivation” or “acute-on-chronic hepatitis”** | HBeAg pos or negative | • occur spontaneously or precipitated by immunosuppression, development of antiviral resistance, or withdrawal of antiviral therapy  • Abnormal ALT  • Moderate to high levels of HBV replication  • Seroreversion to HBeAg positivity can occur if HBeAg negative  • High risk of decompensation in presence of cirrhosis | Treatment indicated |

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| **Antiviral agent** | **Potency against HBV** | **Resistance barrier** | **Activity against HIV** | **Cost** |
| Interferons | Moderate | Not applicable | Moderate | High |
| Tenofovir | High | High | High | Low (high in Hong Kong, other Asian countries) |
| Entecavir | High | High | Weak | High |
| Emtricitabine | Moderate | Low | High | Low |
| Telbivudine | High | Low | Unclear | High |
| Lamivudine | Moderate–high | Low | High | Low |
| Adefovir | Low | Moderate | None (at 10 mg dose) | High |
| SURCE: WHO: first hepatitis B treatment guidelines <http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1> | | | | |

**HBV/HDV coinfection**

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<http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1>

The routes of HDV transmission are the same as for HBV but vertical transmission is rare.

High-prevalence areas include:

* the Mediterranean, Middle East (the Gulf States, Saudi Arabia and Turkey), Pakistan, Central and northern Asia, Japan, Taiwan, Greenland and parts of Africa (mainly horn of Africa and West Africa), the Amazon Basin and certain areas of the Pacific.

The prevalence is low in:

* North America and northern Europe, South Africa and eastern Asia.
* Severe or fulminant hepatitis is more frequently observed in HBV/HDV coinfection compared to HBV monoinfection.

Two major types of HDV infection occur:

1. acute coinfection (persons are infected simultaneously with both HBV and HDV, which can lead to a mild-to-severe or even fulminant hepatitis, but recovery is usually complete and development of chronic delta hepatitis is rare (around 2%).
2. In contrast, super infection with HDV (in a person already chronically infected with HBV), accelerates the course of chronic disease in all age groups, which develops in 70–90% of persons with HDV super infection.

There are limited data to inform definitive guidance on the management of persons with HDV infection. Persistent HDV replication is the most important predictor of mortality and the need for antiviral therapy.

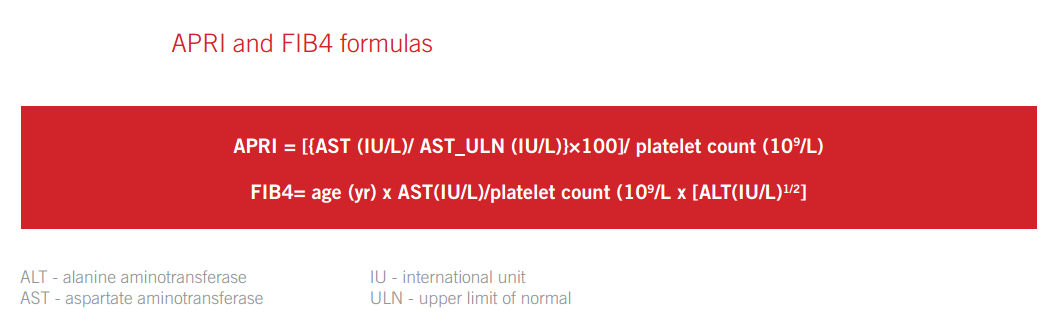
**PEG-IFN** is the only drug effective against HDV;

Antiviral NAs have no or limited effect on HDV replication.

The optimal duration of therapy is not well defined, nor how long patients need to be HDV RNA negative after the end of therapy to achieve a sustained virological response, but more than 1 year of therapy may be necessary.

The overall rate of sustained virological response remain slow, including in children, and most patients relapse after discontinuation of therapy.

**NON-INVASIVE ASSESSMENT OF LIVER DISEASE STAGE**



Cirrhosis = APRI score >2 in adults

**Useful @ sources:**

**IDSA**: <http://www.hepatitisc.uw.edu/page/treatment/drugs>

**EASL**:<http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/recommendations-on-treatment-of-hepatitis-c-2015/report/4>

**European Association for the Study of the Liver**: <http://www.hepmag.com/articles/2512_13704.shtml>

**WHO:** <http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1>

http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/management-of-chronic-hepatitis-b-virus-infection/report/1

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