WORLD HEALTH ORGANIZATION
EUROPE

7 Management of Hepatitis B and HIV Coinfection

Clinical Protocol for the WHO European Region

Contents

I. Epidemiology and natural course of HBV infection

1. Prevalence of chronic hepatitis B

Approximately 400 million people worldwide are chronically infected with the hepatitis B virus (HBV), and approximately 1 million die annually of HBV-related disease. The worldwide prevalence of hepatitis B virus ranges from 0.1% to 20% *(1)*. This wide range is largely due to differences in age at the time of infection. Following acute HBV infection, the risk of developing chronic infection varies inversely with age: 90% for perinatal infection, 25–50% for infection at age 1–5 years and 1–5% for all others *(2)*.

About 45% of the world population live in areas where chronic HBV is highly endemic (≥8% of the population have the hepatitis B surface antigen (HBsAg), 43% live in intermediate-endemicity areas (2–7% HBsAg-positive) and 12% live in low-endemicity areas (0.6% to <2% HBsAg-positive). Intermediately endemic areas include eastern and southern Europe and the Russian Federation, while northern and western Europe have low endemicity (see Table 1).

Table 1. Prevalence of hepatitis *(2)*

Areas of endemicity	Prevalence of HBV carriers	Predominant modes of transmission
Central Asian republics, parts of eastern Europe	High (≥8%)	Perinatal Childhood (horizontal)
Western and northern Europe	Low (<2%)	Sexual contact Injecting drug use
Other countries	Intermediate (2–7%)	Early childhood (horizontal)

2. Modes of transmission and risk factors

HBV is detected in blood and body fluids (semen, saliva, nasopharyngeal fluids), and it can be transmitted either sexually or by exposure to infected blood or fluids. There are four major modes of transmission:

- sexual contact
- mother-to-child transmission at birth
- parenteral (blood-to-blood)
- through other infected bodily fluids.

The world's predominant mode of HBV transmission is perinatal. If a pregnant woman is an HBV carrier and is also hepatitis B e antigen (HBeAg)-positive, her newborn baby has a 90% likelihood of being infected and becoming an HBV carrier. Of these children, 25% will die later from chronic liver disease or liver cancer *(2)*. Other risk factors favouring HBV transmission include:

- receiving blood and/or blood products
- drug-injecting, tattoos and other skin-piercing activities
- unprotected penetrative sex, in particular anal and vaginal sex
- organ transplants
- health care occupational risks
- haemodialysis.

In low-endemicity areas, the highest incidence of HBV infection is among teenagers and young adults. The most common modes of transmission among these two groups are sexual transmission and blood-to-blood transmission due to injecting practices *(2)*.

3. Genotypes

HBV is classified in seven major genotypes, A–G. Genotypes A and D are the most common types in Europe. The seroconversion rates of hepatitis B e antigen (HBeAg) and the rates of morbidity and mortality related to liver disease are similar in patients with genotypes A and D. However, sustained biochemical and virological remission are more common in patients with genotype A who have had HBeAg seroconversion than in the corresponding genotype D patients *(3)*. No correlation between HBV genotypes and response to lamivudine or adefovir treatment has been demonstrated, as it has been with interferon.

4. Epidemiology of HBV infection in HIV-infected patients

HBV and HIV have common routes of transmission and endemic areas, but HBV is about 100 times more infectious. Consequently, more than 70% of HIV-infected people have a blood marker of past or present HBV infection *(2, 4)*. Men who have sex with men (MSM) show higher rates of HBV/HIV coinfection than injecting drug users (IDUs) or heterosexuals *(5)*. The risk of chronic hepatitis B is greater in cases of HBV/HIV coinfection and congenital or acquired immunosuppression as a result of lymphoproliferative disease, immunosuppressant drugs or maintenance haemodialysis. HBV-related liver diseases (including cirrhosis and its complications) is more progressive in cases of HIV coinfection than in monoinfection *(6)*.

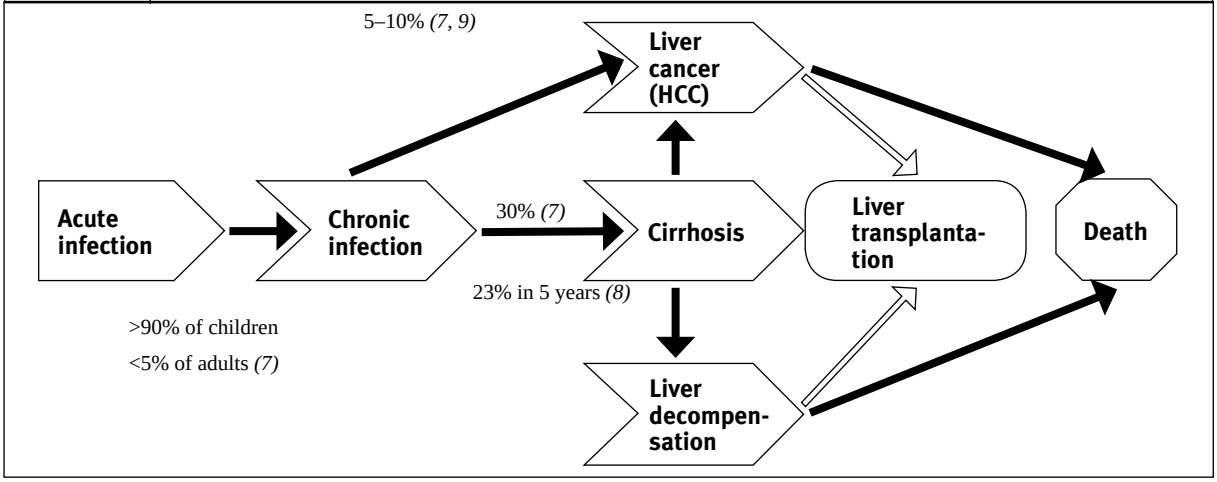
5. Natural course of HBV infection

After an acute HBV infection acquired in adulthood, 90–95% of adults develop a broad, multispecific cellular immune response that eliminates the virus and ultimately leads to the development of protective antibodies for hepatitis B surface antigen (HBsAg). Less than 1% of those who have had an acute infection develop a fulminant hepatitis, and the remaining 5–10% become chronically infected *(2)*.

5.1. Complications of chronic hepatitis B

After an average of 30 years, 30% of patients with chronic active hepatitis B will progress to cirrhosis. Liver failure decompensation occurs in about one quarter of cirrhotic patients with hepatitis B over a five-year period; another 5–10% will go on to develop liver cancer (see Fig. 1). Without treatment, approximately 15% of patients with cirrhosis will die within 5 years.

Fig. 1 . Natural course of chronic HBV infection



HCC: hepatocellular carcinoma.

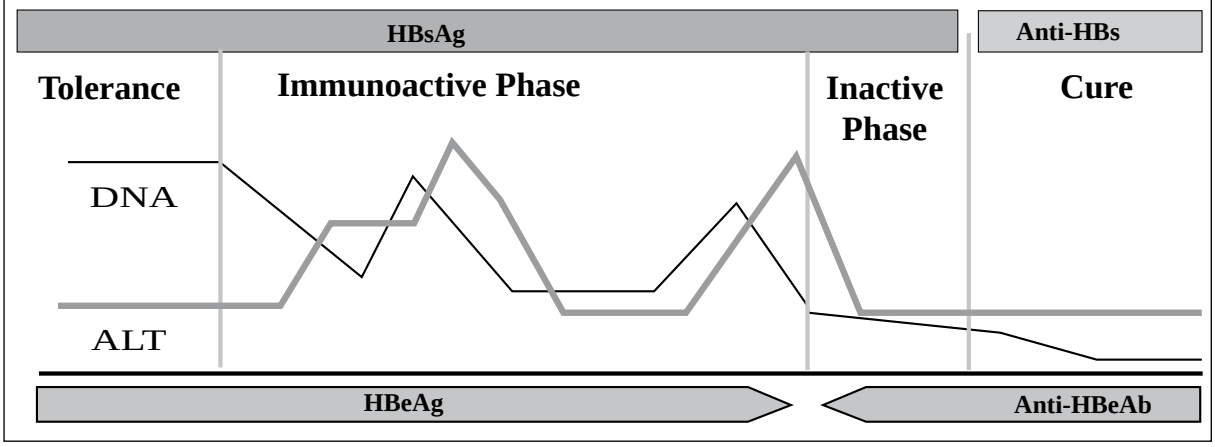
A number of patients with chronic hepatitis B will develop hepatocellular carcinoma (HCC). Those at increased risk for developing HCC include adult males with cirrhosis who contracted hepatitis B in early childhood. Between 60% and 90% of HCC patients have underlying cirrhosis, but only 5% with cirrhosis will develop HCC. Up to 80% of liver cancers in the world are due to HBV. The median survival frequency of HCC patients is <3 months without appropriate treatment, which includes surgery, percutaneous treatments, hepatic irradiation and chemotherapy *(2)*.

5.2. Evolutionary phases of chronic hepatitis B

Chronic hepatitis B generally develops over many years, during which time patients pass through a number of phases, as illustrated in Fig. 2 below *(2)*.

- The immunotolerant phase occurs in younger individuals who are HBeAg-positive, have a high HBV deoxyribonucleic acid (DNA) levels (2×10^4–2×10^8 IU/ml), and persistently normal alanine aminotransferase (ALT) levels.
- The immunoactive phase with HBeAg-positive or HBeAg-negative chronic hepatitis B, mild HBV DNA levels (2×10^3–2×10^7 IU/ml) and persistently elevated ALT levels; the patient is at times symptomatic.
- The non-replicative phase, corresponding to inactive HBsAg carriers. During HBeAg seroconversion, be it spontaneous or under pressure from treatment, there is an inactive HBsAg carrier state in which HBeAg is negative. During this period, HBV DNA is typically $<2 \times 10^3$ IU/ml (often undetectable), with a normal or mildly elevated ALT level. A small number of long-established chronic carriers apparently terminate their active infection and become HBsAg-negative (up to 1% per year) *(7)*.

Fig. 2. Evolutionary phases of chronic hepatitis B infection *(2)*



ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; HBeAb: hepatitis B e antibody; HBeAg: hepatitis B e antigen; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen.

HBV infection in adults generally consists of:

- an early replicative phase with active liver disease (HBeAg-positive chronic hepatitis B)
- a late low- or non-replicative phase with HBeAg seroconversion
- remission or inactivation of liver disease.

Seroconversion from HBeAg to hepatitis B e antibody (HBeAb), either spontaneously or with treatment, is typically accompanied by:

- a decline in HBV DNA levels (<19 IU/ml or <105 copies/ml)
- normalization of liver enzymes
- resolution of necroinflammatory activity on liver histology.

The rate of spontaneous resolution of active replication and seroconversion from HBeAg to HBeAb is 5–20% per year. During this process, some individuals develop an escape variant, a consequence of emerging mutations in the precore region that disrupts HBeAg production. These precore and core mutant viruses develop under selective immune pressure and are able to retain high levels of HBV replication *(8)*. Patients thus affected – HBeAg-negative chronic hepatitis B patients – are clinically identified by the absence of HBeAg and the presence of HBeAb and high HBV DNA levels. This particular pattern is most commonly seen in eastern Asia and southern Europe because of the higher prevalence of non-A genotypes there, which predisposes the population to this mutation.

6. Reciprocal impact of HIV and HBV

6.1. Impact of HIV infection on HBV disease progression

- HBV infection is more frequent and more severe in the HIV-infected *(6, 9)*.
- In HBV/HIV-coinfected patients, necroinflammatory activity in the liver tends to be milder, but higher HBV replication results in more severe liver fibrosis with increased risk (4.2 times greater) for cirrhosis with a more rapid progression to end-stage liver disease.
- In HBV/HIV-coinfected patients with cirrhosis, hepatocellular carcinoma (HCC) may appear more aggressive and at an earlier age than in those not HIV-infected. In addition, it presents with multifocal lesions more frequently *(10)*.
- HIV appears to be a risk factor for reactivation of hepatitis B in patients who have developed hepatitis B surface antibodies (HBsAb, which 60–70% of HIV-infected individuals have), especially in patients with severe immunodeficiency *(11)*.
- Patients coinfected with HIV 1 and HBV, especially those with low CD4+ nadir counts, are at increased risk for liver-related mortality.

6.2. Impact of HBV infection on HIV disease progression

- The majority of the clinical studies that have examined the influence of HBV on HIV disease progression and consider HBsAg a marker of chronic HBV infection have not been able to prove that HBV has any role in HIV disease progression *(6)*.
- There is, however, an increased risk for liver disease-related morbidity and mortality in hepatitis-coinfected HIV patients, as well as more hepatotoxicity under antiretroviral treatment regimens or when active treatment from both HIV and HBV is interrupted.

II. Identification of HBV/HIV

1. Assessment of HBV risk and diagnosis of hepatitis B in HIV-infected patients

1.1. Initial laboratory assessment of HBV status

All HIV-infected patients should be:

- tested for HBsAg (the presence of HBsAg for a minimum of 6 months indicates chronic hepatitis B);
- tested for hepatitis B core antibodies (HBcAb); and
- assessed for previous HBV vaccination (HBsAb).

HBcAb alone without HBsAg could be due to occult hepatitis. In this rare situation, HBV DNA is recommended (see below).

1.2. Evaluation of HBV disease severity

Further evaluation is essential for making a decision regarding treatment, focusing on in-depth laboratory diagnosis and clinical evaluation.

1.2.1. Clinical evaluation for signs and symptoms of advanced liver disease

Examination for signs and symptoms of liver disease is required. The presence or absence of clinical evidence for cirrhosis might be the key issue in defining treatment strategy in HBV/HIV-coinfected patients. The clinical signs of cirrhosis are:

- enlargement and dysmorphy of the liver;
- portal hypertension (hepatic encephalopathy, digestive haemorrhage due to oesophageal varices and splenomegaly);
- vascular spiders, palmar erythema and digital hippocratism (mostly in alcoholic liver cirrhosis rather than viral liver cirrhosis); and
- jaundice, ascites, oedema and a tendency to bleed.

The Child-Pugh classification is a simple, convenient prognostic measure in patients with liver cirrhosis (see Table 2). It may be used to predict patient survival rates and is interpreted thus:

- Class A (5–6 points) → compensated cirrhosis
- Class B (7–9 points) → compensated cirrhosis
- Class C (10–15 points) → decompensated cirrhosis.

Table 2. Child-Pugh classification

Clinical and biochemical parameters	POINTS		
	1	2	3
Bilirubin	<2 mg/dl (<34 µmol/l)	2–3 mg/dl (34–50 µmol/l)	>3 mg/dl (>50 µmol/l)
Albumin	>3.5 g/dl	2.8–3.5 g/dl	<2.8 g/dl
Ascites	Absent	Moderate[a]	Severe/ refractory[b]
Encephalopathy	Absent	Moderate (stage I–II)	Severe (stage III–IV)
Prothrombin time[c]	>60%	40–60%	<40%

[a] Controlled medically.
[b] poorly controlled.
[c] now replaced in some European countries by international normalized ratio (INR) with the following Child-Pugh values: INR <1.70 = 1 point; 1.71–2.20 = 2 points; >2.20 = 3 points.
Source: Pugh RNH et al. *(12).*

1.2.2. ALT level

- Serial measurements are preferred, as ALT may fluctuate significantly.
- Elevated ALT is a marker of liver inflammation.
- An ALT level three times the upper normal limit is correlated with a cirrhosis risk.
- Normal ALT levels can also be associated with liver disease progression, particularly in HBeAg-negative patients.
- Liver enzymes should be monitored on a regular basis, every six months for normal ALT levels. If liver enzymes become abnormal for a period of at least three months, HBV treatment is required.

1.2.3. Determination of HBeAg

- HBeAg-positive patients almost invariably have high HBV DNA levels independent of their ALT levels.
- HbeAg-negative patients may also have progressive liver disease.
- However, in both situations detection and measurement of HBV DNA should be performed, as combining serological test results with DNA levels can determine treatment strategy. In limited-access settings, HBV DNA determination should be privileged.

1.2.4. HBV DNA level

- Results should be expressed in international units (IU) per millilitre (1.0 IU = 5.4–5.8 copies/ml, depending on assay), the WHO standardized quantification unit for HBV DNA, and in decimal logarithm (log_{10}) IU/ml for precise assessment of baseline and significant HBV DNA changes upon treatment.
- If HBV DNA is initially found to be <2000 IU/ml, especially in patients with elevated ALT or other signs of liver disease, serial measurements should be undertaken at least semiannually, since such patients may exhibit wide fluctuations in HBV DNA.
- Different tests produce different absolute results; consequently, the thresholds given for therapeutic goals can only be indicative.
- A single type of HBV DNA assay should be used for monitoring a patient. If a change of assay is planned, both tests should be used in parallel for at least two subsequent samples.
- If only HBcAb is present at the initial assessment, it may be indicative of occult HBV infection (see Table 3). Occult HBV is usually assumed when HBV DNA is detected at low levels by highly sensitive techniques and in the absence of HBsAg. Occult HBV is found more frequently in HIV-positive patients than in HIV-negative patients, but its clinical relevance is uncertain. Currently, there is no evidence for the need to routinely detect or treat occult HBV.

Table 3. Classification of chronic hepatitis B virus infections based on laboratory determinants *(13)*

	HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBV DNA
Chronic active hepatitis B						
HBeAg-positive patients	+	–	+	+	–	+
HBeAg-negative patients[a]	+	–	+	–	+	+
Occult HBV infection	–	–	+	–	+	+[b]
Inactive HBV carrier state	+	–	+	–	+	–

[a] Precore mutant HBV strain;
[b] only detected by polymerase chain reaction (PCR) methods.

- Patients with HBeAg-negative chronic HBV are distinguished from inactive HBV carriers by the presence of $>10^4$ HBV DNA copies/ml (or >2000 IU/ml), elevated ALT and necroinflammatory liver disease. The literature suggests that HBeAg-negative chronic hepatitis B entails a particularly high risk of progressive hepatic fibrosis *(14, 15)*. In contrast, inactive HBV carriers usually have undetectable HBV DNA.

1.2.5. Ultrasound and other evaluations

Ultrasound examination of the liver (if possible Doppler ultrasound examination) can reveal:
- cirrhosis: dysmorphy of the liver
- steatosis: hyperechogenic liver
- possibly early HCC: nodular unique or rarely multiple lesions.

Where available, patients with liver cirrhosis should also have:
- serum alpha-fetoprotein (AFP) assessment to detect HCC; and
- upper gastrointestinal endoscopy for detecting the presence of oesophageal varices (with risk for gastrointestinal bleeding).

In the presence of significant oesophageal varices, prevention of bleeding by non-cardioselective beta blockers is recommended. The most frequently prescribed drug is propanolol at a dosage allowing a pulse reduction of at least 25–30% (40–160 mg daily may be necessary) *(16).*

1.2.6. Histological evaluation

There are a number of advantages of liver biopsy, including:
- wide availability;
- assessment of necrosis, inflammation and fibrosis;
- elimination of other causes of liver damage (opportunistic agents, drug toxicity, alcohol, steatosis, etc.);
- assessment of patients with consistently normal ALT levels who are HBV/HIV-coinfected and have liver cirrhosis.

Activity and fibrosis are two major histological features of chronic hepatitis included in proposed classifications. Interpretation of liver biopsies using the Metavir scoring system (see Table 4) improves consistency in the interpretation of hepatic fibrosis, with a somewhat weaker reproducibility for the hepatic inflammation grade. The fibrosis stage and inflammatory grade are correlated in two thirds of patients.

Table 4. Metavir classification: activity and fibrosis scoring *(17)*

Activity score (A)		Lobular necrosis		
		Absent (0)	**Moderate (1)**	**Severe (2)**
Parcellar necrosis	**Absent (0)**	A0	A1	A2
	Minimal (1)	A1	A1	A2
	Moderate (2)	A2	A2	A3
	Severe (3)	A3	A3	A3

A0 = no histological activity; A1 = minimal activity; A2 = moderate activity; A3 = severe activity.

Table 4a.

Fibrosis score (F)
F0: absence of portal fibrosis
F1: stellar portal fibrosis with no septa
F2: portal fibrosis with some septa
F3: many septa but no cirrhosis
F4: cirrhosis

Source: Simmonds et al. *(18).*

Noninvasive methods for measuring markers of fibrosis (such as FibroTest™) or liver stiffness (such as FibroScan™) have been shown to provide an adequate estimate of the extent of fibrosis. If these methods are available, they can substitute for performing a liver biopsy *(19-22)* (see Table 4a).

See section III below for two algorithms for HBV diagnosis in HIV-infected patients, as well as treatment options for coinfected patients.

1.2.7. Clinical situations not requiring histological evaluation

Decision to initiate HBV treatment does not require histological evaluation for every patient. In particular, HBV treatment may be considered without a liver biopsy when:

- there are clinical signs of cirrhosis;
- the CD4 count is <350 cells/mm^3 and antiretroviral treatment is indicated (see section III.3.1 below); or
- there are no clinical signs of cirrhosis and the CD4 count is >350 cells/mm^3, ALT is more than twice the normal upper limit and HBeAg is positive.

2. Evaluation of comorbidities and co-conditions

2.1. Psychiatric disorders

- Psychiatric disorders are not a contraindication for HBV treatment.
- Patients needing interferon (IFN) should be evaluated for psychiatric disorders. IFN should be avoided for patients with acute psychiatric disorders, and deferred for patients with moderate to severe depression until the condition improves.

2.2. Alcohol abuse

- Assessment of alcohol intake is an important part of evaluation (see Protocol 6, *Management of hepatitis C and HIV coinfection,* Annex 3).
- Heavy alcohol intake (≥50 g/day) contributes to fibrosis of the liver and can be identified by biopsy in patients with HBV independently of other predictors. This intake is equivalent to five or more drinks per day. One drink is defined as 330 ml (12 oz) of beer, 150 ml (5 oz) of wine, or 38 ml (1.25 oz) of hard liquor, containing approximately 10 grams of alcohol.
- There is evidence of a synergistic (more than additive) interaction between heavy alcohol consumption (≥80 ml/day) and chronic HBV or hepatitis C virus (HCV) infections *(23)*.
- Alcohol consumption increases HBV replication, accelerates fibrogenesis and liver disease progression in hepatitis B and C, as well as diminishing the response and adherence to anti-hepatitis treatment (especially if consumption is >50 g/day).
- Active alcohol intake is considered a relative contraindication for interferon-based treatment. This recommendation is based on the documented non-compliance of heavy drinkers with various medical therapies, and the fact that the side-effects of interferon treatment already make compliance extremely difficult *(24)*.
- Psychological, social and medical support should be offered to stop alcohol intake or reduce it to under 10 g/day.

2.3. Drug use

- Patients on opioid substitution therapy should not be excluded from treatment.
- Initiation of HBV treatment in active drug users should be considered on a case-by-case basis (see Protocol 5, *HIV/AIDS treatment and care for injecting drug users)*.
- Psychological and social support by a multidisciplinary team should be provided for such patients.

2.4. Other comorbidities and co-conditions

Testing for comorbidities should include a comprehensive medical history that focuses on cofactors associated with more progressive liver injury, and it should cover other viral liver diseases, tuberculosis (TB) (see Protocol 4, *Management of tuberculosis and HIV coinfection*) and pregnancy. Serological testing for hepatitis delta virus (HDV) might be suggested in chronically HBV-infected patients, especially IDUs. In case of persistent elevated ALT despite correct HBV treatment, pegylated interferon (PEG-IFN) can be added to antiretrovirals (ARVs), but efficacy and tolerability have not been assessed in HIV-coinfected cases *(25)*.

3. Assessment of HIV risk and diagnosis of HIV/AIDS in HBV patients

All patients with HBV should be offered HIV testing and counselling because the infections share routes of transmission, and because HIV accelerates HBV progression. Health care providers should explain to patients the reasons for offering the test and its importance for correct clinical management. However, a patient has a right to refuse an HIV test.

The initial assessment of HIV status should include:

- pretest counselling;
- serological tests (typically, enzyme-linked immunosorbent assay (ELISA) and/or rapid tests) for HIV antibodies, followed by a western blot confirmatory test; and
- post-test counselling irrespective of the result, including information on reducing risky behaviour.

Further clinical evaluation of HIV-infected patients is required to develop a clinical management strategy for HBV/HIV-coinfected patients. For detailed information, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

III. Clinical management of HBV/HIV patients

By the end of the laboratory and clinical evaluation, patients can be put into one of three treatment categories:
1. not requiring hepatitis B or HIV treatment
2. requiring only hepatitis B treatment
3. requiring only HIV treatment or both hepatitis B and HIV treatment.

For clinical management of patients with HBV/HIV coinfection the key issue is the treatment of HBV and HIV and a strategy for its initiation. This decision should be based on analysis of the following parameters:
- HBV DNA levels
- severity of liver disease
- CD4 count and indications for antiretroviral treatment (ART)
- contraindications.

HBV treatment should be considered for any HBV/HIV-coinfected patient with evidence of active liver disease (high ALT level, significant serum HBV DNA level, necro-inflammation lesions or fibrosis in liver biopsy), irrespective of the CD4 count.

1. Coinfected patients not requiring treatment

These patients have the following status:
- CD4 count of ≥350 cells/mm^3; and
- mild or not progressing HBV disease (HBV DNA <20 000 in HBeAg-positive patients, or HBV DNA <2000 in HBeAg-negative patients; normal ALT; no severe liver disease if a biopsy has been performed).

Since there is no immediate need for treatment, the patient's health should be carefully monitored by:
- a CD4 count every three to six months;
- clinical monitoring of HIV-related symptoms every three to six months;
- ALT measurements every six months for patients with inactive HBV infection (since liver disease may reactivate even after many years of quiescence), and AFP or ultrasound for HCC.
- HBeAg-positive patients with elevated ALT levels and compensated liver disease should be observed for three to six months for spontaneous seroconversion from HBeAg to HBeAb prior to initiation of treatment.

2. Coinfected patients requiring only hepatitis B treatment

HBV/HIV-coinfected patients needing only hepatitis treatment have the following features:
- CD4 count of >350 cells/mm^3;
- HbeAg-positive and HBV DNA >20 000 IU/ml, or HbeAg-negative and HBV DNA >2000 IU/ml;
- clinical cirrhosis and detectable HBV DNA (>200 IU/ml); and
- histologically proven active disease (Metavir score ≥A2 or F2), or persistently elevated ALT levels in the absence of other causes of ALT elevation.

2.1. Anti-HBV drugs for treatment of hepatitis B in HIV-coinfected patients not requiring ART (doses and schedules)

Since no large-scale randomized controlled trials have been conducted to determine the efficacy of anti-HBV drugs in HBV/HIV-coinfected patients, recommendations for treatment and monitoring

need to be derived from what data are available plus what is already known about the treatment of HBV mono-infected patients.

Three antiviral drugs are recommended for use, PEG-IFN-α 2a, standard IFN-α 2a or 2b, and adefovir (ADF).

2.1.1. IFN and PEG-IFN

The highest effectiveness of interferon has been demonstrated in patients with HBeAg, ALT levels more than twice the upper limit of normal and low HBV DNA levels. PEG-IFN is becoming a standard treatment for HBV, and it is the preferred option in patients with these features and a CD4 count of >500/mm^3.

Dosage and administration of PEG-IFN-α 2a (26) are:
- 180 µg/week for 48 weeks, independent of HBeAg/HBeAb status.

Dosage of INF-α 2a or 2b (26) is:
- for HBeAg-positive cases, 10 million units (MU) subcutaneous 3 times weekly, or 5 MU daily for 4–6 months; and
- for HbeAg-negative cases, same dosage for 12 months.

2.1.1.1 Contraindications

Absolute contraindications are:
- pregnancy and breastfeeding;
- decompensated liver disease (due to an increased risk for thrombopenia, death from liver failure or sepsis);
- uncontrolled psychiatric disease;
- significant leukopenia or thrombocytopenia;
- unstable coronary artery disease, diabetes or hypertension; or
- uncontrolled seizure disorder.

Relative contraindications are:
- autoimmune diseases (e.g. psoriasis and rheumatoid arthritis)
- prior history of depression or psychiatric illness.

2.1.2. Adefovir (ADF)

With ADF, a nucleotide analogue, a progressive and efficient suppression of HBV DNA is observed. The rate of HBV-resistant strains is very low in the short term (3% after 2 years) but has recently been shown to be as high as 28% after five years of monotreatment *(27)*.

ADF dosage is 10 mg orally once daily *(28)*.
- The optimal duration of treatment is indefinite in the absence of other treatment.
- It is recommended to continue treatment with ADF for at least 12 months.
- ADF dosage should be adapted to creatinine clearance (CrCl):
  - if CrCl is 20–49 ml/min, 10 mg every 48 hours
  - if CrCl is 10–19 ml/min, 10 mg every 72 hours
  - if the patient is on haemodialysis, 10 mg every 7 days following dialysis.

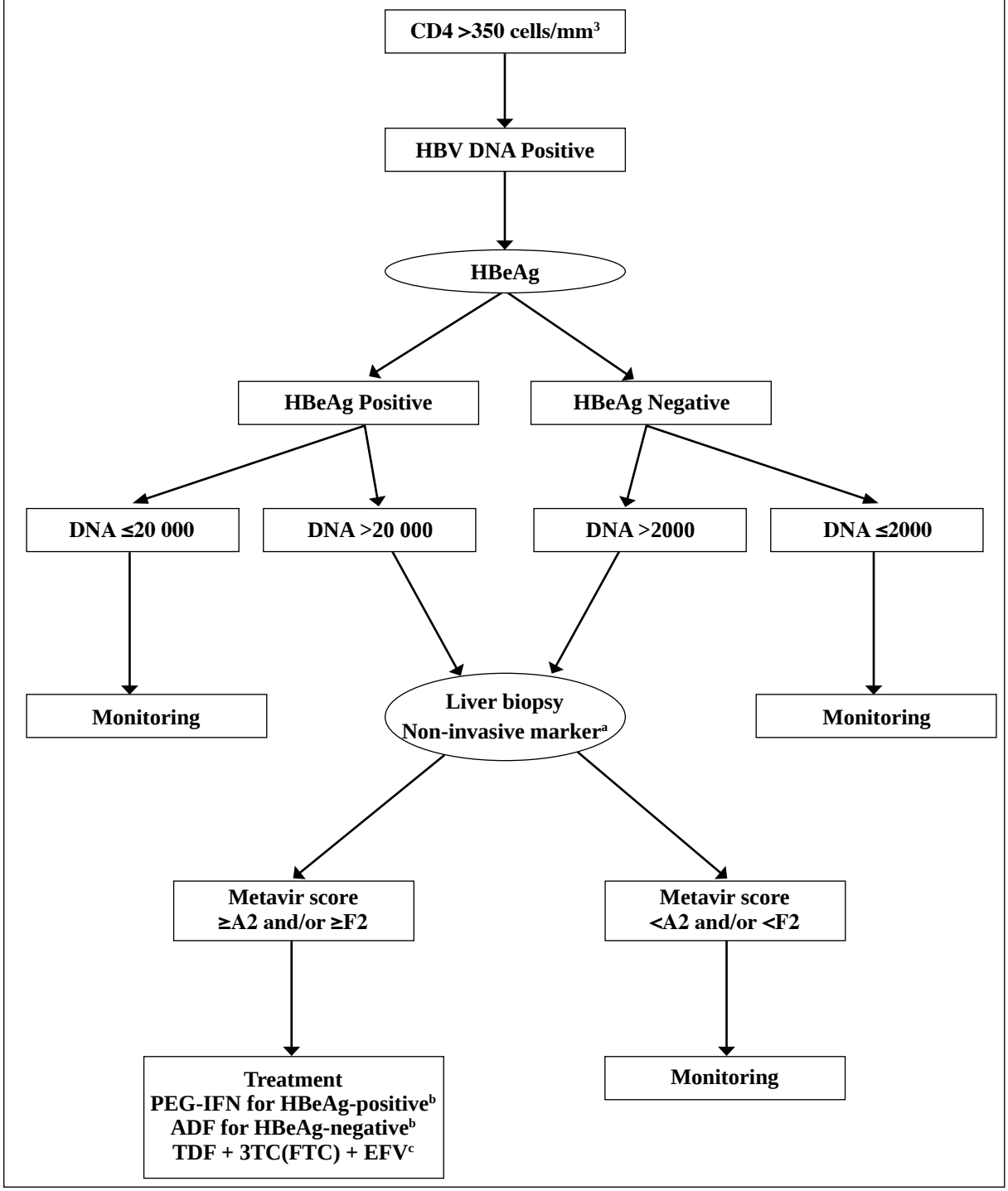
Contraindications are pregnancy and nephrotoxicity.

2.2. Evaluation and treatment algorithms for chronic hepatitis B in HIV-infected patients not requiring ART

2.2.1. Algorithm 1

The approach in this algorithm focuses on a determination of HBV DNA (in the absence of clinical cirrhosis). See Fig. 3.

Fig. 3. Algorithm 1

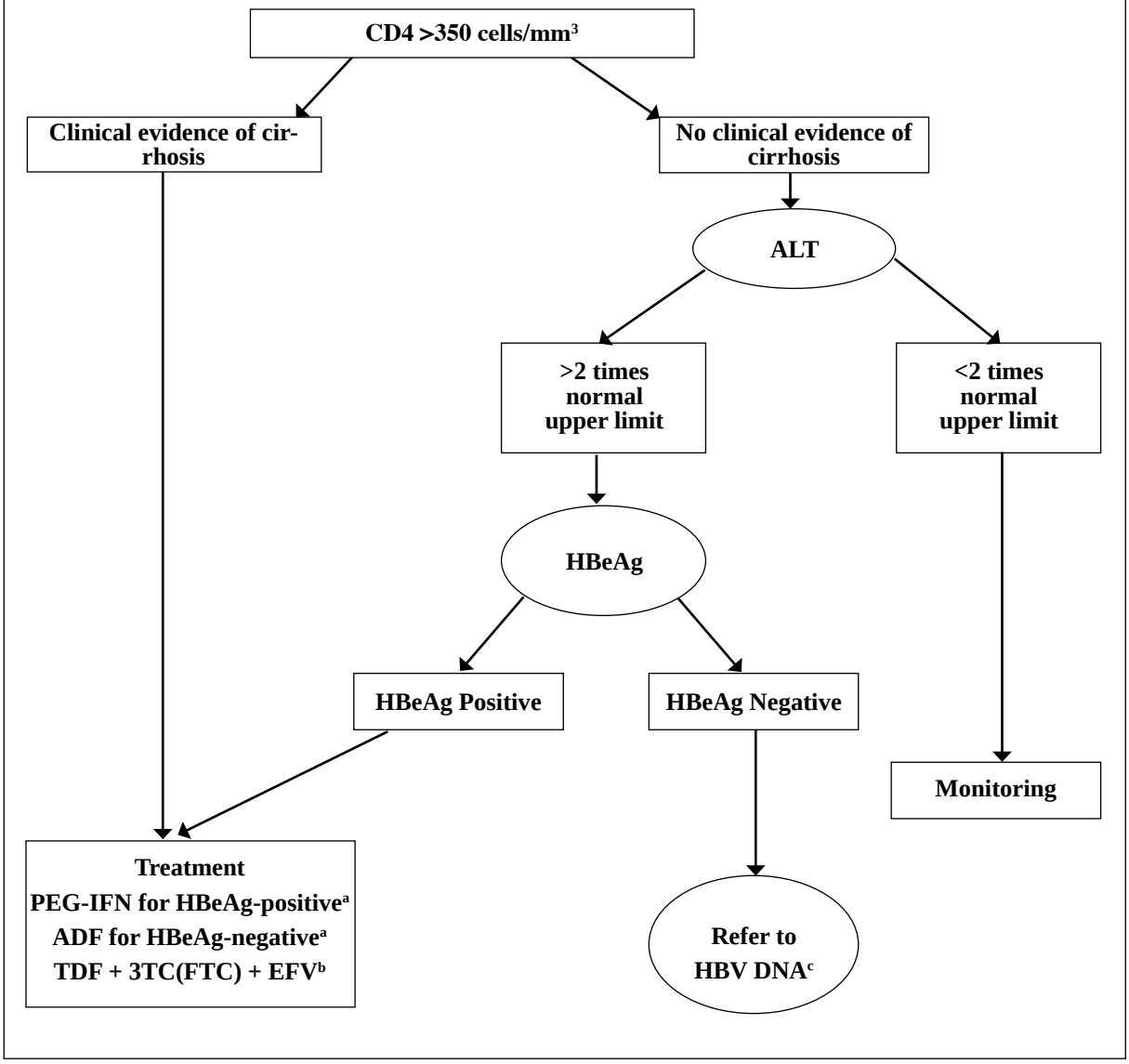


[a] Non-invasive markers: FibroTest -serum markers, FibroScan- image technique.
[b] Either PEG-IFN or ADF is the choice for HBV/HIV-coinfected patients who do not need ART. ART can be considered for patients with CD4 counts of 350–500 cells/mm3 if PEG-IFN, IFN or ADF are not available.
[c] Premature use of ART can expose patients to ART side-effects and a risk of developing HIV resistance to tenofovir (TDF) or lamivudine (3TC), which can compromise future ART.

2.2.2. Algorithm 2

The second algorithm's approach is focused on clinical evaluation, in particular for settings where HBV DNA is not available. This approach allows identifying those HBV/HIV-coinfected patients in need of hepatitis B treatment for whom a decision regarding treatment can be made without determining the HBV DNA level (i.e. patients with clinical cirrhosis, and patients with no clinical signs of cirrhosis, but with elevated ALT levels and positive HBeAg). However, patients with suspected chronic hepatitis B (HBeAg-negative with ALT more than twice the upper limit of normal) should be referred to a higher level of medical care for evaluation of HBV DNA and the appropriate course of treatment.

FIG. 4. ALGORITHM 2



[a] PEG-IFN or ADF is the best choice for HBV/HIV-coinfected patients who do not need ART. ART can be considered for patients with CD4 counts of 350–500 cells/mm^3 if IFN or ADF are not available.
[b] Premature use of ART can expose patients to ART side-effects and a risk of developing HIV resistance to TDF or 3TC, which can compromise future ART.
[c] In case of negative HBeAg, the further diagnostic algorithm is the same as shown in Algorithm 1.

2.2.3. Treatment options for HBV/HIV-coinfected patients with decompensated liver disease *(29)*

- Patients with decompensated liver disease require long-term, indefinite treatment, as virological relapse after discontinuation of treatment can be accompanied by a rapid clinical deterioration.
- ADF is safe in patients with decompensated liver disease, and is frequently associated with significant clinical improvement. Prolonged treatment is, however, associated with 28% drug resistance after five years in monoinfected patients. Thus, close monitoring for HBV DNA is recommended every six months in order to detect drug resistance in case of a viral load increase of more than 1 log, in which case genotyping should be performed. Interferon is contraindicated in patients with decompensated liver disease due to its very poor tolerability profile.

3. Coinfected patients requiring only HIV or both hepatitis B and HIV treatment

For these patients medication decisions are based on recognition of the dual effect of some antiretroviral drugs on HBV and HIV viruses, such as lamivudine (3TC) and tenofovir (TDF) *(30-32)*.

3.1. Considerations regarding treatment of hepatitis B

3.1.1. Symptomatic patients with a CD_4 count of 200 – 350 cells/mm^3

The decision to treat for HBV is mainly based on HBV DNA levels.

- In HBeAg-positive patients with HBV DNA >20 000 IU/ml and HBeAg-negative patients with HBV DNA >2000 IU/ml, the ART regimen must include two dual-activity drugs (anti-HBV and anti-HIV).
- In patients with low levels of HBV DNA, an ART regimen containing two dual-activity drugs is optional but highly recommended in anticipation of an early switch due to a reactivation of hepatitis.

3.1.2. Patients with CD_4 count < 200 cells/mm^3

When CD4 count is <200 cells/mm^3 and ART has been initiated there is a risk of a severe reactivation of hepatitis B during immune reconstitution, which may include a life-threatening hepatitis flare. Irrespective of indications for HBV treatment, the ART regimen for these patients must therefore include two dual-activity drugs in order to minimize the risk of HBV reactivation.

3.1.3. HIV-infected patients with clinical evidence of cirrhosis

- Clinical cirrhosis is an absolute indication for treatment.
- The HBV DNA threshold for initiation of HBV treatment is lower than in patients without cirrhosis (over 200 IU/ml, i.e. as soon as detectable).
- No medications are contraindicated for patients with compensated cirrhosis.
- Patients with decompensated cirrhosis should be referred for palliative care.
- Patients with cirrhosis require clinical observation, liver function monitoring and drug monitoring.
- It might be necessary to adjust the dose of ARV metabolized by the liver. If this is not feasible, then didanosine (ddI) and stavudine (d4T) have to be avoided and a regimen with a protease inhibitor (PI) should be closely monitored (see Protocol 6, *Management of hepatitis C and HIV coinfection* for recommendations on antiretroviral dosage adjustment in patients with end-stage liver disease (ESLD).

3.2. Considerations regarding treatment of HIV infection

3.2.1. Initiation of HAART

Initiation of ART in HBV/HIV-coinfected patients should follow the current recommendations for HIV-monoinfected patients (see Table 5). (For further details, please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*)

Table 5.	Recommendations for initiating HAART in HBV/HIV-coinfected patients
CD4 count	**Recommendations**
≤200 cells/mm^3	Antiretroviral treatment is recommended. ART regimens should contain two dual-activity drugs (targeting both HBV and HIV).
200–350 cells/mm^3	Antiretroviral treatment should be considered with a high viral load or rapid decline in CD4 count, but should be started before the CD4 count falls to less than 200 cells/mm^3. If HBV treatment is indicated, ART regimens containing two dual-activity drugs are also indicated or highly recommended.

3.2.2. First line HAART regimens

Table 6.	First-line HAART for HBV/HIV-coinfected patients	
	ARV drug classes	**HAART regimens**
Preferred first line	2 NRTIs + 1 NNRTI	TDF[a] + (3TC or FTC[b]) + EFV[c]
Alternative first line	3 NRTIs	ZDV + (3TC or FTC[b]) + TDF

[a] If TDF is not available, 3TC should be a mandatory component of the regimen.
[b] FTC is equivalent to 3TC and is available together with TDF as a fixed-dose combination *(33, 34)*.
[c] Nevirapine (NVP) can be considered instead of efavirenz (EFV) for patients without hepatic dysfunction and with close monitoring. It should be avoided in women with CD4 count >250 cells/mm^3 or in men with CD4 count >400 cells/mm^3.

3.2.3. Second line HAART regimens

Table 7.	Second-line HAART for HBV/HIV-coinfected patients	
	ARV drug classes	**HAART regimens**
Note: TDF and 3TC or FTC should be utilized for hepatitis treatment in addition to the second-line HAART.	2 NRTIs + 1 boosted PI	ABC + (ddI or d4T[a]) + (LPV/r or SQV/r or NFV)
	1 NNRTI + 1 NRTI + 1 boosted PI[b]	EFV + (ABC or d4T[a]) + (LPV/r or SQV/r or NFV)
	2 PIs (1 boosted)	LPV/r + SQV

[a] If zidovudine (ZDV) was not used in the first line, d4T can be considered an option in second-line ART.
[b] An optional regimen supported by a recent study is LPV/r + EFV *(35)*.

3.3. HIV-infected patients with 3TC-resistant HBV strains

- 3TC (lamivudine) resistance develops more rapidly in HBV/HIV-coinfected patients, and even at the higher doses (300 mg daily), it appears in almost 50% and 90% of coinfected patients after two and four years, respectively, of 3TC treatment *(36, 37)*.
- In the presence of suspected lamivudine resistance, the first step is to confirm it, if resistance testing is available *(38, 39)*. Otherwise resistance may be suspected if the HBV viral load increases more than 1 log in a compliant patient taking 3TC, and the patient should be switched to TDF *(40–42)*.
- TDF is the essential ARV for the HAART regimen in 3TC-resistant patients.

4. Monitoring and evaluation of HBV/HIV-coinfected patients

4.1. Hepatitis B treatment response

Relevant response is defined as:

- durable normalization of ALT levels;
- sustained HBV DNA suppression (at least a 1 log decrease of HBV DNA after three months of treatment and an undetectable viral load <200 IU/ml in the long term) *(43)*;
- durable HBeAb seroconversion in initially HBeAg-positive patients, very rarely observed with nucleotide–nucleoside analogues and in HIV-positive patients.

4.1.1. Monitoring of HBV DNA

See Table 8. Note in addition the following:

- In HBeAg-positive patients with HBV DNA <20 000 IU/ml and in HBeAg-negative patients with HBV DNA <2000 IU/ml, DNA levels should be monitored every six months.
- In patients on treatment (including ARVs with anti-HBV activity), an initial response is defined as at least 1 log drop in HBV DNA levels within one to three months. HBV DNA should then be measured at least every six months and if possible every three months.
- Resistance should be suspected in compliant patients if HBV DNA levels increase by 1 log or more. If possible, resistance testing should be performed.

Table 8. Monitoring during treatment

		Before treatment	Month 1	Month 2	Month 3	Every three months	Every six months
Efficacy	**ALT**	X		X	X	X	
	HBV DNA	X			X	X (if available)	X

4.1.2. Monitoring of ALT

- If the ALT level was initially normal, it should be carefully monitored after one month, then every three months over the course of treatment, and every three to six months if no treatment is indicated.
- For patients receiving PIs and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs), serum aminotransferase level follow-up is warranted every month during the first three months of starting any new ART; after this, a follow-up should be performed every three months to identify any drug-related hepatotoxicity.

4.2. Monitoring and evaluation of ART in HBV/HIV-coinfected patients

- CD4 cell count should be monitored every three to six months.
- HIV viral load (if available) should also be monitored every six months.

Please refer to the Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents* for further information.

4.3. Monitoring of adherence to treatment

- Patient counselling is important to avoid discontinuation of HBV drug regimens.
- Patients should be counselled about the side-effects and toxicity of HBV and ARV drugs and advised to consult a physician early for toxicity management.
- If patients do not understand the signs of side-effects, they may not report them to their physicians, jeopardizing adherence, limiting treatment efficacy and increasing the risk of developing resistance.

For more information on adherence monitoring and support refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

4.4. Management of hepatotoxicity

All medical staff should be aware of the risk of side-effects to allow them to make early recommendations and interventions.

Hepatotoxicity is a significant side-effect of ARV use that may increase morbidity and mortality among treated HBV/HIV-coinfected patients. The management of liver toxicity is based mainly on its clinical impact, severity and pathogenic mechanism.

4.4.1. Immune reconstitution in HBV/HIV-coinfected patients

The liver damage induced by chronic HBV is mainly immune-mediated. The immunodeficiency caused by HIV infection is responsible for attenuating the inflammatory reaction in the liver of HBV/HIV-coinfected patients. The inhibition of HIV replication with ART leads to the syndrome of immune reconstitution, with clinical hepatitis following the first weeks after initiation of ART, typically in patients with very low CD4 count and/or very high levels of HIV ribonucleic acid (RNA) before ART *(44)*. These symptoms are usually prevented by including a dual-activity drug in the ARV regimen (see above).

4.4.2. Drug-related hepatotoxicity

- Liver toxicity may also occur in patients receiving nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), especially d4T and ddI, and may lead to severe microsteatosis with lactic acidosis (in exceptional cases). The condition is potentially severe, with a high mortality rate, and in case of symptomatic lactic acidosis requires immediately switching to another ARV with a different toxicity profile.
- The rate of severe hepatotoxicity (grade 3 or 4) associated with NNRTIs is relatively low but may be significantly higher in HBV- and HCV-coinfected patients *(45, 46)*.
- The major toxicities associated with nevirapine (NVP) are hepatotoxicity and hypersensibility reactions (rash); both may be severe and life-threatening. Symptomatic NVP-associated hepatic or serious rash toxicity, although uncommon, is three to seven times more frequent in women than in men *(47)*.
- If CD4 >250/mm^3, there is about 10 times greater risk of severe symptomatic hepatotoxicity than in patients with CD4 <250/mm^3.
- The risk of hepatotoxicity and rash are highest in the first six weeks of NVP treatment; starting NVP at half doses during the first six weeks minimizes the risk.
- Elevated serum aminotransferase levels are relatively common in HIV-infected patients receiving PI-based ART (2–8.5% of PI-treated patients) *(48, 49)*.
- HBV/HIV coinfection has been associated with a high risk of developing drug-induced liver injury, and with a greater risk of severe liver injury than in patients who have concurrent liver disease from other causes.
- If no other cofactors exist, the degree of hepatotoxicity is the main determinant of the clinical approach. (see Table 9).

Table 9. Standardized hepatotoxicity scale *(50)*

Toxicity grade	ALT and AST changes relative to the upper limit of normal	Increase from baseline
1	1.25–2.5 times	1.25–2.5 times
2	2.6–5.0 times	2.6–3.5 times
3	5.1–10.0 times	3.6–5.0 times
4	>10.0 times	>5.0 times

- If hepatotoxicity is severe, switching the ART regimen to one with lower potential hepatotoxicity is recommended.
- If hepatotoxicity is mild to moderate (grades 1 and 2), it is reasonable to continue the same ART regimen with a close follow-up of liver enzymes.

4.4.3. Hepatotoxicity of TB drugs in the context of chronic HBV infection *(51, 52)*

- The rate of hepatotoxicity is significantly higher in TB patients with HCV or HBV coinfection (59%) than in those without (24%) *(52)*.
- Commonly used anti-TB drugs, such as isoniazid, rifampicin, and pyrazinamid are hepatotoxic.
- Pyrazinamide and isoniazid are the most hepatotoxic and should be avoided in TB patients with known chronic liver disease.
- It is not necessary to adapt dosage of anti-TB drugs in cases of hepatic insufficiency.
- In decompensated liver disease, a regimen without rifampicin should be used.
- Streptomycin, ethambutol and a reserve drug such as fluoroquinolone can be used if treatment is necessary in patients with fulminant liver disease. Consultation with a specialist is required.
- Alternative anti-TB drugs with lower hepatotoxicity may be used in case of liver dysfunction, for example, rifabutin, amikacin, ofloxacin and levofloxacin. The treatment of these special cases should be decided in consultation with an acknowledged expert.
- Hepatotoxicity appears in the first two months of TB treatment, thus requiring close initial monitoring of liver functions.

IV. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to treatment and its success. Such indicators assist managers in decision-making on ways to strengthen and expand these services to all those in need.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV patients ("seen for care" – this will be the denominator for the data below);
- number of HIV patients coinfected with HBV (HbsAg-positive);
- number of HIV-positive patients with active hepatitis;
- number of HIV-positive patients with active hepatitis receiving:
  - HAART with 3TC and/or TDF;
  - ART without 3TC and/or TDF;
  - exclusively on hepatitis B treatment (e.g. IFN or ADF);
- number of HIV-infected patients vaccinated against HBV; and,
- number of HBV/HIV coinfected patients who have died (in a given time period) including cause of death (e.g. liver-related deaths, HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

References

1. Custer B et al. Global epidemiology of hepatitis B virus. *Journal of Clinical Gastroenterology,* 2004, 38(10 Suppl):S158–S168.
2. *Hepatitis B.* Geneva, World Health Organization, WHO, 2002 (http://www.who.int/csr/disease/hepatitis/HepatitisB_whocdscsrlyo2002_2.pdf, accessed 29 March 2006).
3. Fung SK, Lok AS. Hepatitis B virus genotypes: do they play a role in the outcome of HBV infection? *Hepatology,* 2004, 40(4):790–792.
4. Thio C. Hepatitis B in the HIV-infected patient: epidemiology, natural history and treatment. *Seminars in Liver Disease,* 2003, 23:125–136.
5. Alter MJ. Epidemiology of viral hepatitis and HIV coinfection. *Journal of Hepatology,* 2006, 44, Suppl 1:S6–S9.
6. Konopnicki D et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS,* 2005, 19(6):593–601.
7. Niederau K et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *The New England Journal of Medicine,* 1996, 334:1422–1427.
8. Conjeevaram HS, Suk-Fong Lok A. Management of chronic hepatitis B. *Journal of Hepatology,* 2003, 38:S90–S103.
9. Thio CL et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *The Lancet,* 2002, 360(9349):1921–1926.
10. Puoti M et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS,* 2004, 18(17):2285–2293.
11. Levine OS et al. Seroepidemiology of hepatitis B virus in a population of injecting drug users; association with drug injection patterns. *American Journal of Epidemiology,* 1995, 142(3):331–341.
12. Pugh RNH et al. Preoperative assessment of patients with liver disease. *British Journal of Surgery,* 1973, 60:646–649.
13. Torbenson M, Thomas DL. Occult hepatitis B. *The Lancet Infectious Diseases,* 2002, 2(8):478–486.
14. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology,* 2001, 34(6):1225–1241.
15. Bonino F, Brunetto MR. Chronic hepatitis B e antigen (HBeAg) negative, anti-HBe positive hepatitis B: an overview. *Journal of Hepatology,* 2003, 39(Suppl. 1):S160–163.
16. Wildur K, Sidhur K. Beta blocker prophylaxis for patients with variceal haemorrhage. *Journal of Clinical Gastroenterology,* 2005, 39(5):435–440.
17. Bedossa P, Poynard T, METAVIR Comparative Group. Inte- and intra-observer variation in the assessment of liver biopsy of chronic hepatitis C. *Hepatology, 1*994, 20:15–20.
18. Simmonds et al. Epidemiological, clinical and therapeutic associations of hepatitis C types in western European patients. *Journal of Hepatology,* 1996, 24(5):517-524.
19. Myers R et al. Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B. *Journal of Hepatology,* 2003, 39:222–230.
20. Sandrin L et al. Transient elastography: a new non-invasive method for assessment of hepatic fibrosis. *Ultrasound in Medicine & Biology,* 2003, 29:1705–1713.
21. De Lédinghen V et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. *Journal of Acquired Immune Deficiency Syndrome,* 2006, 41(2).
22. Nunes D et al. HIV infection does not affect the performance of non-invasive markers of fibrosis for the diagnosis of hepatitis C virus-related liver disease. *Journal of Acquired Immune Deficiency Syndrome*, 2005, 40(5).
23. Hassan MM et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology,* 2002, 36:1206–1213.
24. Lucas GM et al. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 outcomes treatment in an urban clinic. *AIDS,* 2002, 16:767–774.
25. Ferenci P, Formann E, Romeo R. Successful treatment of chronic hepatitis D with a short course of peginterferon alfa-2a. *American Journal of Gastroenterology,* 2005, 100(7):1626–1627.
26. Cooksley W. Treatment with interferons (including pegylated interferons) in patients with chronic hepatitis B. *Seminars in Liver Disease,* 2004, 24(Suppl. 1):45–53.
27. S Hadziyannis et al. Long-term adefovir dipivoxil treatment induces regression of liver fibrosis in patients with HBeAg-negative chronic hepatitis B: results after 5 years of therapy. *American Association*

for the Study of Liver Diseases, 11–15 November, 2005, San Francisco, California. (Poster Number LB14).
28. Marcellin P et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *The New England Journal of Medicine,* 2003, 348:808–816.
29. Soriano V et al. Care of patients with chronic hepatitis B and HIV coinfection: recommendations from an HIV-HBV international panel. *AIDS,* 2005, 19(3):221–240.
30. Bani-Sadr F et al. Ninety-six week efficacy of combination therapy with lamivudine and tenofovir in patients coinfected with HIV-1 and wild type hepatitis B virus. *Clinical Infectious Diseases,* 2004, 39:1062–1064.
31. Dore G et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and experienced patients coinfected with HIV-1 and hepatitis B virus. *Journal of Infectious Diseases,* 2004, 189:1185–1192.
32. Nelson M, Portsmouth S, Stebbing J. An open-label study of tenofovir in HIV-1 and hepatitis B virus coinfected individuals. *AIDS,* 2003, 17:F7–F10.
33. Gish R et al. Dose range study of pharmacokinetics, safety and preliminary antiviral activity of emtricitabine in adults with hepatitis B virus infection. *Antimicrobial Agents and Chemotherapy,* 2002, 46:1734–1740.
34. Bang L, Scott L. Emtricitabine. *Drugs,* 2003, 63:2413–2424.
35. Allavena C et al. Efficacy and tolerability of a nucleoside reverse transcriptase inhibitor–sparing combination of lopinavir/ritonavir and efavirenz in HIV-1 infected patients. *Journal of Acquired Immune Deficiency Syndrome,* 2005, 39(3):300–306.
36. Bessesen M et al. Chronic active hepatitis B exacerbations in HIV-infected patients following development of resistance to or withdrawal of lamivudine. *Clinical Infectious Diseases,* 1999, 28:1032–1035.
37. Benhamou Y et al. Long-term incidence of hepatitis B virus resistance to lamivudine in HIV-infected patients. *Hepatology,* 1999, 30:1302–1306.
38. Liaw YF. Impact of YMDD mutations during lamivudine therapy in patients with chronic hepatitis B. *Antimicrobial Agents and Chemotherapy,* 2001, 12 Suppl 1:67–71.
39. Liaw YF. Management of YMDD mutations during lamivudine therapy in patients with chronic hepatitis B. *Journal of Gastroenterology and Hepatology,* 2002, 17 Suppl 3:S333–S337.
40. Lada O et al. In vitro susceptibility of lamivudine-resistant hepatitis B virus to adefovir and tenofovir. *Antiviral Therapy,* 2004, 9:353–363.
41. Núñez M et al. Activity of tenofovir on hepatitis B virus replication in HIV-coinfected patients failing or partially responding to lamivudine. *AIDS,* 2002, 16:2352–2354.
42. Schildgen O et al. Successful therapy of hepatitis B with tenofovir in HIV-infected patients failing previous adefovir and lamivudine treatment. *AIDS,* 2004, 18 (17):2325–2327.
43. Mommeja-Marin H et al. Serum HBV-DNA as a marker of efficacy during therapy for chronic hepatitis B infection: analysis and review of the literature. *Hepatology,* 2003, 37:1309–1319.
44. Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. *Clinical Infectious Diseases,* 2004, 39: 129–132.
45. Dieterich DT et al. Drug-induced liver injury associated with the use of non-nucleoside reverse-transcriptase inhibitors. *Clinical Infectious Diseases,* 2004, 38 Suppl 2:S80–S89.
46. Martínez E et al. Hepatotoxicity in HIV-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001, 15:1261–1268.
47. Sulkowski MS et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology,* 2002, 35(1):182–189.
48. Sulkowski MS. Hepatotoxicity associated with antiretroviral therapy containing HIV-1 protease inhibitors. *Seminars in Liver Disease,* 2003, 23(2):183–194.
49. Sulkowski MS et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA,* 2000, 283(1):74–80.
50. Pol S, Lebray P, Vallet-Pichard A. HIV infection and hepatic enzyme abnormalities: intricacies of the pathogenic mechanisms. *Clinical Infectious Diseases,* 2004, 38 Suppl 2:S65–S72.
51. Aaron L et al. Tuberculosis in HIV-infected patients: a comprehensive review. *Clinical Microbiology and Infection,* 2004, 10(5):388–398.
52. Pan L et al. Effect of anti-tuberculosis therapy on liver function of pulmonary tuberculosis patients infected with hepatitis B virus. *World Journal of Gastroenterology,* 2005, 11(16):2518–2521.