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7 Management of hepatitis B and HIV coinfection

Clinical Protocol for the WHO European Region (2011 revision)

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Abbreviations and acronyms

3TC	lamivudine
ABC	abacavir
ADF	adefovir
AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
Anti-HBc	hepatitis B core antibody
Anti-HBe	hepatitis B e antibody
Anti-HBs	hepatitis B surface antibody
ART	antiretroviral therapy
ARV	antiretroviral drug
AST	aspartate aminotransferase
ATV	atazanavir
CD4 cell	CD4+ lymphocytes
CrCl	creatinine clearance
ddI	didanosine
d4T	stavudine
DNA	deoxyribonucleic acid
DRV	darunavir
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
ESLD	end-stage liver disease
FTC	emtricitabine
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis delta virus
HIV	human immunodeficiency virus
IDU	injecting drug user
IFN	interferon
INR	international normalized ratio
IU	international unit
LPV	lopinavir
MSM	men who have sex with men
MU	million units
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside or nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PEG-IFN	pegylated interferon
PI	protease inhibitor
/r	low dose ritonavir (for boosted PI)
RNA	ribonucleic acid
SQV/r	saquinavir/ritonavir
TB	tuberculosis
TDF	tenofovir
WHO	World Health Organization
ZDV	zidovudine

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This document is an update of the version of this clinical protocol released in 2007. It is one of 13 clinical protocols released by the WHO Regional Office for Europe as a part of the HIV/AIDS Treatment and Care Clinical Protocols of the WHO European Region. This update was edited by Jens Lundgren, Lars Peters and Irina Eramova.

The updated version of the protocol is built on new evidence in the area of HBV/HIV treatment and the global WHO 2010 recommendations for a public health approach antiretroviral therapy for HIV infection in adults and adolescents. The process included consultation with Regional clinical experts through a 2010 meeting in Kyiv (Ukraine) and electronic communication with them to ensure that the updated version of the protocol corresponds to the countries needs and reflects diverse capacity to implement it.

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I. Epidemiology and natural course of HBV infection

1. Prevalence of chronic hepatitis B

Approximately 350 – 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% *(1,2)*. 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, 25–35% for infection at age 1–5 years and less than 10% for adults *(1)*.

About 45% of the world population live in areas where chronic HBV is highly endemic (≥8% of the population are hepatitis B surface antigen (HBsAg) positive), 43% live in intermediate-endemicity areas (2–7% HBsAg-positive) and 12% live in low-endemicity areas (0.6% to <2% HBsAg-positive). In the WHO European Region the HBsAg seroprevalence ranges from 0.3% to 12% with up to 3.5 million carriers. Central Asian republics and parts of eastern Europe are high endemic areas. Intermediately endemic areas include eastern and southern Europe and the Russian Federation, while northern and western Europe are low endemic areas (see Table 1).

Table 1. Prevalence of hepatitis and predominant modes of transmission in Europe

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)

Source: Custer (2)

2. Modes of transmission and risk factors

HBV is detected in blood and body fluids (semen, saliva, nasopharyngeal fluids), and there are four major modes of transmission:

- sexual contact
- mother-to-child transmission in pregnancy and at birth (perinatal)
- parenteral (blood-to-blood)
- horizontal transmission through close personal contact or sharing of infected items. This mode of transmission is seen mainly in early childhood.

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, 25% will die in adult life from chronic liver disease or liver cancer *(3)*. Although HBsAg, HBeAg and HBV DNA have been detected in breast milk no differences in HBV transmission rate according to feeding practices in early childhood have been demonstrated *(4)*. Other conditions favouring HBV transmission include:

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

In low-endemic areas, the highest incidence of HBV infection is among teenagers and young adults. The most common modes of transmission amongst these two groups are sexual transmission and parenteral transmission from unsafe injecting practices *(3)*.

3. Genotypes

HBV is classified in eight major genotypes (A to H). Genotypes A and D are the most common types in Europe. The seroconversion rates of 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 virologic remission are more common in patients with genotype A who have had HBeAg seroconversion following IFN therapy than in the corresponding genotype D patients *(1)*. No correlation between HBV genotypes and response to any of the nucleos(t)ides has been demonstrated *(5)*.

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 *(6)*. Consequently, in some settings up to two thirds of all HIV-infected people have a blood marker of past or present HBV infection *(7)*. Men who have sex with men (MSM) show higher rates of HBV/HIV coinfection than injecting drug users (IDUs) or heterosexuals *(8)*. The risk of chronic hepatitis B is greater in congenital and acquired immunosuppression including HIV infection, and due to usage of immunosuppressant drugs or chronic haemodialysis *(7,9,10)*.

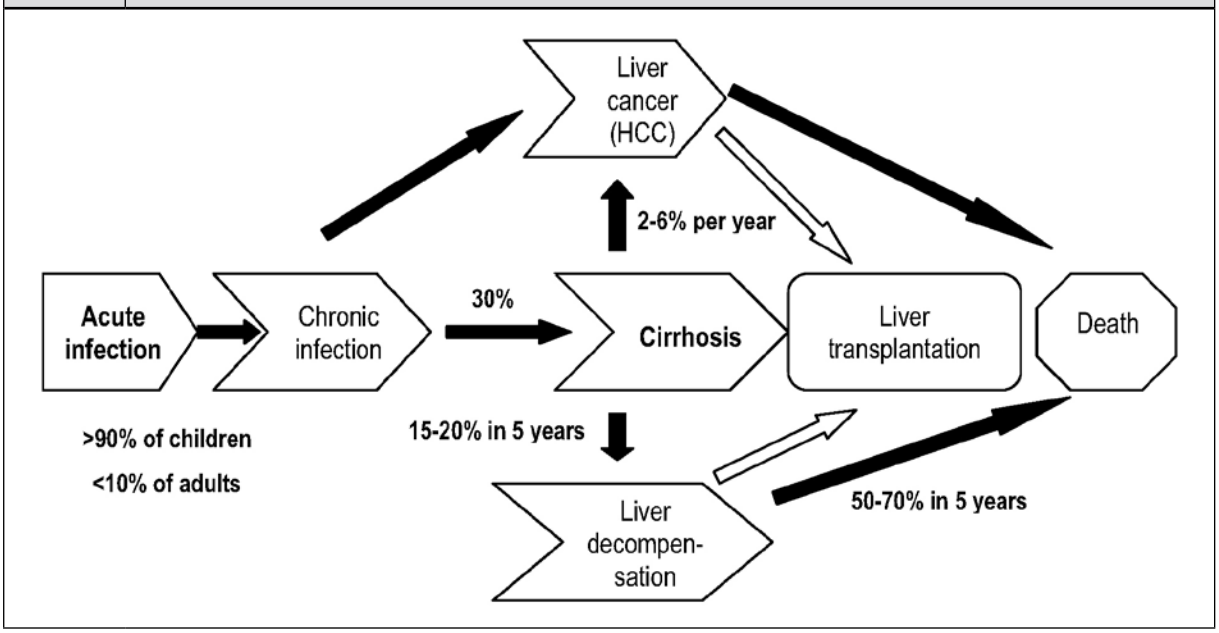
5. Natural course of HBV infection

After acute HBV infection in adulthood, more than 90% of adults develop a broad, multispecific cellular immune response that eliminates the virus and ultimately leads to the development of protective antibodies against HBsAg. Around 1% of those who have icteric acute infection develop fulminant hepatitis *(11)*.

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. Hepatic 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 *(3,11)*.

Fig. 1. Natural course of chronic HBV infection



Source: Liew et al. (3); Liang (11)

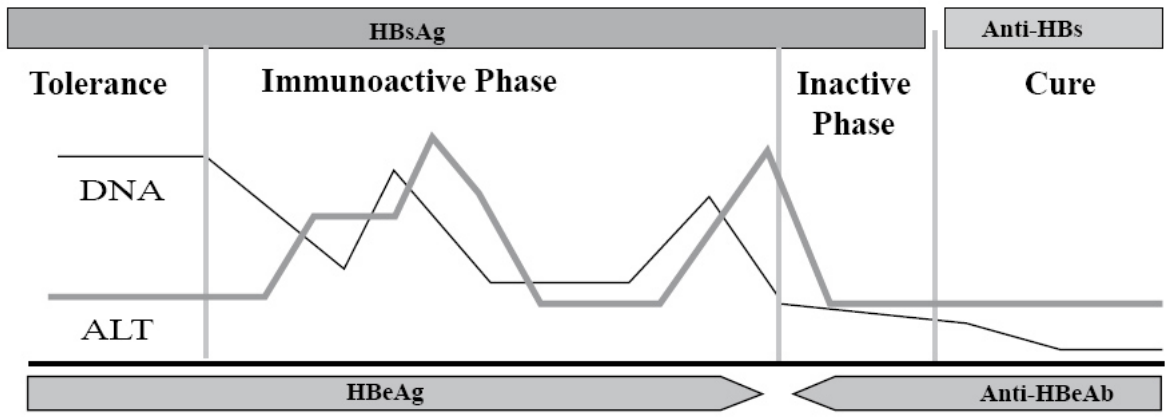
The lifetime risk for hepatocellular carcinoma (HCC) in a chronically HBV infected person is approximately 10–25%. Those at increased risk for developing HCC include adult males with cirrhosis who contracted hepatitis B in early childhood. Between 80% and 90% of HCC patients have underlying cirrhosis. More than 50% of HCC cases worldwide and 70–80% of HCC cases in highly HBV endemic regions are due to HBV. The median survival of HCC patients is <5 months without appropriate treatment, which includes surgery, percutaneous treatments, hepatic irradiation and chemotherapy *(12)*.

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 *(1)*.

- The immunotolerant phase occurs in younger individuals who are HBeAg-positive, have a high HBV DNA levels (>2 x 10^4 IU/ml), and persistently normal ALT levels.
- The immunoactive phase with HBeAg-positive or HBeAg-negative chronic hepatitis B, moderate to high HBV DNA levels (2 x 10^3–2 x 10^7 IU/ml) and persistently elevated ALT levels; the patient is at times symptomatic.
- The inactive phase, corresponding to inactive, non-replicative HBsAg carriers. Following 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 x 10^4 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 (the rate of clearance is around 0.5% per year) *(1)*.

Fig. 2. Evolutionary phases of chronic hepatitis B infection



Source: McMahon (1)

ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; Anti-HBeAb: hepatitis B e antibody; HBeAg: hepatitis B e antigen; Anti-HBs: 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; and
- remission or inactivation of liver disease.

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

- a decline in HBV DNA levels (<2000 IU or <10000 copies/mL);

- normalization of liver enzymes; and
- resolution of necroinflammatory activity on liver histology.

The rate of spontaneous resolution of active replication and seroconversion from HBeAg to anti-HBe is 4–10% 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. Patients thus affected – HBeAg-negative chronic hepatitis B patients – are clinically identified by the absence of HBeAg and the presence of anti-HBe 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 to the emergence of this mutation *(1)*.

5.3. Vaccination against HBV

- Hepatitis B vaccination is recommended in all HIV patients who are negative for HBsAg and anti-HBs.
- The response to the HBV vaccine varies by the CD4-cell count level with response rates around 25% reported in patients with CD4-cell counts below 200 cells/mm^3. Hence, in patients where HIV treatment is indicated ART should be initiated prior to HBV vaccination *(13)*.
- Anti-HBs levels >10 IU/L after three vaccinations (0,1 and 6 months) is considered protective *(14)*.
- An accelerated dosing schedule (0,1 and 3 weeks) may improve compliance without affecting the efficacy *(15)*.
- In case of an insufficient response (anti-HBs <10 IU/l) revaccination should be considered.
- Revaccination with double dose at 3-4 vaccination time points (months 0, 1, 6 and 12) may help to improve response rates to HBV vaccination *(16)*.
- Patients who fail to seroconvert after hepatitis B vaccination and remain at risk for HBV-infection should have annual tests for HBV infection.
- Patients who are anti-HBc positive and anti-HBs negative should be tested for anti-HBs response 2 – 4 weeks after a first HBV vaccination and may skip remaining vaccinations in case of sufficient anti-HBs response (anti-HBs > 10 IU/l).
- Household and sexual contacts to HBV infected persons should also be offered vaccination if they are negative for HBV seromarkers.

6. Reciprocal impact of HIV and HBV

6.1. Impact of HIV infection on HBV disease progression

- HBV infection is more frequent seen and associated with increased severity of liver disease in HIV-infected patients *(7,17)*.
- 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 and a more rapid progression to end-stage liver disease *(17)*.
- Patients coinfected with HIV and HBV, especially those with low CD4+ nadir counts, are at increased risk for liver-related mortality *(18)*.
- HIV appears to be a risk factor for reactivation of hepatitis B in patients who have developed hepatitis B surface antibodies, especially in patients with severe immunodeficiency *(19)*.

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 *(8,20)*.
- However, patients receiving antiretroviral therapy have an increased risk of hepatotoxicity when commencing anti-HIV therapy *(21)* and also increased risk of hepatic flares when active treatment for both HIV and HBV is interrupted *(22)*.

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); and
- tested for hepatitis B core antibodies (anti-HBc IgG) and anti-HBs.

Patients positive for HBsAg should be tested for quantitative HBV DNA and screened for hepatitis delta antibodies (anti-HDV).

Positive anti-HBs and negative anti-HBc indicates prior vaccination. Anti-HBc alone without HBsAg and anti-HBs could be due to occult hepatitis or a false positive anti-HBc. In this rare situation, assessment of 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 although their sensitivity and specificity are generally low. 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 and laboratory investigations suggestive of cirrhosis are:

- enlargement and dysmorphy of the liver often associated with characteristic dampening of hepatic vein signal on Doppler ultrasonography;
- signs suggestive of portal hypertension (hepatic encephalopathy, upper gastro-intestinal haemorrhage due to oesophageal varices, splenomegaly and ascites);
- vascular spiders, palmar erythema and digital clubbing (mostly in alcoholic liver cirrhosis rather than viral liver cirrhosis);
- jaundice, oedema and a tendency to bleed; and
- reversal of AST/ALT ratio, decline in platelet counts, increase in prothrombin time and a decline in serum albumin.

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[c]	Absent	Moderate (stage I–II)	Severe (stage III–IV)
Prothrombin time[d]	>60%	40–60%	<40%

Source: Pugh (23)

[a] Controlled medically.

[b] Poorly controlled.

[c] According to the West Haven criteria.

[d] 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.

Another commonly used prognostic score is the Model for End-stage Liver Disease (MELD), which predicts survival among different populations with advanced liver disease. MELD incorporates three widely available laboratory variables including the international normalized ratio (INR), serum creatinine, and serum bilirubin. The original mathematical formula for MELD is: MELD = 3.8 (ln serum bilirubin (mg/dL)) + 11.2(ln INR) + 9.57(ln serum creatinine (mg/dL)) + 6.4 *(24)*. An online MELD prognostic score tool is available at (www.mayoclinic.org/gi-rst/mayomodel5.html).

A limitation to the use of the Child-Pugh and MELD prognostic scores in HIV-infected patients is the common use of the protease inhibitor atazanavir, which causes elevation of bilirubin levels in over 30% of patients *(25)*. Indinavir is also associated with hyperbilirubinemia in up to 25% of patients *(26)*.

1.2.2. Serum alanine aminotransferase (ALT) level

- A normal ALT is <19 IU/L for women and <31 IU/L for men.
- Serial measurements are preferred, as ALT may fluctuate significantly.
- Elevated ALT is a marker of liver inflammation or other hepatocyte damage.
- Normal ALT levels can also be associated with liver disease progression, particularly in HBeAg-negative and HIV coinfected patients.
- Liver enzymes should be monitored on a regular basis, every three to six months for normal ALT levels. If liver enzymes become abnormal for a period of at least three months, HBV treatment should be considered.

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.
- In limited-access settings, HBV DNA determination should be prioritized.

1.2.4. HBV DNA level

- Results should be expressed in international units (IU) per millilitre (1.0 IU/ml = 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 <2 000 IU/ml, especially in patients with elevated ALT or other signs of liver disease, serial measurements should be undertaken at least bi-annually, 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 anti-HBc 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 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 *(27)*.
- Patients with HBeAg-negative chronic HBV are distinguished from inactive HBV carriers by the presence of >2000 IU/ml (or $>10^4$ HBV DNA copies/ml), elevated ALT and necroinflammatory liver disease. In contrast, inactive HBV carriers usually have low or undetectable HBV DNA.

Table 3. Classification of chronic hepatitis B virus infections based on laboratory determinants

	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	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.

1.2.5. Ultrasound and other evaluations

Ultrasound examination of the liver (if possible Doppler ultrasound examination) can reveal:
- cirrhosis: dysmorphy of the liver and associated dampening of hepatic vein Doppler signal;
- steatosis: hyperechogenic liver; and
- possibly early HCC: nodular single or rarely multiple lesions.

Where available, patients with liver cirrhosis should also have:
- serum alpha-fetoprotein (AFP) assessment and hepatic ultrasound at 6-monthly intervals for early detection of HCC; and
- upper gastrointestinal endoscopy for detecting the presence of oesophageal varices (with risk for gastrointestinal bleeding) at the time of diagnosis and at 1-2 year intervals thereafter.

In the presence of significant oesophageal varices, prevention of bleeding by non-cardioselective beta-blockers is recommended. The most frequently prescribed drug is propranolol at a dosage allowing an exercise induced heart rate reduction of at least 25–30% (40–160 mg daily may be necessary) *(28)*.
Although cirrhosis is a strong risk factor for HCC, HBV-related HCC in HBV may occur in the absence of cirrhosis. Hence, regular screening for HCC should also be considered for HBV patients with a high risk of HCC (a family history of HCC or HBV acquired at birth or during early childhood).

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, non-alcoholic steatosis, etc.); and
- assessment of patients with persistently normal ALT levels who are HBV/HIV-coinfected and may have advanced liver fibrosis.

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 4a and 4b) 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 (a, b). Metavir classification: activity and fibrosis scoring

Table 4a

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

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

Table 4b

Fibrosis score (F)
F0: no fibrosis
F1: portal fibrous expansion
F2: peri-portal fibrosis with few septae
F3: numerous septae and portal-portal bridging
F4: cirrhosis

Source: Goodman (29)

Non-invasive methods for measuring fibrosis such as serum markers of fibrosis or hepatic elastography (FibroScan™) correlate well with cirrhosis and a fibrosis score <F2 *(30-32)*. If these methods are available, they may in such cases substitute for performing a liver biopsy. For F2 and F3 the correlation between non-invasive methods and liver biopsy is weaker, and patients with scores in this intermediate range may be considered for liver biopsy if this affects decision-making (see below).

Most serum markers of fibrosis are relatively expensive and not performed as part of routine clinical care. However, two fibrosis indices based on routine tests, FIB-4 (based on ALT, AST, platelet count and patient age) and APRI (AST-to-platelet ratio), have shown good correlation with cirrhosis and <F2 in patients with HBV infection, but have not been validated in HBV/HIV coinfected patients *(33,34)*.

Liver stiffness cut-offs for the thresholds of significant fibrosis and cirrhosis, as assessed by hepatic elastography, may be different to cut-offs used for chronic HCV *(35)*.

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 and/or laboratory tests indicative of cirrhosis;

- the CD4 count is <350 cells/mm^3 or in case of symptomatic HIV and antiretroviral treatment is indicated (see Table 6 below); or
- there are no clinical signs of cirrhosis and the CD4 count is >350 cells/mm^3, ALT is elevated and HBV DNA levels are >2000 IU/ml (or HBeAg positivity in the absence of HBV DNA assessment).

2. Evaluation of co-morbidities 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. In patients with HIV/HCV coinfection the risk of depression in those who received concomitant treatment with IFN and efavirenz was similar to patients receiving IFN alone *(36)*.

2.2. Alcohol abuse

Assessment of alcohol intake is an important part of evaluation (see Protocol 6, *Management of hepatitis C and HIV coinfection, 2007,* 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 g/day) and chronic HBV or hepatitis C virus (HCV) infections *(37)*.
- 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 heavy 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 *(38)*.
- Psychological, social and medical support should be offered to stop alcohol intake or reduce it to less than 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, 2007*).
- Psychological and social support by a multidisciplinary team should be provided for such patients.

2.4. Other co-morbidities and co-conditions

Testing for co-morbidities and co-conditions 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, in press*) and pregnancy (see Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants, 2011 revision*).

3. Assessment of HIV risk 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. Moreover, many of the currently used oral anti-HBV agents have activity against HIV and may compromise future anti-HIV therapy options if used as single agents to treat HBV.
Health care providers should explain to patients the reasons for offering the test and its importance for correct clinical management. However, a patient has the right to refuse an HIV test.

The initial assessment of HIV status should include:

- pre-test verbal consent;
- serological tests (typically, enzyme-linked immunosorbent assay (ELISA) and/or rapid tests) for HIV antibodies, and if positive 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, 2011 revision*.

III. Clinical management of HBV/HIV patients

Observational data have shown faster fibrosis progression rates in HIV patients coinfected with either HBV or HCV although there is limited evidence of a difference in fibrosis progression at higher CD4 counts (>350 cells/mm^3) *(18)*. However, as some of the drugs used to treat HIV and HBV are the same, and given the limited options to treat HBV alone without risk of selection of HIV resistance mutations, the WHO guidelines recommends ART at any level of CD4 count in all HBV/HIV-coinfected patients with evidence of active liver disease *(39)* (see below).

1. Coinfected patients not requiring HIV or HBV treatment

These patients have the following status**:**

- CD4 count of ≥ 350ells/mm^{3}and no HIV-related symptoms; and
- mild or non-progressing HBV disease (HBV DNA <2000 IU/ml; normal ALT; no evidence of significant 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; and
- ALT measurements every three to six months for patients with inactive HBV infection (since liver disease may reactivate even after many years of quiescence).

2. HBV/HIV coinfected patients requiring hepatitis B treatment

HBV/HIV-coinfected patients needing hepatitis B treatment have the following features:

- HBeAg-positive and/or HBV DNA >2 000 IU/ml (or any detectable HBV DNA in patients with cirrhosis) and elevated ALT or histologically proven active disease (Metavir score ≥ A2 and/or ≥F2) in patients with normal ALT.
- In patients with HBV DNA < 2 000 IU/ml and elevated ALT, hepatitis B treatment is indicated if liver biopsy or non-invasive markers show Metavir score ≥ A2 and/or ≥F2
  (see also 2.2.1 Algorithm 1).

2.1. Anti-HBV drugs for treatment of hepatitis B in HIV-coinfected patients

Since most large-scale randomized controlled trials have been conducted to determine the efficacy of anti-HBV drugs in HBV-monoinfected patients, recommendations for treatment and monitoring of HBV/HIV coinfected patients are derived from trials in both HBV/HIV coinfected and HBV-monoinfected patients. The eight drugs available for HBV treatment are shown in Table 5.

Table 5.	Anti-HBV drugs for treatment of hepatitis B	
Drug	**Dose**	**Activity against HIV**
Interferon (INF)-α 2b	5 MU daily or 10 MU 3 times/week s.c. for 16-48 weeks (see text)	Yes[a]
PEG-INF-α 2a	180 μg once weekly s.c. for 48 weeks	Yes[a]
Adefovir (ADF)	10 mg x 1 daily	No[c]
Entecavir	5.5 mg x 1 daily (1.0 mg/day if 3TC resistant)	Yes[b]
Emtricitabine (FTC)[d]	200 mg x 1 daily	Yes[b]
Lamivudine (3TC)	300 mg x 1 daily[e]	Yes[b]
Telbivudine	600 mg x 1 daily	No[f]
Tenofovir (TDF)	300 mg x 1 daily	Yes[b]

[a] Interferon or pegylated interferon can inhibit HIV-1 replication, but without risk of selection of HIV resistance mutations.

[b] Designate drugs that have sufficient dual-activity against both HIV and HBV, and hence should be used in HIV-infected persons only if combined with other drugs to provide effective treatment also against HIV. Most of these drugs have sufficient HIV activity to be used to construct an effective ART regimen; the exception to this rule is entecavir that should be used as an add on drugs to also treat HBV in cases where the other drugs used in ART have insufficient HBV activity.

[c] ADF is active against HIV when administered at higher doses than those used in HBV treatment, but apparently not when dosed to prevent HBV replication only.

[d] Not approved by the US Food and Drug Administration for HBV treatment.

[e] In HBV-monoinfection the dose of 3TC is 100 mg x 1 daily.

[f] A report suggesting HIV activity *(40)* has not been confirmed by others *(41,42)*.

2.1.1. IFN and PEG-IFN

A durable treatment response is rarely achieved after treatment with IFN or PEG-IFN in HBV/HIV coinfected patients and the drugs are therefore not recommended as first-line therapy of HBV infection *(43)*.

INF and PEG-INF are more effective in genotype A than in genotype D infections and in patients who are positive for HBeAg and have elevated ALT levels more than twice the upper limit of normal and low HBV DNA levels *(44,45)*.

Dosage and administration of PEG-IFN-α 2a:

- 180 μg/week for 48 weeks, independent of HBeAg/anti-HBe status *(46)*.

Dosage of INF-α 2b:

- 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 48 weeks *(46)*.

Contraindications

Absolute

- pregnancy and breastfeeding;
- decompensated liver disease (due to an increased risk of thrombocytopenia, death from liver failure or sepsis);
- uncontrolled psychiatric disease;
- significant leucopoenia or thrombocytopenia;

- unstable coronary artery disease, diabetes or hypertension; or
- uncontrolled seizure disorder.

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

2.1.2. Adefovir

Adefovir (ADF) is a nucleotide analogue that on average reduces HBV DNA levels 3.5 log10 copies/ml after 48 weeks of therapy in HBV monoinfected patients *(47)*, but is less potent than TDF *(48)*. Much of the data on the successful use of ADF in HBV/HIV coinfected patients is in patients with 3TC-resistant HBV *(49-51)*.

Only one of these studies has reported use beyond 48 weeks *(51)*; in that study 25% achieved undetectable HBV DNA (400 copies/ml) by week 144 and no breakthrough or ADF resistant mutations were observed. However, in one study of HBeAg negative hepatitis B patients treated with ADF monotherapy for up to 240 weeks the cumulative risk of ADF resistance was 20% *(52)*.

ADF is active against HIV when administered at higher doses than those used in HBV treatment, but apparently not when dosed to prevent HBV replication only *(53)*.

ADF dosage should be adapted to the estimated glomerular filtration rate (eGFR):
- if eGFR is 30–49 ml/min, 10 mg every 48 hours;
- if eGFR is <30 ml/min, 10 mg every 72 hours; or
- if the patient is on haemodialysis, 10 mg every 7 days following dialysis.

Contraindications are pregnancy and breastfeeding (limited experience).

2.1.3. Entecavir

Entecavir is a guanosine analogue that is highly potent against HBV, but can select for HIV resistance mutations (M184V) *(54)*. Therefore, entecavir should only be used in HBV/HIV coinfected patient in addition to (and should not replace components of) fully suppressive ART.
Patients with impaired renal function entecavir dose should be reduced:
- if eGFR is 30–49 ml/min, 0.25 mg once daily;
- if eGFR is 10–29 ml/min 0.15 mg once daily; or
- if <10 ml/min or haemodialysis, 0.5 mg once weekly

In patients with 3TC refractory/resistant infection the dose should be doubled.
Contraindications are pregnancy and breastfeeding (limited experience).

2.1.4. Lamivudine

Lamivudine (3TC) is a nucleoside analogue with activity against both HIV and HBV. 3TC monotherapy in coinfected patients is associated with a high risk of HBV resistance (25% per year) and the drug should therefore preferably always be combined with TDF.

In patients with impaired renal function 3TC dose should be reduced:
- if eGFR is 30-49 ml/min, 150 mg once daily;
- if eGFR is 15-29 ml/min, 100 mg once daily;
- if eGFR is 5-14 ml/min, 50 mg once daily; or
- if eGFR is <5 ml/min, 25 mg once daily.

If the 150 mg formulation is not available, FTC can be used as an alternative drug when a dose reduction of 3TC is needed.

2.1.5. Emtricitabine (FTC)

FTC is a nucleoside analogue, which is similar to 3TC in structure, efficacy and resistance pattern. It is FDA approved for HIV but not HBV therapy. The fixed dose combination of FTC and TDF (Truvada) is recommended by many guidelines as first line nucleotide backbone in HIV therapy *(55,56)*.

In patients with impaired renal function FTC dose should be reduced:

- if eGFR is 30-49 ml/min, 200 mg every 48 hours;
- if eGFR is 15-29 ml/min, 200 mg every 72 hours; or
- if eGFR is <15 ml/min, 200 mg every 96 hours.

2.1.6. Telbivudine

Telbivudine is a relatively new nucleoside analogue with greater activity against HBV than both 3TC and ADF, but its efficacy is limited by a high risk of resistance (25% at 24 months in HBV monoinfected patients) with cross-resistance against 3TC/FTC but not ADF. The experience in HBV/HIV coinfection is still limited. A case report suggesting HIV activity in a single HBV/HIV coinfected patient *(40)* has not been confirmed by others *(41,42)*. Due to the high risk of resistance, monotherapy with telbivudine is not recommended.

2.1.7. Tenofovir

Tenofovir (TDF) is a nucleotide analogue with potent activity against both HBV and HIV and is the preferred drug, as part of a full ART regimen, to treat HBV in HIV coinfected patients. Although development of HBV resistance seems to be very rare, it is recommended that TDF is always combined with another drug with anti-HBV activity (e.g. 3TC or FTC) when used as part of ART in HBV/HIV coinfected patients. TDF is active against 3TC/FTC resistant HBV. The fixed dose combination of FTC or 3TC and TDF is recommended by many guidelines as first line nucleoside/nucleotide backbone in HIV therapy *(55,56)*. Although TDF is associated with an increased risk of nephrotoxicity *(57),* dose adjustment in individuals with altered creatinine clearance can be considered:

- creatinine clearance ≥50 ml/min, 300 mg once daily;
- creatinine clearance 30−49 ml/min, 300 mg every 48 hours; or
- creatinine clearance ≥10−29 ml/min (or dialysis), 300 mg once every 72−96 hours.

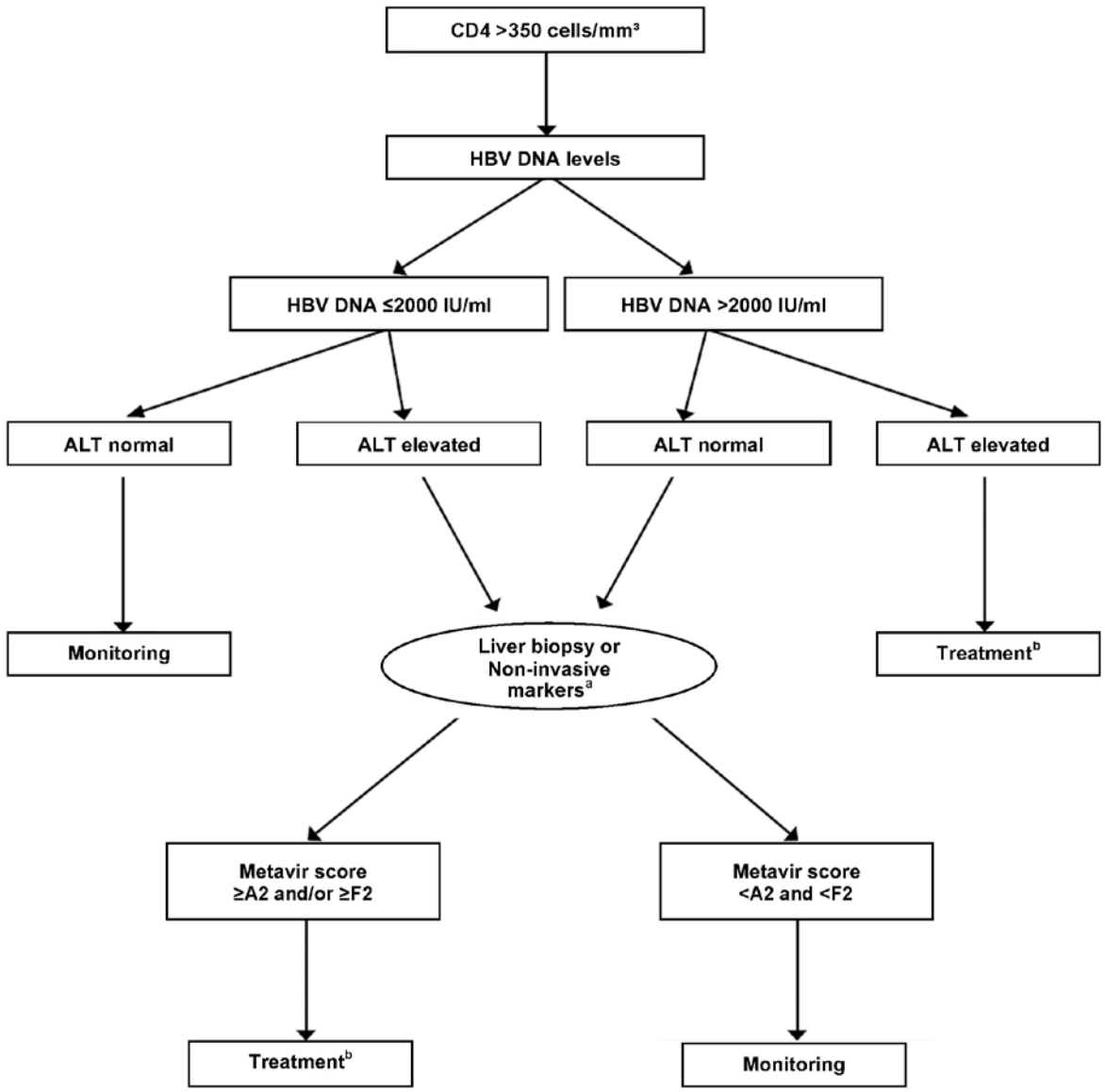
2.2. Evaluation and treatment algorithms for chronic hepatitis B in HIV-infected patients

In all patients with a CD4 count ≤350 cells/mm^3 ART is recommended irrespective of whether there is an indication to treat the HBV infection or not. The ART regimen should contain two drugs active against both HIV and HBV. This would preferably be TDF and FTC or 3TC (see Table 6). In patients with a CD4 count >350 cells/mm^3 early ART is indicated if there is an indication for treatment of the HBV infection (see Algorithm 1, 2 and Table 6).

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

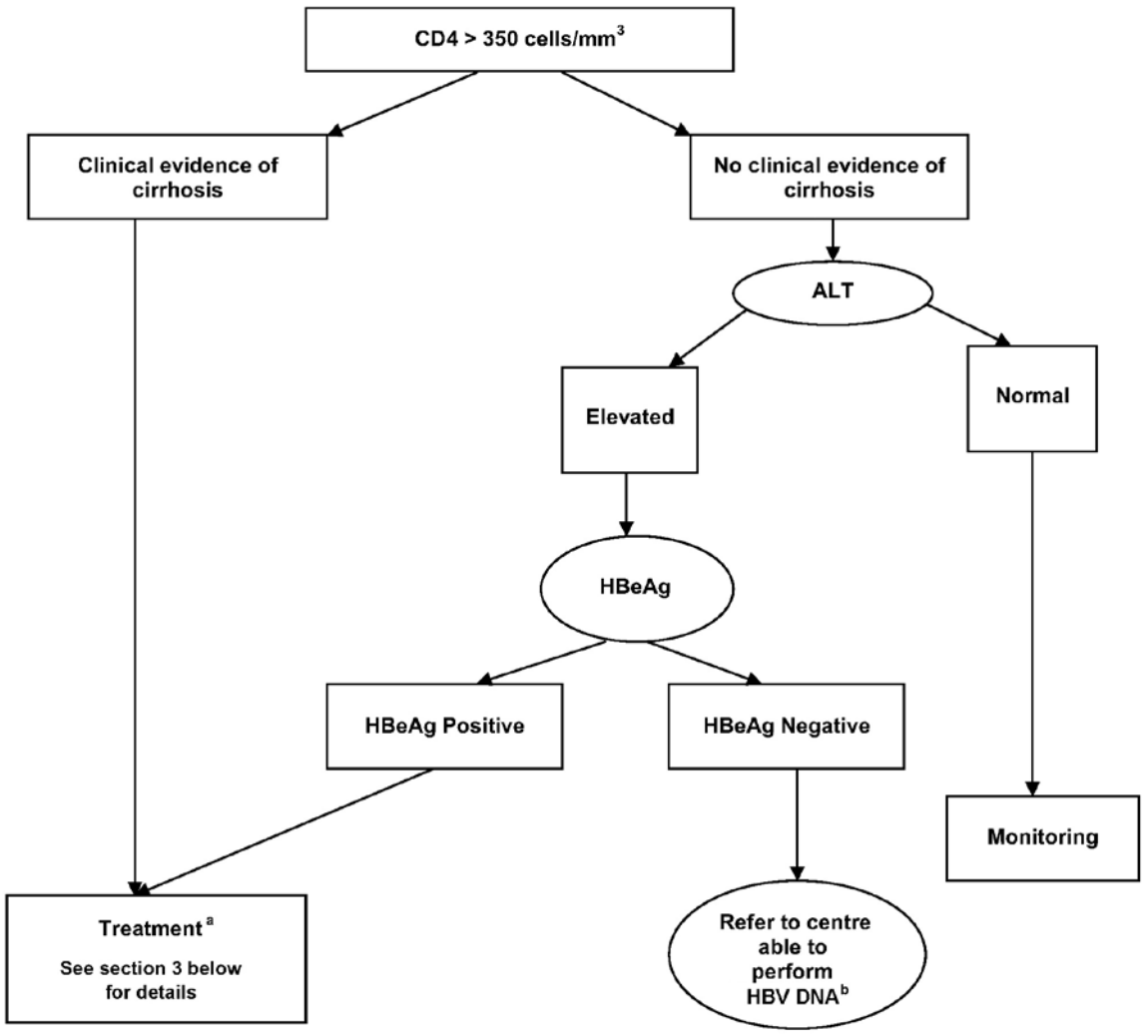


[a] Non-invasive markers: Serum fibrosis markers and/or hepatic transient elastography (FibroScan).
[b] Early ART (including TDF + FTC or 3TC) is recommended. PEG-IFN or ADF can be considered if ART is not available.

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 e-Ag negative chronic hepatitis B (HBeAg-negative with elevated ALT) 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] Early ART (using drug regimens that contain TDF + FTC or 3TC) is recommended. PEG-IFN or ADF can be considered if ART is not available.

[b] Further evaluation and management at referral centre as in Algorithm 1.

2.2.3. HBV/HIVco-infected patients with clinical evidence of cirrhosis or decompensated cirrhosis

- All patients with cirrhosis and any detectable HBV DNA should receive HBV therapy. Treatment should be long-term and uninterrupted, as virological relapses after discontinuation of treatment are frequent and can be accompanied by a rapid clinical deterioration *(58)*.
- No medications are contraindicated for patients with compensated cirrhosis. Interferon is contraindicated in patients with decompensated liver disease due to its very poor tolerability profile.
- Patients with cirrhosis should be screened at six month intervals with serum alpha-fetoprotein and hepatic ultrasound for the occurrence of hepatocellular carcinoma. Routine screening is also advised for esophageal varices at the time of diagnosis and at 1 – 2 year intervals thereafter.
- It might be necessary to adjust the dose of ARV metabolized by the liver**.** 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, 2007,* for recommendations on antiretroviral dosage adjustment in patients with end-stage liver disease (ESLD).
- HBV/HIV coinfected patients with ESLD require the same measures for treatment of ascites, hepatorenal syndrome, variceal bleeding, hepatic encephalopathy and other manifestations of hepatic decompensation as HIV negative HBV patients.
- Creatinine clearance using Cockcroft Gault estimation in the setting of advanced or decompensated liver cirrhosis overestimates the true glomerular filtration rate *(59)* and use of the arithmetic mean urea and creatinine clearance or inulin clearance is recommended.

Table 6. Recommendations for initiating ART in HBV/HIV-coinfected patients

CD4 count	Recommendations
≤350 cells/mm^3	ART is recommended irrespective of whether indication to treat the HBV is present or not. ART regimens should preferably contain two dual-active drugs (targeting both HBV and HIV) (this is an absolute requirement in patients with CD4 count < 200 cells/mm^3 and in patients with cirrhosis).
>350 cells/mm^3	Early ART is recommended if there is an indication to treat HBV (see algorithms 1 and 2). The ART regimen should preferably contain two dual-active drugs (targeting both HIV and HBV). This would preferably be TDF and FTC or 3TC. In settings without access to two dual-active drugs, it is recommended to use TDF (preferred) or 3TC/FTC (alternative) as part of ART in patients where the HBV infection requires therapy; where 3TC or FTC alone are used as part of ART and TDF not available, consideration should be given to using ADF as a second anti-HBV agent. Conversely, in such settings, in patients without a need for HBV therapy, it is recommended to completely avoid using dual-active drugs as part of ART. If there is an indication for HBV therapy, but ART is not available or the patient is unwilling to initiate ART, treatment with IFN/PEG-INF or ADF can be considered. For patients commencing therapy with IFN/PEG-IFN or ADF careful attention should be paid to monitoring HBV DNA for primary non-response, partial virological response (for ADF) and virological non-response (for IFN and PEG-IFN) and viral breakthrough (see section 3.1.1) when therapy will need to be stopped (IFN/PEG-IFN) and/or modified (ADF).

2.2.4. First line ART regimens

In Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents, 2011 revision,* extensive discussion is provided on the considerations for appropriate choice of ARV's to manage HIV in various settings and scenarios. Complexity among HBV/HIV co-infected patients is increased by the choices of drugs with dual antiviral activity and possible impaired tolerability due to liver impairment. Table 7 provides an overview of first line ART regimens and their components in HBV/HIV co-infected patients – for each is indicated preferred and alternative options.

Table 7.	First-line ART regimens for HBV/HIV-coinfected patients			
	ART regimen	**NRTI component**	**NNRTI component**	**PI/r component**
Preferred	2 NRTIs + 1 NNRTI	TDF + (3TC or FTC[a])	EFV	LPV/r or ATV/r[b]
Alternative	2 NRTI + PI/r	(ABC or ZDV)[c] + (3TC or FTC)[c]	NVP[d]	DRV/r

[a] FTC is equivalent to 3TC and is available together with TDF as a fixed-dose combination.
[b] ATV causes elevation of bilirubin levels in over 30% of patients, but without changes in liver enzymes and liver function tests *(25)*.
[c] If TDF is not tolerable (or not available), either of these drugs can be used to treat HIV – however, as they are not effective against HBV, 3TC or FTC should be a mandatory component of the regimen and it is recommended to include one additional anti-HBV active agent irrespective of its activity against HIV (see Table 5 for possible choices).
[d] Nevirapine (NVP) can be considered instead of efavirenz (EFV) for patients without hepatic dysfunction and with close monitoring. It should be used with caution and monitored closely in women with CD4 count >250 cells/mm^3 or in men with CD4 count >400 cells/mm^3.

2.2.5. Second line ART regimens

In Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescent, 2011 revision,* extensive discussion is provided on the considerations for appropriate choice of ARV's to manage HIV in patients experiencing virological failure. The added complexity in making rational choices among HBV/HIV co-infected persons relates to maintaining suppression of HBV replication also after the switch of drugs to regain control of the HIV replication. To do this, the rational for the choices of drugs as part of first line ART in HBV/HIV can be applied. The principle of this is to include at least two dual-active drugs in the second-line ART regimen (if possible). It might be necessary to continue dual-active drugs used as part of first line also in second line regimens (possible as add on drugs to the second line ART regimen provided now solely to suppress HBV replication), which is reasonable as long as the course of HBV treatment during the first line was considered effective.

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

- 3TC resistant HBV strains develop rapidly in HBV/HIV-coinfected patients, and even at the higher doses (300 mg daily), it appears in almost 50% and 90% of co-infected patients after two and four years, respectively, of 3TC treatment *(60)*.
- The clinical symptom associated with emerging 3TC resistance is hepatic flares, with elevated ALT levels.
- In the presence of suspected 3TC resistance, the first step is to confirm it, if resistance testing is available. Otherwise resistance may be suspected if the HBV viral load increases more than 1 $\log_{10}$ in a compliant patient taking 3TC *(61)*.
- If 3TC resistance is present, it is recommended to add TDF to the ART regimen or replace one of the NRTIs with TDF.
- It is generally recommended to prevent the emergence of 3TC resistance. This is done with avoiding using 3TC as the single HBV active drug when composing an ART regimen in a person also infected with HBV.

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

3.1. 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 within 48 weeks) *(62)*;

- durable anti-HB seroconversion in initially HBeAg-positive patients; and
- anti-HBs seroconversion is rarely observed with nucleotide–nucleoside analogues and in HIV-positive patients.

3.1.1. Monitoring of HBV DNA

See Table 8. Note also the following.

- In HBV DNA positive patients not receiving anti-HBV treatment HBV DNA levels should be monitored every six to twelve months.
- In patients on HBV treatment (including ARVs with anti-HBV activity), a primary non-response is defined as <1 log drop in HBV DNA levels within three months. HBV DNA should then be measured at least every six months and if possible every three months.
- For patients on IFN/PEG-IFN, virological non-response is defined as HBV DNA >2000 IU/ml 24 weeks after starting therapy.
- For patients on ADF therapy, sub-optimal or partial virological response is defined as a decrease in HBV DNA after starting therapy, but detectable HBV DNA (>15 IU/ml) after 48 weeks of therapy.
- Virological breakthrough on treatment is defined as >1 log increase in HBV DNA levels above nadir HBV DNA levels and signifies either non-adherence or resistance. If possible, a resistance test should be performed.

3.1.2. Recommendations for changing or modifying HBV therapy

- Patients with CD4 >500 cells/mm3 receiving ADF monotherapy for HBV: if primary non-response, partial virological response, or viral breakthrough switch to early ART including TDF and 3TC or FTC.
- Patients with CD4 >500 cells/mm3 receiving INF/PEG-INF therapy for HBV: if primary non-response, non-response at 24 weeks, or breakthrough, stop therapy and start early ART including TDF and 3TC or FTC.
- Patients on TDF who develop significant renal or bone toxicity should switch to entecavir and make appropriate change to ART to ensure that HIV is well controlled.

3.1.3. Monitoring of ALT

- ALT should be monitored after one and three months, 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.

Table 8. Monitoring during treatment

	Before treatment	Month 1	Month 3	Every three months
ALT	X	X	X	X
HBV DNA	X		X	X

3.2. 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, 2011 revision,* for further information.

3.3. 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, 2011 revision*.

3.4. 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 co-infected patients. The management of liver toxicity is based mainly on its clinical impact, severity and pathogenic mechanism.

3.4.1. 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 response 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-RNA before ART *(63)*. These symptoms are usually prevented by including a dual-activity drug in the ARV regimen (see above).

3.4.2. Drug-related hepatotoxicity

- The incidence of hepatotoxicity in observational studies is 4.5 to 11.4%. Grade 4 events occur with a rate of 2.6 per 100 person-years *(64,65)*.
- Risk factors for hepatotoxicity, in most studies, are elevated baseline alanine aminotransferase (ALT) level and coinfection with HCV or HBV *(64-66)*.
- 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 *(67,68)*.
- 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 and seen more often in patients with high CD4 cell counts *(69,70)*.
- NVP, as part of the initial ART regimen, should be used with caution and monitored closely in persons with moderate to severe liver impairment, women with CD4 cell count > 250/mm^3 and men with CD4 cell counts > 400/mm^3.. Conversely, this CD4 count is not relevant in patients already suppressed on ART in whom it is considered to switch to NVP.
- The risk of hepatotoxicity and rash are highest in the first six weeks of NVP treatment; starting NVP at half doses during the first two weeks minimizes the risk.
- Liver toxicity may also occur in patients receiving nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), especially zidovudine (ZDV), 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 *(64)*.
- The protease inhibitors, ritonavir (full dose), tipranavir and darunavir have been associated with hepatotoxicity *(64)*.
- If no other cofactors exist, the degree of hepatotoxicity is the main determinant of the clinical approach. See Table 9.
- 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.

Table 9. Standardized hepatotoxicity scale

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

Source: (www.actg.org)

3.4.3. Drug-induced hepatotoxicity and anti-tuberculosis drugs

The rate of hepatotoxicity is significantly higher in TB patients with HCV or HBV coinfection (59%) than in those without (24%) *(71)*.

- Commonly used anti-TB drugs, such as isoniazid, rifampicin, and pyrazinamide are hepatotoxic.
- It is not necessary to adapt dosage of anti-TB drugs in cases of hepatic insufficiency.
- The crucial efficacy of isoniazid and rifamycins in antituberculous regimens, warrants their use, if at all possible, even in the face of pre-existing liver disease.
- Hepatotoxicity is uncommon with rifabutin at its usual dose 150mg-300mg/day.
- HBV/HIV co-infected patients starting antituberculous therapy need to be monitored very carefully with regular ALT/AST measurements.
- Treatment without pyrazinamide may be possible with extension of isoniazid, rifampicin and ethambutol use to 9 months, as long as drug susceptibility testing is available.
- In patients with cirrhosis, rifampicin and ethambutol combined with levofloaxacin, gatifloxacin or moxifloxacin or cyloserine, for 12 to 18 months may be considered.
- For patients with encephalopathic liver disease, ethambutol combined with a fluroquinilone, cycloserine and capreomycin or aminoglycoside for 12 to 18 months may be considered.

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 bi-annually):

- number of HIV-positive patients seen for care (the denominator for the data below);
- number of HIV-positive patients coinfected with HBV (HBsAg-positive);
- number of HBV-positive (HBsAg+) tested for, and co-infected with HDV;
- number of HIV-positive patients with active hepatitis B;
- number of HBV/HIV co-infected patients with clinical/biopsy or non-invasive test assessed cirrhosis;
- number of HIV-positive patients with active hepatitis/cirrhosis receiving:
  - ART with 3TC or FTC and/or TDF;
  - ART without 3TC or FTC and/or TDF;
  - exclusively on hepatitis B treatment (e.g. IFN or ADF);
- number of HBV/HIV co-infected cirrhotic-positive patients evaluated for oesophageal varices and offered HCC screening;
- 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); and
- number of HIV-infected patients vaccinated against HBV.

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