

Special report

SHORT STATEMENT OF THE FIRST EUROPEAN CONSENSUS CONFERENCE ON THE TREATMENT OF CHRONIC HEPATITIS B AND C IN HIV CO-INFECTED PATIENTS[☆]

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1. Introduction

Despite recent advances in the management of hepatitis and HIV co-infection, there is no clear consensus among hepatology, infectious diseases and virology experts on treatment of co-infections and patient management. This encouraged the organisation of a European Consensus Conference to review current knowledge on the treatment of chronic hepatitis B and C in HIV co-infected patients, with the view to developing this consensus statement.

An organising committee drafted questions to be addressed at the conference, and following 2-days of presentations and discussions, an independent Jury Panel assessed the evidence and prepared this statement with the aim of addressing eight questions:

- What are the reasons to treat viral hepatitis in HIV co-infected patients in the HAART era?
- How should viral hepatitis be diagnosed and how should disease severity be assessed in HIV-infected patients?
- What are the current treatment options?
- Which patients should be treated and when?
- How should co-infected patients be treated (treatment algorithms)?
- How should anti-hepatitis treatment be monitored?
- How should end-stage liver disease be managed?
- What are the most important areas for future research?

This process essentially follows the consensus process used for preparing NIH Consensus Statements. This short version of the consensus summarises the main conclusions and recommendations from the conference. We will subsequently publish a more detailed version of these recommendations with additional information on the background and supporting data. And in a supplement to *Journal of Hepatology*, articles prepared by individual presenters will be published to elaborate on the recommendations made here. Statements and recommendations were graded for their strength and quality using a grading system based on the Infectious Diseases Society of America (IDSA) system (Table 1).

[☆] In our strive to keep our readership aware of the developments on the management of liver disease in patients co-infected with HIV, the *Journal of Hepatology* endeavoured to publish a concise statement generated by members of the Jury of the First European Consensus Conference on treatment of HBV and HCV in HIV co-infected patients. This document was distributed as a loose leaflet insert in the abstract book of the EASL Annual Meeting and is published bound in the current issue of the *Journal of Hepatology* for reference—Mario U. Mondelli, Co-Editor.

Endorsed by the European Association for the Study of the Liver (EASL), the European AIDS Clinical Society (EACS), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European Federation of Internal Medicine (EFIM), the International AIDS Society (IAS), the French Society of Infectious Diseases (SPILF) and the European AIDS Treatment Group (EATG). Hosting societies include the French Association for the Study of Liver Disease (AFEF) and the French Society of Internal Medicine (SNFMI). Supported by the French Agency for Research on AIDS (ANRS) and the French Ministry of Health.

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2. Background

Globally, an estimated 370–400 million people are chronic carriers of hepatitis B virus (HBV) and over 180 million people are chronic carriers of hepatitis C virus (HCV). Overlapping routes of transmission of these hepatitis viruses and HIV, result in a high frequency of co-infection. Worldwide, several million people are

Table 1
Grading scheme for recommendations

Category	
<i>Strength of recommendation</i>	
A	Both strong evidence for efficacy and substantial clinical benefit to support recommendation
B	Moderate evidence for efficacy—or strong evidence for efficacy but only limited clinical benefit—support recommendation for use
C	Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g. drug toxicity, drug interactions) or cost of the treatment under consideration
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use
<i>Quality of evidence</i>	
I	Evidence from at least one properly designed randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), or from multiple time-series studies. Or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

co-infected with HBV and HIV or HCV and HIV. Prevalence of HBV and HCV in HIV-infected patients in Europe is high and estimated to be 40% for HCV and 8% for HBsAg-positivity. The prevalence of co-infection is influenced by geographic and ethnic origin.

Sexual activity and/or injection drug use are the most common routes of transmission. Higher rates of HBV co-infection are seen in men who have sex with men compared to injection drug users and people with heterosexually-acquired HIV infection. The primary modes of transmission for both HCV and HBV are parenteral, sexual and vertical from mother to child with a risk for HBV > HIV > HCV for the latter setting. Although sexual transmission of HCV occurs in <1% monogamous couples, there have been increasing reports of sexual transmission between men who have sex with men. Blood may contain up to 10^8 – 10^9 50% chimpanzees doses (CID50)/ml of HBV whereas HCV reaches only 10^6 50% CID50/ml. Both HBV and HCV may survive drying in contrast to HIV—HBV is still infectious after 7 days in the dry state, but HCV is infectious only for hours.

All hepatitis B surface antigen (HBsAg)-positive and HCV-RNA-positive patients are potentially infectious.

Infection with HBV or HCV and the related liver damage is an important cause of mortality and morbidity among HIV-infected patients.

In patients infected with HBV, HIV can lead to higher rates of chronicity, decreased rates of anti-HBe and anti-HBs seroconversion, and increased viral replication, probably through the impairment of innate and adaptive cellular and humoral immune responses. Similarly, in HCV-

infected patients, HIV accelerates the course of HCV-associated liver disease progression, particularly in patients who are more severely immune deficient. As a consequence, both HBV/HIV and HCV/HIV co-infection is associated with increased liver fibrosis progression and increased rate of liver decompensation, cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality. Therefore, it is recommended to avoid the development of severe immune deficiency (defined as <200 CD4 cells/mm³) in HBV or HCV co-infected persons (BII).

There is no evidence that HBV affects HIV disease progression. There is no evidence that HBV alters the response of HIV to antiretroviral therapy (ART). But starting ART may be associated with an increased risk of transaminase flares. This may reflect both immune restoration disease against HBV and/or drug toxicity.

Similarly, HCV has little or no effect on the response to ART, or on immunological, virological and HIV-related clinical disease progression.

At present in Europe, only a minority of HCV/HIV and HBV/HIV co-infected patients are treated for their hepatitis. Effort must be made, via multidisciplinary healthcare infrastructures, to increase the applicability and availability of treatment especially in the more vulnerable groups (such as in immigrants, injection drug users, prisoners, people with psychiatric illnesses and people with excessive use of alcohol).

3. General recommendations for counselling

3.1. Alcohol consumption

Continued alcohol consumption increases HCV replication, accelerates fibrogenesis and liver disease progression in hepatitis B and in hepatitis C, and also diminishes the response and adherence to anti-hepatitis treatment (especially if consumption is >50 g/day). Therefore, psychological, social and medical support should be made available to encourage patients with a high alcohol intake to limit alcohol consumption and preferably to stop drinking (AII).

3.2. Active drug users

Active drug use should not be an absolute exclusion criteria since full benefits of HBV and HCV therapy are not compromised when active drug users are successfully retained in treatment. Patients who require treatment should be offered opiate substitution therapy, including heroin maintenance programmes, where medically available. If the patient is not ready to stop drug use, any assessment for initiation of HBV or HCV treatment should be made on a case-by-case basis (AIII).

Substitution therapy as a step towards cessation should be considered. Help provided (e.g. through needle- and

syringe-exchange programmes) reduces the risk of further reinfection, including parenteral viral transmission (AIII).

3.3. Sexual transmission

Since HBV and HIV and, occasionally, HCV are transmitted sexually, the use of condoms is recommended (AII).

3.4. Vaccination

HIV-infected patients should be screened for hepatitis A and B. Patients lacking anti-HAV IgG antibodies or HBsAg and anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection, regardless of their CD4 count (AII).

The response to the vaccine is dependent on CD4 count at the time of vaccination, and may be reduced in patients with a CD4 cell count <500 cells/mm³. In all patients, the anti-HBs antibody titre should be monitored 4 weeks after the end of the HBV vaccination schedule. When there is insufficient response (anti-HBs <10 IU/l) re-vaccination should be considered (BIII). In patients eligible for highly active antiretroviral therapy (HAART), vaccination should be deferred until a clinically significant immune reconstitution has been achieved (AII). People who fail to seroconvert after vaccination and remain at risk of HBV infection should be annually monitored for serological markers of HBV (HBsAg and antibodies to the hepatitis B core antigen (anti-HBc)) (AII).

Isolated anti-HBc may be a marker of resolved HBV infection where anti-HBs has disappeared. In such cases, one dose of HBV vaccine may reveal an immune response. Some experts believe that vaccination for HBV should be recommended in HIV-infected patients with isolated anti-HBc positivity (CIII). In the absence of anti-HBs response one might consider HBV-DNA testing to assess occult HBV infection (see below) (CIII).

3.5. Screening for late-stage complications of hepatitis B or C

Patients with liver cirrhosis should be monitored for the presence of oesophageal varices using upper-gastrointestinal endoscopy every 1–2 years (AI).

Patients with advanced HBV- or HCV-associated fibrosis/cirrhosis (F3/F4) have a high risk of developing HCC, and therefore surveillance with ultrasound and serum alpha-fetoprotein (AFP) is advised (AII). As the development of HCC in co-infected patients may be faster, monitoring intervals shorter than 6 months should be considered (BII).

In cases of decompensated cirrhosis, it may be necessary to adjust the dose of antiviral drugs metabolised by the liver (BII). When available, drug monitoring may be helpful.

4. HCV/HIV co-infection

4.1. Screening for HCV

All HIV-infected patients should be screened for HCV. Screening for HCV in HIV-infected patients should be done using a third generation anti-HCV antibody test (AII). A positive result should be followed by evaluation for the presence of HCV-RNA (AII). Detection of HCV-RNA indicates active disease. A negative anti-HCV antibody test excludes HCV infection—except if the patient has acute HCV (diagnostic window) or has a blunted immune response, in which case HCV-RNA should be measured to document the infection (AIII).

4.2. Counselling

4.2.1. Use of antiretroviral therapy

Initiation of treatment with nevirapine is associated with a risk of hepatic toxicity, which manifests as significant increases in ALT. This is more frequent in women who commence therapy with a higher CD4 cell count (see labelling for nevirapine). Most events are sub-clinical and usually reverse spontaneously. In HCV/HIV co-infected patients, nevirapine should be used with caution (AII).

Initiation of antiretroviral therapy in HIV/HCV co-infected patients should follow the current recommendation for initiation of antiretroviral in HIV mono-infected patients (BII). However, for patients with CD4 cell count levels that are just above the recommended threshold for initiation of ART, commencement of ART should be considered before the start of HCV therapy because of the risk of a decrease in CD4 cell count during IFN-based anti-HCV therapy (BIII).

4.3. Liver biopsy and other evaluations

Liver biopsy provides information on histological disease, extent of inflammation (grading), extent of fibrosis (staging) and also about co-morbidities. The decision to perform a liver biopsy should be individualized as the resulting information about grading and staging will influence the decision to treat (AIII). This is particularly important in patients who are less likely to achieve a sustained virological response (SVR), for example, patients infected with genotype-1, when the risk-benefit of treatment is doubtful (for example, when there is a high risk of adverse events), and when patients' motivation for treatment is low.

Several non-invasive methods to evaluate inflammation and fibrosis are currently under investigation (for example, serum fibrosis markers and tissue elastography) but their usefulness in HCV co-infected patients requires validation.

4.4. Treatment

The combination of PEG-IFN- α and ribavirin is the treatment of choice for HCV infection.

4.4.1. Goals of therapy

The primary aim of anti-HCV treatment is sustained virological response (SVR) defined as undetectable serum HCV-RNA 24 weeks after the end of therapy—evaluated using sensitive molecular tests (AI). Long-term follow-up studies in HCV mono-infected patients indicate that SVR is clinically related to viral eradication in a vast majority of patients and improvement in histology, which is associated with decreased risk of disease progression (cirrhosis, decompensation and HCC).

4.4.2. When should treatment for HCV start?

Acute hepatitis C. Treatment of acute hepatitis C may reduce the risk of chronicity. Therefore, if serum HCV-RNA is not eliminated spontaneously within 3 months of onset of disease (clinically and/or laboratory documented), treatment should be offered (CIII). Treatment with PEG-IFN is recommended for 6 months in HCV mono-infected patients. Data in co-infected patients are limited—use of monotherapy or combination therapy in this population remains undetermined.

Chronic hepatitis C. If chronic hepatitis C is detected early in the course of HIV infection (before initiation of HAART is necessary), treatment for chronic hepatitis C is advised (AIII). However, if a co-infected patient has severe immune deficiency (CD4 count <200 cells/mm³), the CD4 cell count should be improved using HAART before commencing anti-HCV treatment (AII).

4.4.3. Candidates for treatment

Treatment for HCV offers the possibility of eradicating HCV within a defined treatment period. This is potentially advantageous for the subsequent management of the patient with HIV, and every patient should therefore be considered for treatment when the benefits of therapy will outweigh the risks.

There are several baseline parameters that can predict a greater likelihood of achieving a SVR:

- Patients infected with genotypes 2 and 3.
- A low viral load ($<800,000$ IU/ml).
- Absence of cirrhosis.
- Age <40 years.
- Higher ALT levels ($>3 \times$ ULN).

Conversely, low CD4 cell count can reduce the chance of SVR. Several studies using standard IFN plus ribavirin suggest a lower SVR in patients with a low CD4 count (<200 cells/mm³) at baseline. There is currently insufficient evidence to conclude that SVR to PEG-IFN plus ribavirin therapy is negatively affected by low baseline CD4 cell count.

We recommend treatment, without liver biopsy or other liver assessment, for patients infected with HCV genotypes 2 or 3, and patients infected with HCV genotype 1 if the HCV viral load is low, if there are no major contraindications present and patients are motivated to undergo

therapy (AI). The SVR is in the order of 40–60% in these patient groups. In case of the availability of a liver biopsy demonstrating lower grades of liver fibrosis (F0-1), regardless of HCV genotype, treatment can be deferred (BIII). A liver biopsy is especially important to perform for patients with suspected low chance of SVR (either because of an a priori low chance of response and/or excess risk of severe adverse events).

In patients infected with HCV genotype 1 and with a high HCV viral load, recommendation for treatment should also take into account liver disease stage. In particular, patients with histological evidence of advanced liver disease (fibrous septa) should be considered for treatment (AII).

Because ALT levels do not necessarily reflect the stage of fibrosis—especially in HIV/HCV co-infected patients—a ‘normal’ ALT level alone should not be used as an argument to defer treatment (AII). A biopsy in this situation can help to make a more informed decision on whether to start or defer treatment.

Patients on opioid substitution therapy should not be deferred from treatment. Psychological and social support in a multidisciplinary team should be provided for these patients. Initiation of anti-HCV therapy in active drug users should be considered on a case-by-case basis (CIII).

Treatment with IFN can reveal and worsen depression. Treatment for hepatitis C should therefore be deferred in patients with moderate to severe depression until the condition improves (EII). In patients with mild psychiatric illness, treatment for hepatitis C should not be deferred and support for the psychiatric condition (counselling and/or antidepressant medication) should be offered (BIII).

IFN-based therapies are contraindicated in patients with decompensated liver cirrhosis (Child Pugh stage B or C) (EI). Liver transplantation, where feasible, should be the primary treatment option for these patients (CII).

4.4.4. Management and therapeutic options

The standard dose for PEG-IFN 2a is 180 µg once weekly, and for PEG-IFN 2b it is 1.5 µg/kg bodyweight, once weekly.

Although clinical trials in HIV/HCV co-infected patients used a fixed dose of 800 mg ribavirin once daily for all genotypes, studies from HCV mono-infected patients support the use of 1000–1200 mg ribavirin once daily for treatment of infections with genotypes 1 and 4, and 800 mg ribavirin once daily for genotypes 2 and 3. We therefore recommend an initial ribavirin dose of 1000–1200 mg once daily for HIV/HCV co-infected patients with a high HCV genotype 1 or 4 viral load (BIII). For all other patients, a dose of 800 mg once daily is recommended (AII).

Regardless of genotype, duration of treatment in co-infected patients should be 48 weeks (BI).

4.4.5. Assessment of response

If an early virological response (EVR) of at least 2 log₁₀ reduction in viral load compared to baseline is not achieved

at week 12, treatment should be stopped, because the negative predictive value to achieve SVR is 99–100% (AII).

In patients who achieve at least a 2 log₁₀ reduction in viral load at week 12, treatment should be continued. In mono-infected patients testing for HCV-RNA at week 24 is recommended, and in patients who remain positive for serum HCV-RNA at week 24 (negative predictive value for achieving SVR is 100%), treatment should be discontinued. A similar algorithm applies for HIV/HCV co-infected patients (AII).

The population of non-responders is heterogeneous, non-response is observed with any therapy for HCV, and can range from ‘no viral decline during treatment’ to ‘end-of-treatment virological response and subsequent virological relapse’. The decision to retreat patients with PEG-IFN plus ribavirin should be considered based on the type of response/non-response and tolerability to the previous treatment, the extent of liver damage and the HCV genotype (CIII).

If the therapeutic aim in patients with biopsy-proven advanced fibrosis/cirrhosis is to delay or prevent disease progression in non-responders at week 12 and/or week 24, continuation with PEG-IFN monotherapy can be considered (CIII). Dose, duration and clinical benefits of such maintenance therapy should be confirmed in clinical trials in HIV/HCV co-infected patients (AIII).

4.4.6. Concomitant use of antiretroviral therapy

During PEG-IFN plus ribavirin combination therapy, didanosine is contraindicated in patients with cirrhosis (EI) and should be avoided in patients with less severe liver disease (EII). Stavudine, especially in combination with didanosine, is associated with an excess risk of lactic acidosis and should be avoided (EII). In addition, the use of zidovudine should be avoided due to an excess risk of anaemia and neutropenia (DII).

A potential negative impact of protease inhibitor (PI) use on SVR in patients with HIV/HCV co-infection treated with PEG-IFN plus ribavirin has been suggested in a subgroup analysis of one study—this requires clarification. The jury do not recommend against the use of PIs (CIII).

4.4.7. Monitoring and follow-up

A full blood count and liver tests (transaminases and bilirubin) should be performed during the first month of therapy at weeks 1, 2 and 4, and thereafter on a monthly basis. CD4 cell count should be monitored monthly. Additional laboratory tests can then be carried out at the physician’s discretion and should include assessment of thyroid stimulating hormone (TSH) at least every 3 months.

Virological response should be monitored by serum HCV-RNA quantification before initiation of treatment and 12 weeks after starting therapy using the same molecular test. Patients who achieve a 2 log₁₀ drop but remain HCV-RNA-positive should be tested again at week 24 by a sensitive test with a lower limit of detection of 50 U/ml.

Assessment of SVR should be made 24 weeks after completion of the therapeutic course by a qualitative test.

4.4.8. Management of adverse events

Effort should be made to keep patients on the optimal dose of PEG-IFN plus ribavirin and to proactively manage side effects of therapy. Such management should include use of:

- Paracetamol (possibly combined with non-steroidal anti-inflammatory drugs) for influenza-like syndrome (AII).
- Erythropoietin for severe anaemia (BI).
- Growth factors to correct severe neutropenia (CIII).
- Selective serotonin reuptake inhibitor antidepressants for clinically-relevant depression (AII).
- Thyroid hormone substitution in hypothyroidism (AII).
- Beta-blockers to relieve symptoms of hyperthyroidism (CIII).

5. HBV/HIV co-infection

5.1. Screening for HBV

All HIV-positive patients should be tested for HBsAg and anti-HBc antibodies, and questioned about their HBV vaccination history (AII).

If patients are negative for HBsAg and positive for anti-HBc, they should be tested for anti-HBs (AII). In patients with isolated anti-HBc positivity, a test for serum HBV-DNA might be considered to assess occult HBV infection (see below) (CIII).

All patients who are HBsAg-positive should be tested for anti-HDV (AII). However, none of the currently available nucleotide/nucleoside analogues are effective for the treatment of HDV infection, and the only assessed treatment is high dose interferon- α (IFN) (5 MU daily or 10 MU three-times weekly for 12 months), which has limited efficacy and often poor tolerability in the long term in HBV/HDV patients without HIV and has not been assessed in HIV co-infected cases.

In people who are HBsAg-positive, further evaluation of the severity of HBV disease and the virological profile is important (AII). Tests and evaluations may include those listed below, but the extent of the examinations may be different in different circumstances.

All patients should have:

- Examination for signs and symptoms of advanced liver disease.
- Alanine aminotransferase (ALT) determination
 - serial measurements are preferred as ALT may fluctuate significantly, particularly when patients are HBeAg-negative
 - although there is not an absolute correlation between ALT levels and disease activity, the higher the ALT

levels, the higher the likelihood of the presence of significant disease and the faster the progression of fibrosis.

- HBeAg and anti-HBe
 - HBeAg-positive patients almost invariably have high HBV-DNA levels, independently of ALT levels
 - anti-HBe-positive cases may or may not have high virus replication, as defined by HBV-DNA testing
- HBV-DNA measurements
 - results should be expressed in International Units (IU) per millilitre, the universal, standardized HBV DNA quantification unit (please refer to conversion tables for calculation of IU/ml from non-standardised copies/ml or genome equivalents/ml)
 - the results should be expressed in decimal logarithm (log) IU/ml, for precise assessment of baseline and significant HBV DNA changes upon therapy
 - serial measurements should be done if HBV-DNA is initially found at low levels (≤ 2000 IU/ml in anti-HBe-positive patients with elevated ALT or other signs of liver disease), as HBV-DNA may show wide fluctuations in such cases
 - only one type of assay should be used for monitoring in the same individual, and if a change of assay is planned, both tests should be used in parallel for at least two subsequent samples
 - tests should preferably be quantitative, have a high sensitivity and cover a wide range of quantification ($80\text{--}10^{10}$ IU/ml). Optimum tests are real-time nucleic acid amplification tests
 - tests should either be approved according to European regulations or validated in a similar way using internationally recognised standards, and should be able to detect isolates of different HBV genotypes
 - HBV-DNA assays should be performed in a laboratory that participates in external quality control
 - different tests produce different absolute results and this is why the thresholds given in these recommendations are only indicative. The reason is that there is no standardization of quantification units and the dynamic ranges of quantification of the different assays are only partially overlapping (these issues should be resolved with international units and real-time PCR assays).

5.2. Liver biopsy and other evaluations

In specific circumstances, additional evaluation is needed:

- Measurement of the stage of liver fibrosis and of necroinflammatory activity is essential to define the stage of disease and the risk of progression to clinically significant liver complications and is most useful when a decision to treat or not to treat has to be taken. The current gold standard for assessment is liver biopsy (BII).

- liver stiffness measurements or measurement of non-invasive markers of fibrosis can be considered alone or in combination to avoid performing a liver biopsy (CIII). These alternatives remain to be fully validated in the setting of HBV/HIV co-infection.
- Ultrasound examination of the liver that can reveal cirrhosis, steatosis and possibly early HCC.

5.2.1. Occult HBV infection

If only anti-HBc is present at the initial assessment, this may be indicative of 'occult' HBV infection. 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 people, but its clinical relevance is uncertain. Currently, there is no evidence for the need to routinely detect or treat occult HBV (CIII). However, occult HBV may become relevant in specific clinical settings. For example, if chemotherapy for cancer is initiated and there is a risk of reactivation, pre-emptive anti-HBV therapy may be considered (BIII). More research is needed before the clinical relevance of occult HBV can be fully established.

5.3. Treatment

5.3.1. Goals of therapy

The most ambitious goal of treatment for HBV is to achieve HBsAg clearance with anti-HBs seroconversion, but this endpoint can be reached only in a minority of patients (less than 10% of HBV mono-infected patients having received interferon treatment, and likely to be even less among HIV/HBV co-infected patients). A more realistic goal therefore is to efficiently and persistently suppress HBV replication to reduce liver inflammation and to stop or delay progression of fibrosis, thereby preventing the development of end-stage complications such as cirrhosis, decompensation, HCC and liver-related death (AII).

Drugs that are currently licensed in Europe for the treatment of HBV include standard IFN- α 2a and 2b and pegylated-IFN- α (PEG-IFN) 2a, lamivudine, and adefovir. All these drugs have antiviral activity, and IFN has additional immune modulatory effects. Tenofovir and emtricitabine are approved for HIV and are also active against HBV. Drugs under development with anti-HBV but not anti-HIV activity include entecavir, clevudine, telbivudine and a number of other compounds.

Data on the efficacy of some of these drugs in HIV/HBV co-infected individuals are still very limited and no large-scale randomised controlled trials have been conducted to define their efficacy and safety when used alone or in combination. Therefore, recommendations for the treatment of HBV in HIV co-infected patients need to be derived from what is known about the treatment of HBV mono-infected

patients, and from the limited data available in HBV/HIV co-infected patients.

5.3.2. When should treatment for HBV start?

Most cases of acute hepatitis B resolve spontaneously and do not need antiviral therapy (AII). In cases of acute fulminant hepatitis B, lamivudine-therapy should be considered despite the risk of selecting for lamivudine-resistant HIV (AIII). As other drugs with sole anti-HBV activity become available, these are likely to become the preferred approach rather than using lamivudine. Therapy with tenofovir or adefovir should be avoided because in most such cases, liver failure is often accompanied with renal failure (CIII).

In patients with HIV and chronic hepatitis B, the decision to treat or not to treat should be based as much as possible on an integrated evaluation of the diagnostic parameters described in Section 5.3.1 (AIII).

5.3.3. Candidates for treatment

The criteria to decide whether to treat include:

- HBV-DNA level.
- Liver disease activity and stage (derived from ALT profile, liver necroinflammatory activity and fibrosis assessment, when indicated).
- Careful evaluation of the presence of cirrhosis.

In HBV-HIV co-infected patients, the HBV-DNA threshold for starting therapy has not been defined.

In HBeAg-positive HBV mono-infected patients, HBV DNA >approximately 20,000 IU/ml is the cut off to indicate antiviral therapy, while a cut-off >approximately 2000 IU/ml is more often used for HBeAg-negative (anti-HBe-positive) patients. These thresholds can also be applied to co-infected patients (BIII).

5.3.4. Management and therapeutic options

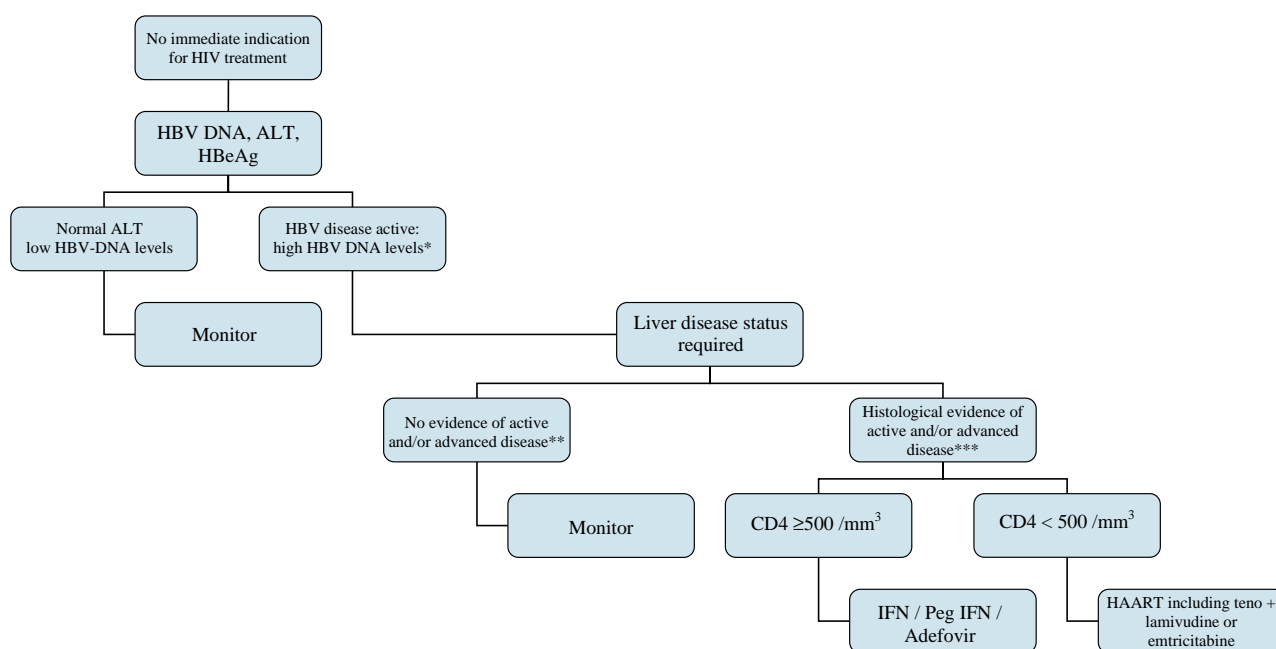
The diagnostic algorithm and the treatment options vary depending on different clinical scenarios that should take into consideration: HBV-DNA levels, severity of liver disease, CD4 count and indication for HAART, contraindications and previous treatments for HBV.

1. HBV/HIV co-infected patients with no immediate indication for HIV treatment (Fig. 1)

The decision to start anti-HBV therapy should be taken after obtaining evidence that liver disease is active and progressive (AIII).

When initiation of HAART is not indicated and HBV disease is mild and not (or slowly) progressing, the best current strategy may be to monitor the patients without treatment intervention (BIII). More data and the approval of new anti-HBV drugs without anti-HIV activity may, in the near future, allow more informed treatment decisions in these patients.

In patients with high HBV-DNA levels (> 20,000 IU/ml for HBeAg-positive patients and >2000 IU/ml for HBeAg-negative patients), the presence of liver inflammation and stage of liver fibrosis should be assessed by liver biopsy or



*HBV DNA >20,000 IU/ml for HBeAg positive patients and >2000 IU/ml for HBeAg negative patients.

** Metavir <A2 and/or <F2.

*** Metavir ≥A2 and/or ≥F2.

Fig. 1. Management and therapeutic options in HBV/HIV co-infected patients with no immediate indication for HIV treatment.

validated non-invasive markers, unless hepatic ultrasound is clearly indicative of cirrhosis (BIII).

In the presence of histological evidence of active and/or advanced disease (by liver biopsy this means moderate to severe inflammation and/or fibrous septa—Metavir \geq A2 and/or \geq F2) therapy is indicated (AII).

In HBV mono-infected patients, HBeAg positivity, elevated ALT, and/or infection with genotype A or B virus predict a better response to treatment with IFN (AI).

IFN-based therapy may be an option for HBV/HIV co-infected patients who do not need to start HAART (CD4 count $>$ 500 cells/mm³) (BII). As in the treatment of HBV mono-infected patients, the recommended dose and duration depend on HBeAg/anti-HBe status. Most recently Peg IFN has been licensed for hepatitis B and is becoming the standard therapy. PEG-IFN 2a (180 μ g once weekly) should be given for 48 weeks independently of HBeAg/anti-HBe status (BIII). When using standard (not pegylated) IFN, HBeAg-positive patients should be treated with 5–6 MU/day or 10 MU three times weekly for 4–6 months (BIII). HBeAg-negative patients should receive 3–6 MU three times weekly for at least 12 months (BIII).

Although the benefit of IFN therapy is expected to be higher in HBeAg-positive patients, anti-HBe-positive patients can also be treated with IFN, particularly when ALT levels are persistently elevated, but the likelihood of sustained response is lower (BIII).

IFN-based therapy should be used as a finite course of therapy and a favourable response defined by sustained (off therapy) anti-HBe seroconversion in initially HBeAg-positive patients, and by sustained (off therapy) ALT normalisation and HBV-DNA suppression ($<$ 2000 IU/ml) in initially HBeAg-negative patients (AII).

These recommendations are largely derived from data obtained in HBV mono-infected patients due to the very

limited and incomplete information on the effect of IFN therapy in HBV/HIV co-infected patients.

In patients with CD4 count $>$ 500 cells/mm³ and with contraindications to the use of IFN (including those with advanced liver disease and cirrhosis, those who do not tolerate IFN and IFN non-responders), adefovir at a dose of 10 mg daily (the dose currently used in the treatment of HBV mono-infected patients and thought to have no activity against HIV) may be an option. However, this is controversial due to the theoretical risk of inducing HIV resistance (CIII). In this scenario, the use of drugs with potent antiviral activity solely against HBV and no activity against HIV (such as entecavir, telbivudine) may be the best solution when these agents become available.

In patients with a CD4 count lower than 500 cells/mm³ the best option is to consider earlier initiation of HAART including two drugs with dual activity against both HBV and HIV (tenofovir plus either lamivudine or emtricitabine) (BIII).

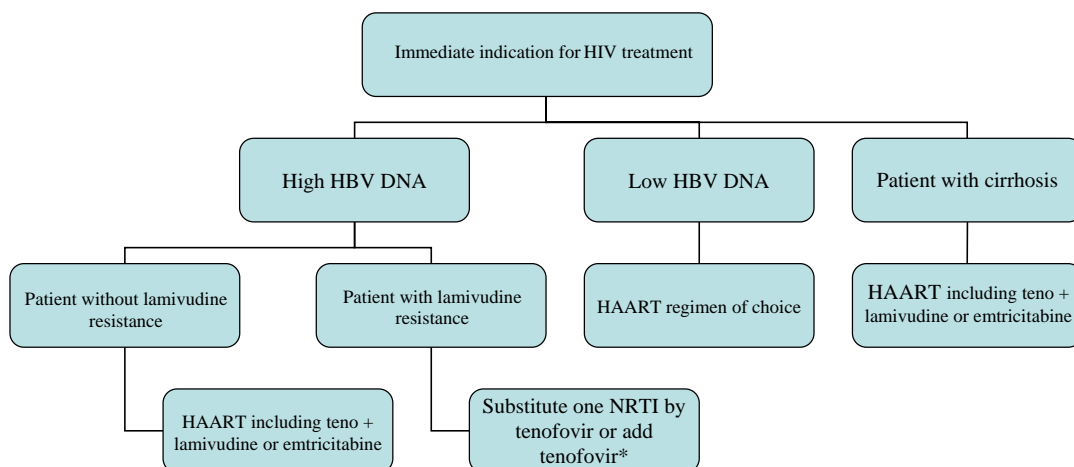
Monotherapy using drugs with activity against HIV must be avoided (AI).

Current research in HBV suggests that, as in HIV, combination therapy reduces the risk of selecting for resistance. Avoidance of monotherapy for HBV may thus be equally important.

2. HBV/HIV co-infected patients with an indication for anti-HIV therapy (Fig. 2)

In this scenario, the decision on how to treat should be based mainly on HBV-DNA levels, without a stringent need for measurement of the liver necroinflammatory activity and stage of fibrosis. Liver biopsy may be useful to assess the stage of disease at baseline to allow meaningful follow-up of the disease course (CIII).

If HBV-DNA is high ($>$ 2,000 IU/ml), HAART including two drugs with dual anti-HBV and anti-HIV activity is recommended (AIII).



*If feasible and appropriate from the perspective of maintaining HIV suppression.

Fig. 2. Management and therapeutic options in HBV/HIV co-infected patients with an indication for anti-HIV therapy.

In patients with low HBV-DNA levels (<2000 IU/ml), the recommendation is to initiate the HAART regimen of choice (it is optional to use a HAART regimen containing two dual-activity drugs) (CIII).

3. HBV/HIV co-infected patients with lamivudine-resistant HBV requiring HBV therapy

In the presence of suspected lamivudine-resistance, the first step is to confirm the lamivudine resistance in HBV (BIII).

If confirmed, we recommend a HAART regimen that has maximal activity against both HIV and HBV. If HIV is already controlled substitute one of the nucleoside reverse transcriptase inhibitors (NRTIs) with tenofovir, if feasible and appropriate from the perspective of maintaining HIV suppression (BIII). If HIV is not controlled, tenofovir can be added in the context of currently accepted practices for management of HAART treatment failure (AIII).

4. HBV/HIV co-infected patients with cirrhosis

In these cases, the HBV-DNA threshold for starting therapy for HBV is lower (>200 IU/ml) (BIII). IFN-based therapy is rarely indicated and often contraindicated due to the very poor tolerability profile (DIII).

The risk of severe reactivation of hepatitis B during immune reconstitution after starting HAART, with life-threatening hepatitis flare, should be considered in this setting, particularly when CD4 counts are <200 cells/mm³. In this specific situation, and particularly in the presence of high baseline HBV-DNA levels, reduction of HBV-DNA levels may be preferred before starting HAART to reduce the likelihood of immune reconstitution. However, given the lack of available drugs with sole anti-HBV activity, this cannot currently be done safely. Furthermore, an induction treatment with two drugs with dual activity against HBV and HIV carries the risk of selecting drug-resistance in HIV, particularly in those with high HIV-RNA levels. For these reasons, initiation for full HAART regimens in this setting remains the preferred approach (BIII).

Some experts believe that adefovir (10 mg daily) should be considered in these cases but this approach is controversial, as stated above (CIII).

In this scenario, the use of drugs with potent antiviral activity solely against HBV and no activity against HIV may be the best solution in the near future.

In patients with decompensated liver cirrhosis (Child Pugh stage B or C), (E1) liver transplantation, where

Table 2 Future research

General

As the transmission of HIV, HBV and HCV continues to expand across the European continent, there is a clear and important need to enhance efforts to prevent and control these infections

Studies addressing the optimal time—during the course of chronic HIV infection—to commence antiretroviral therapy in HBV and HCV co-infected patient should be initiated

Studies on the epidemiology and the social impact of HBV and HCV in patients infected with HIV should be actively investigated, with a special emphasis on vulnerable populations

Phases II and III trials of new drugs should be performed in HIV/HBV and HIV/HCV co-infected patients as a priority due to the accelerated course of the hepatitis infections in these populations

As the current therapies are suboptimal—in terms of efficacy, tolerability and quality of life—the development of new drugs to circumvent these issues should be actively pursued

Studies to validate the utility of non invasive methods of liver disease progression should be performed

HCV/HIV co-infection

Studies on the use of maintenance therapy in patients with no SVR and with advanced liver disease are strongly recommended (including evaluation of optimal dose and duration of treatment)

The optimal ribavirin dose for treatment of HCV genotype 1 and the potential benefits of prolonged treatment should be investigated

A shorter duration of treatment for patients with HCV genotype 2 and 3 should be investigated

Long-term follow-up studies of patients with and without SVR are strongly encouraged (to determine late relapses, duration of histological improvement, and the effect of clinically relevant outcomes such as decompensation, HCC and death)

Studies on pathophysiology, including extrahepatic viral reservoirs and the specific immune response to HCV, should be conducted

The optimal treatment for acute HCV infection in HIV-infected patients should be investigated

HBV/HIV co-infection

Better understanding of the pathogenesis and mechanisms of HBV-related liver damage in HIV co-infected patients is needed

Prevalence, diagnosis and clinical significance of HBV genotypes and of occult HBV in HIV patients should be investigated

The significance and threshold (if any) of HBV-DNA serum levels in relation to liver disease activity and progression and indication for anti-HBV therapy should be better defined in HIV co-infected cases

The efficacy, safety and tolerability of PEG-IFN and the optimal treatment schedule for HBV treatment in HIV co-infected patients need to be investigated in clinical studies of adequate design and size

Correlates of disease progression and treatment response need to be identified—including the predictive value of viral load, the effect of anti-HBV therapy on liver disease: biopsy or non-invasive markers, the impact of long-term treatment on HBsAg clearance and intrahepatic cccDNA, the impact of HBV drug resistance on liver disease, and the role of cross-resistance testing in patients with HBV treatment failure

The value of combination versus monotherapy should be evaluated

The prevalence and natural history of HBeAg-negative chronic hepatitis C in HIV co-infected patients should be better defined

The impact of HBV treatments on liver-related morbidity and mortality in HIV patients receiving HAART needs to be understood

feasible, should be the primary treatment option for patients (CII).

5.3.5. Monitoring and assessment of response

A clinically relevant response to anti-HBV therapy is defined as a durable anti-HBe seroconversion in initially HBeAg-positive patients, and as a durable normalisation of ALT and adequate (<2000 IU/ml) and durable HBV-DNA suppression in initially HBeAg-negative patients.

When using nucleotide and nucleoside analogues with anti-HBV activity, an initial response is defined as at least 1 \log_{10} drop in HBV-DNA levels within 1–3 months. HBV-DNA should then be measured every 3 months. The extent of treatment efficacy is measured by the \log_{10} HBV DNA reduction or by HBV DNA negativation below the lower limit of detection of the assay.

Resistance should be suspected in compliant patients if HBV-DNA levels increase by 1 \log_{10} or more. Where available, resistance testing should be performed.

5.3.6. Treatment discontinuation

Discontinuation of anti-HIV drugs with additional activity against HBV has to be approached with caution. Resistance of HIV and HBV are separate and independent. Stopping the anti-HBV treatment can result in potentially fatal hepatitis flares, particularly in patients with more advanced liver disease, and should therefore be avoided whenever possible (EII). Patient counselling is important to avoid discontinuation of effective anti-HBV drugs.

6. Future studies and recommendations

A wide variety of unresolved issues exist in the management of patients co-infected with hepatitis B or C

and HIV. During the conference, a number of potential areas for future research were identified (Table 2).

7. Consensus Development Conference Committees

Presidents: Y. Benhamou (France), D. Salmon-Ceron (France).

International Organising Committee: J.M. Pawlotsky (France), J. Rockstroh (Germany), V. Soriano (Spain).

Local Organising Committee: Patrice Cacoub (France), Gilles PIALOUX (France).

Scientific Committee: M. Battegay (Switzerland), M. Carneiro de Moura (Portugal), M. Colombo (Italy), M. Dupon (France), G. Dusheiko (UK), R. Esteban (Spain), B. Gazzard (UK), A. Hatzakis (Greece), A. Horban (Poland), C. Katlama (France), J. Lange (Netherlands), M. Manns (Germany), P. Marcellin (France), S. Mauss (Germany), M. Puoti (Italy).

Experts: M. Alter (USA), J.M. Pawlotsky (France), M. Koziel (USA), T. Poynard (France), M. Puoti (Italy), S. Pol (France), J. Rockstroh (Germany), A. Hatzakis (Greece), X. Forns (Spain), N. Afdhal (USA), P. Yeni (France), M. Nunez (Spain), A. Craxi (Italy), D. Thomas (USA), G. Dusheiko (UK), V. Soriano (Spain), M. Sulkowski (USA), F. Zoulim (France), R. Chung (USA), S. Mauss (Germany), M. Buti (Spain), C. Perronne (France), M. Guarinieri (Italy), G. Brook (UK), G. Gaeta (Italy), J.M. Miro (Spain), R. Bruno (Italy), M. Manns (Germany).

Jury Panel: Alfredo Alberti (Italy) (President), Nathan Clumeck (Belgium) (President), Simon Collins (UK), Wolfram Gerlich (Germany), Jens Lundgren (Denmark), Giorgio Palù (Italy), Peter Reiss (Netherlands), Rodolphe Thiebaut (France), Ola Weiland (Sweden), Yazdan Yazdanpanah (France), Stefan Zeuzem (Germany).

Bibliographic group: C. Nuria (Spain), L. Piroth (France), M. Rumi (Italy), M. Vogel (Germany).