European AIDS Clinical Society

Guidelines

Clinical management and treatment of chronic hepatitis B and C co-infection in HIV-infected adults

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These Euroguidelines result from the short statement of the first European Consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. J Hepatol 2005; 42:615-624, the updated recommendations from the HCV-HIV International Panel (Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, Mauss S, Bräu N, Hatzakis A, Pol S, Rockstroh J. Care of patients coinfected with HIV and hepatitis C virus: 2007. AIDS. 2007;21:1073-1089), the previous recommendations from the hepatitis panel of the European AIDS Clinical Society (JK Rockstroh, S Bhagani, Y Benhamou, R Bruno, S Mauss, L Peters, M Puoti, V Soriano, C Tural and the EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. HIV Medicine 2008; 9, 82–88) and from a discussion with the following panel:

Panel Members

Jürgen Rockstroh,
Bonn, *Germany*
Chair

Yves Benhamou,
Paris, *France*

Sanjay Bhagani,
London, *United Kingdom*

Raffaele Bruno,
Pavia, *Italy*

Diego García,
Alicante, *Spain*

Stefan Mauss,
Duesseldorf, *Germany*

Lars Peters,
Copenhagen, *Denmark*

Massimo Puoti,
Brescia, *Italy*

Vicente Soriano,
Madrid, *Spain*

Cristina Tural,
Barcelona, *Spain*

and the EACS Executive Committee

General recommendations for counselling in patients with HIV and hepatitis co-infection

SCREENING

1. All HIV-infected patients should be screened for hepatitis C at diagnosis and then on an annual basis. Screening for HCV in HIV infected patients should be done using anti-HCV antibody test. A positive result should be followed by evaluation for the presence of HCV-RNA and the genotype should be determined. Patients with risk factors (ongoing IVDU, mucosal traumatic sex; ongoing unprotected anal intercourse, recent sexually transmitted infection) with unexplained increase in hepatic transaminases and a negative HCV antibody test should be offered an HCV-RNA test for early detection of a recent infection.
2. HIV-infected patients should be screened for hepatitis A and B. Patients from high prevalence countries for HBV, in particular those with elevated liver transaminases should be screened for HBV-DNA in addition to HBs Ag to rule out occult HBV infection.
3. Hepatitis delta antibodies should be screened for in all HBsAg+ patients.
4. Patients with liver cirrhosis should be screened at 6-monthly intervals with serum alpha-fetoprotein and hepatic ultrasound for the occurrence of hepatocellular carcinoma. Routine screening is also advised for oesophageal varices at the time of diagnosis and at 1 – 2 year intervals thereafter.

VACCINATION

5. Patients lacking anti-HAV IgG antibodies or anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection regardless of their CD4-count. The response to the HBV vaccine is influenced by the CD4-count and level of HIV-RNA. In patients with low CD4-counts (<200/µl) and ongoing HIV replication, HAART should be initiated first prior to respective vaccination. Patients 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).

   In case of insufficient response (anti-HBs < 10 IU/l) revaccination should be considered. Double dose revaccination (40µg) at 3-4 vaccination time points (months 0, 1, 6 and 12) may help to improve response rates to HBV vaccination. Patients who fail to seroconvert after hepatitis B vaccination and remain at risk for HBV-infection should have annual serological tests for evidence of HBV infection.

HAART:

6. Hepatitis B and/or C co-infected patients benefit from early HAART because liver fibrosis progression is reduced with immune reconstitution and suppression of HIV-RNA. Stopping HAART has been associated with enhanced risk for AIDS and non-AIDS related events in the SMART study and this risk was enhanced for patients with hepatitis co-infection. Particular prudence is warranted in HIV/HBV co-infected patients who stop anti-HBV containing HAART.

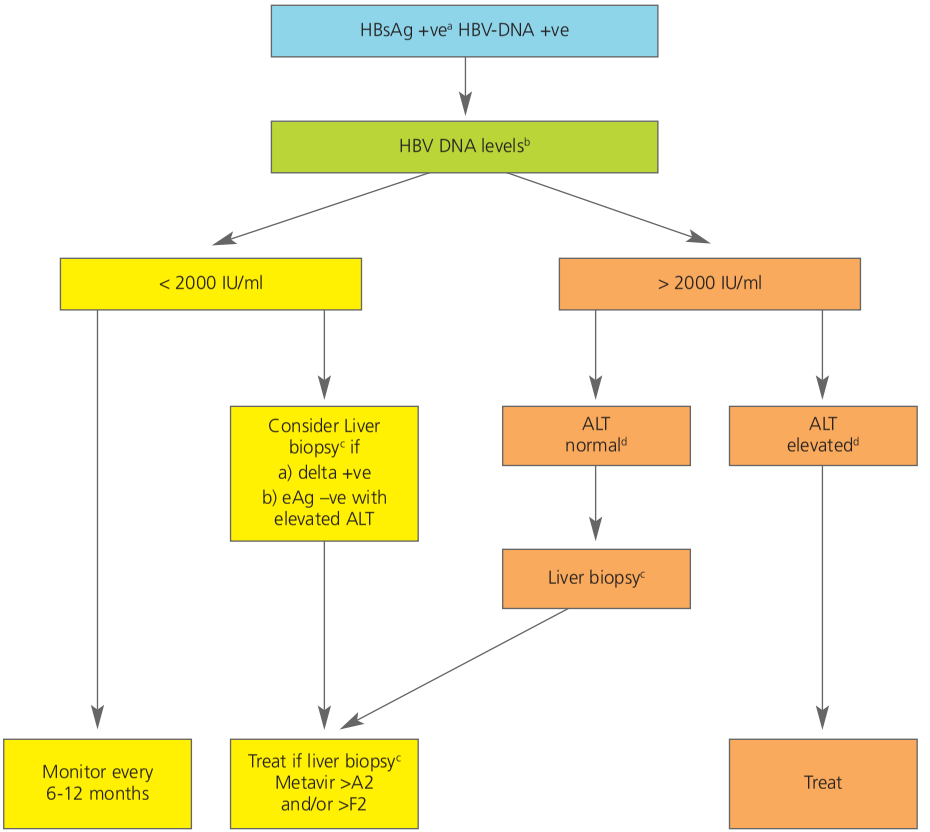
END STAGE LIVER DISEASE (ESLD):

7. HIV-positive patients require the same measures for the treatment of oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or ascites as HIV-negative patients.
8. HIV-coinfected patients who suffer from ESLD warrant particular attention in the management of liver insufficiency. Apart from considerations of treatment of HBV or HCV, antiretrovirals metabolized via the liver may need to be dose adjusted and in individual cases therapeutic drug monitoring of the respective drug is advisable.
9. Creatinine clearance using Cockcroft Gault estimation in the setting of advanced or decompensated liver cirrhosis overestimates the true glomerular filtration rate and use of the arithmetic mean urea and creatinine clearance or inulin clearance is recommended.
10. Patients with a MELD-score > 15, CD4-cell count > 100/µl and options for efficacious and durable HAART should be evaluated for liver transplantation (OLTX). OLTX outcomes in HIV/HBV coinfected patients are particularly promising, whereas post-transplant survival in HIV/HCV co-infected patients has been somewhat lower than in HCV-monoinfected patients mainly due to the complicated course of HCV re-infection after transplantation.

PREVENTION/SUPPORT

11. Psychiatric, psychological, social and medical support should be made available to patients with a high alcohol intake to stop drinking or to limit alcohol consumption.
12. Substitution therapy (opioid replacement therapy) in patients with active drug abuse as a step towards cessation of active drug use should be considered; help provided (e.g. through needle- and syringe-exchange programs) reduces the risk of re-infection including parenteral viral transmission (harm reduction strategy).
13. Since HBV and HIV and occasionally HCV are transmitted sexually, adequate counselling including the use of condoms is advisable. Information on the risk of HCV transmission due to mucosal traumatic sexual practices associated with a high likelihood of blood contact should be provided and risk reduction should be discussed.

Figure 1: Assessment of treatment indication for HBV infection in HIV-positive individuals



a) Chronic HBV-infection defined as HBsAg or HBV-DNA positive > 6 months

b) Serum HBV-DNA levels have been demonstrated to be associated with a linear increased risk for development of liver cirrhosis and HCC; please note that the conversion from copies to IU/ml varies depending on which test assay was used; in general 1 IU/ml equals around 5 copies or genome equivalents; one picogram HBV-DNA equals $2{,}8 \times 10^5$ genome/ml

c) Patients with replicating HBV and normal liver enzymes may have significant liver damage, therefore consider assessment of liver damage; this may be done using either liver biopsy or non invasive tools, including serum fibrosis markers or FibroScan. Non invasive methods for the evaluation of liver fibrosis are not fully validated in patients with Hepatitis B (especially in those with normal liver enzymes) and proposed cut offs are not the same as identified in patients with hepatitis C. While liver biopsy may provide additional information on inflammation and other lesions (e.g. steatosis), non-invasive markers can be used at more frequent intervals.

d) Please note normal ALT is < 19 IU/l for women, and < 31 IU/l for men

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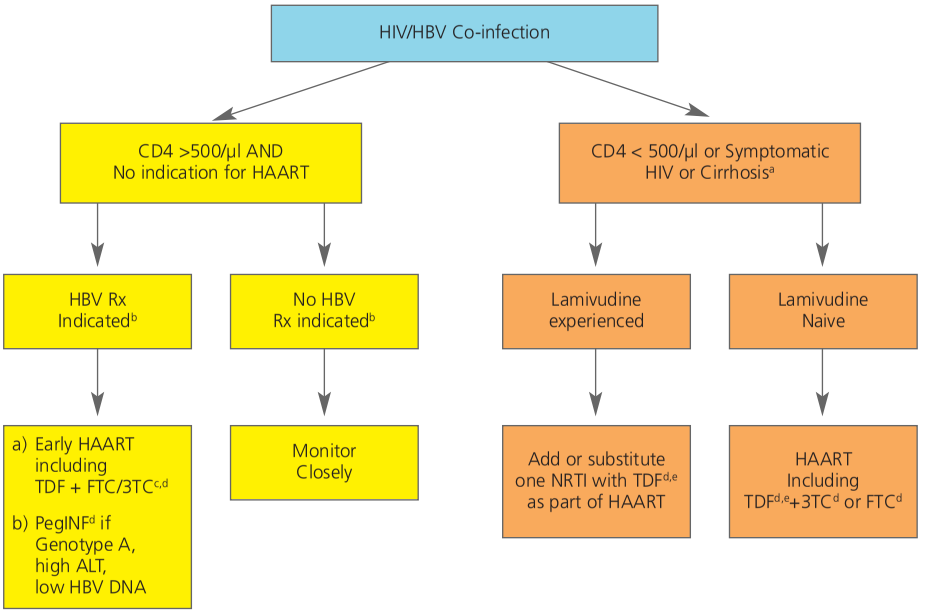
Figure 2: Treatment of chronic HBV infection in HIV-positive individuals



a) Cirrhotic patients should be referred for variceal assessment, have regular HCC monitoring and should be referred early for transplant assessment. Patients with liver cirrhosis and low CD4-counts require careful surveillance in the first months after starting HAART in order not to overlook immune-reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes.

b) See Figure 1 for assessment of HBV Rx indication. Some experts strongly believe that any HBV-infected patient requiring HAART should receive TDF + 3TC or FTC unless history of TDF intolerance, particularly in HIV/HBV co-infected patients with advanced liver fibrosis (F3/F4).

c) Antiretroviral naïve Asian, HBe-Ag+, HIV coinfected patients initiating HAART with TDF or TDF+FTC reached unexpected high rates of HBe (and even HBs) seroconversion, strengthening the rationale for early HAART. If a patient is unwilling to go on early HAART, adefovir and telbivudine may be used as an alternative to control HBV alone. A recent case report suggested possible anti-HIV activity of telbivudine. In-vitro data using an assay which was able to demonstrate anti-HIV-activity of entecavir however, failed to detect an influence of telbivudine on the replicative capacity of HIV-1.

d) Treatment length: 48 weeks for Peg-INF; recent data suggests that on-treatment quantification of HBsAg in patients with HBeAg-negative chronic hepatitis B treated with Peg-INF may help identify those likely to be cured by this therapy and optimize treatment strategies. The optimal treatment duration for nucleos(t)ide analogues with anti-HBV activity has not yet been determined and experts recommend life-long therapy if anti-HBV nucleos(t)ides are given as part of HAART. Patients not requiring HAART and on treatment with telbivudine +/- adefovir, or those on HAART where nucleoside back-bone needs changing, anti-HBV therapy may be stopped cautiously in HBeAg+ patients who have achieved HBe-seroconversion for at least six months or, after confirmed HBs-seroconversion in those who are HBeAg-. In patients with liver cirrhosis a stop of effective anti-HBV treatment is not recommend to avoid liver decompensation due to flares of liver enzymes.

e) In some cases of tenofovir intolerance (i.e. renal disease), entecavir + adefovir or tenofovir in doses adjusted to renal clearance in combination with effective HAART may be advisable. NRTI substitution should only be performed if feasible and appropriate from the perspective of maintaining HIV suppression. Caution is warranted to switch from a tenofovir based regimen to drugs with a lower genetic barrier, e.g. FTC/3TC, in particular in lamivudine pretreated cirrhotic patients as viral breakthrough due to archived YMDD mutations has been observed. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from tenofovir to entecavir.

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Clinical Management and Treatment of Chronic Hepatitis B & C

Treatment recommendations for therapy of hepatitis C in HIV co-infection

1. HCV treatment 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 co-infected patient should therefore be considered for treatment when the benefits of therapy outweigh the risks. This also needs to be seen in the context of faster liver fibrosis progression in HIV/HCV co-infection and with better HCV treatment outcome with improved management in these patients.
2. Information on liver fibrosis staging is important for making therapeutic decisions in co-infected patients. However, a liver biopsy is not mandatory for considering treatment of chronic HCV. Current therapy is particularly recommended in patients with a high likelihood of achieving sustained virological response (SVR): genotypes 2 or 3 and patients infected with genotype 1 if the viral load is low (<400.000 IU/ml). More recently, insulin resistance (which can be determined using the homeostasis model assessment of insulin resistance HOMA IR) has been repeatedly reported as a negative predictor of achievement of SVR and therefore may also be considered during pre-treatment evaluation and, if possible, should be effectively managed before treating HCV infection.
3. In case of the availability of a liver biopsy or FibroScan demonstrating lower stages of liver fibrosis (F0-1), regardless of HCV genotype, treatment can be deferred. In these cases, fibrosis assessment should be carried out at frequent intervals to monitor for fibrosis progression. A liver disease stage assessment is especially important to perform in patients with a low chance of SVR.
4. The combination of Peg-INF alpha and ribavirin (RBV) is the treatment of choice for HCV infection. The standard dose for Peg-INF 2a is 180 µg once weekly, and for Peg-INF 2b it is 1.5 µg/kg bodyweight once weekly. An initial weight adapted dose of RBV of 1000 (wt ≤ 75kg) - 1200 (wt > 75kg) mg/day (administered bid) is recommended for all HCV genotypes in the HIV setting.
5. The primary aim of anti-HCV treatment is sustained virological response defined as undetectable serum HCV-RNA 24 weeks after the end of therapy, evaluated using sensitive molecular tests.
6. If chronic hepatitis C is detected early in the course of HIV infection (before the initiation of HAART is necessary), treatment for chronic HCV is advised. However, if a co-infected patient has significant immunodeficiency (CD4 count < 350 cells/µl), the CD4 count should be improved using HAART prior to commencing anti-HCV treatment. Patients with a CD4 relative percentage >25% are more likely to achieve SVR than lower CD4 percentage.
7. If an early virological response (decline of at least 2 log10 reduction in HCV-RNA at week 12 compared to baseline) is not achieved, treatment should be stopped (figure 3).
8. During Peg-INF plus ribavirin therapy, ddI is contraindicated in patients with cirrhosis and should be avoided in patients with less severe liver disease. D4T and AZT should also be avoided if possible. The role of abacavir is uncertain at this point but cohort data suggests lower SVR results in patients receiving abacavir containing HAART. Data investigating RBV plasma levels have shown that the interaction between abacavir and ribavirin may be negligible if weight based ribavirin is used.
9. In patients with acute HCV infection, HCV therapy is recommended if HCV-RNA is confirmed positive (1 week apart) by week 12 post HCV transmission, as SVR rates following treatment of acute HCV-infection are higher than for treatment of chronic HCV. Most experts recommend therapy for 24 weeks with Peg-INF and ribavirin; however the duration of therapy and use of ribavirin is currently under discussion. HCV-RNA levels at week 4 and 12 may help to guide treatment duration.

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Table 1: Diagnostic procedures for hepatitis C in HIV co-infection

Diagnosis of hepatitis C
HCV-Ab (positive 1-5 months after infection, may rarely be lost with immunosuppression)
HCV-RNA levels[a] (in particular important for the prediction of response to treatment)
Status of liver damage
Grading of fibrosis (e. g. FibroScan, liver biopsy, serum fibrosis markers[b])
Hepatic synthetic function (e. g. coagulation, albumin, CHE)
Ultrasound and AFP every 6 months in cirrhotics (gastroscopy upon diagnosis of cirrhosis and every 1-2 years thereafter)
Before HCV treatment
HCV genotype and serum HCV-RNA
Autoantibodies (ANA, LKM1)[c]
TSH, thyroid autoantibodies
Monitoring of HCV treatment
Differential blood count and liver enzymes every 2-4 weeks
HCV-RNA at week 4 (to evaluate rapid virological response),and weeks 12, 24, and 48 (72 if applicable) and 24 weeks after stopping HCV therapy
CD4-count every 12 weeks
TSH every 12 weeks

a) Low viral load defined as less than 400,000 – 500,000 IU/ml when using PegINF+RBV. There is no standard conversion formula for converting the amount of HCV-RNA reported in copies/ml to the amount reported in IU/ml. The conversion factor ranges from about one to five HCV-RNA copies per IU/ml.
b) Serum fibrosis markers include APRI, FIB-4, Hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices; recently more complex tests such as Fibrometer, Fibrotest and Hepascore have shown to more accurately predict liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.
c) Patients with positive anti LKM or ANA with homogeneous pattern should be evaluated for concurrent autoimmune hepatitis especially in the presence of ALT elevation during treatment.

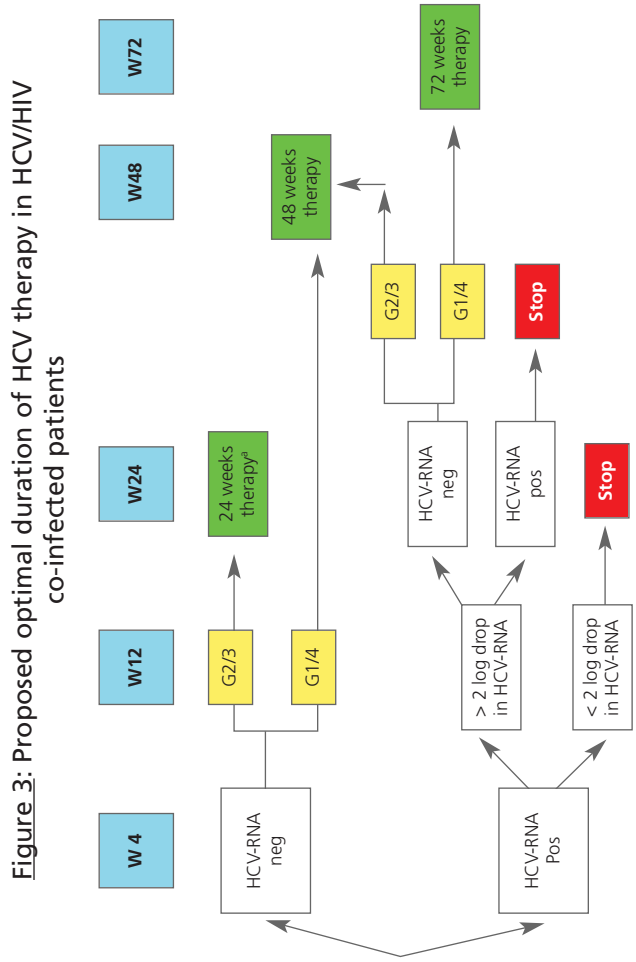

Figure 3: Proposed optimal duration of HCV therapy in HCV/HIV co-infected patients

a) In patients with baseline low viral load (<400 000 IU/ml) and minimal liver fibrosis.

Table 2: Classification of and interventions for HCV/HIV-co-infected non-responders/ relapsers to prior interferon-based therapies

CATEGORY	SUBGROUP	SUGGESTED INTERVENTION
Suboptimal treatment	Suboptimal schedule • Interferon (monotherapy or with ribavirin) • Low ribavirin dose • Short length of therapy	Re-treatment using combination therapy with Peg-INF plus weight-based ribavirin dosing
	Limiting toxicities & poor adherence	Optimal support (SSRI, paracetamol/ NSAID, adherence support, use of hematopoietic growth factors[a])
Optimal treatment with virological failure	Relapse (HCV-RNA negative at the end of treatment)	Re-treatment using combination therapy with Peg-INF plus weight-based ribavirin dosing (consider longer treatment duration)
	Non Response (no HCV-RNA negativization during treatment)	Wait until new antivirals become available either through clinical trials or are licensed.

a) Data on the use of hematopoietic growth factors in HIV/HCV co-infection so far is limited to an improvement in quality of life but not antiviral efficacy; treatment with growth factors is currently mostly off-label in Europe.