18. HIV and HBV/HCV Coinfections
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HIV and HCV Coinfection

Epidemiology and transmission

Coinfection with HIV and HCV occurs frequently, due to the fact that both are transmitted via the same pathways (parenteral, sexual, vertical). 240,000 people (30% of HIV-infected individuals) are estimated to be infected with both viruses in the USA.

Several European countries have even higher rates of coinfection. In Spain, at least 50% of the 130,000 HIV-infected patients are also HCV-positive as a result of the high incidence of i.v. drug users. More than 90% of coinfected individuals are positive for HCV RNA, i.e. have chronic hepatitis C.

As HCV is ten times more infectious than HIV on blood-to-blood contact, intravenous drug users and recipients of blood products are particularly susceptible to coinfection. For example, on routine testing of blood products from HIV-infected hemophiliacs treated before the discovery of HCV in the early nineties, HCV antibodies and HCV RNA were detected in the serum of over 90% of patients. The probability of transmission from needlestick injuries after exposure to HCV-contaminated blood is 2–8%, compared to only 0.3% after exposure to HIV-contaminated blood.

In contrast, sexual transmission of HCV occurs significantly less frequently than HBV or HIV. As a result, HCV is rare in homosexual men and coinfection is more seldom in this group. However, recently there have been reported clusters of cases of acute hepatitis C among homosexual HIV-positive men, clearly indicating that HCV can be sexually transmitted. The risk of transmission probably depends on the number of sexual partners and the performance of sexual practices that are prone to injuries. In total, about 4–8% of all HIV-infected homosexuals are also infected with HCV.

Perinatal transmission of hepatitis C is rare in immunocompetent individuals (<1%). The transmission rate rises with increasing immunosuppression in HIV-positive mothers, and is estimated to be as high as 20%. On the other hand, HIV-positive mothers treated effectively with HAART do not appear to have an increased risk for materno-fetal transmission of the hepatitis C virus (in combination with cesarean section; Pembreya 2005).

Clinical course and pathogenesis

Course of hepatitis C in HIV/HCV-coinfected patients

The clinical course of hepatitis C and HIV coinfection is determined by the HIV-associated immunosuppression. Progression of immunosuppression accelerates the course of hepatitis C. This was first shown in data from the American Multicenter
Hemophilia Cohort Study (MHCS), in which 10% of adult hemophiliacs with HCV coinfections developed hepatic failure after a latent period of 10–20 years, even before the onset of AIDS-defining opportunistic infections or neoplasms (Eyster 1993). Rapid progression of liver disease was found particularly in patients with CD4+ T-cell counts below 100/µl. In the group of HIV-negative but HCV-positive patients, there was not a single case of liver failure during the same period of observation. In this group, the latent period until liver failure or hepatocellular carcinoma develop is estimated to be 30–40 years. Several studies, some of which included histological analyses, have confirmed the accelerated course of hepatitis C with concurrent HIV infection.

The improved treatment options for HIV infection have increased the likelihood of patients actually living to experience the development of liver failure. The associated decrease in mortality with HIV infection has resulted in a relative increase in hepatitis-associated mortality. In some centers, liver failure is now the most frequent cause of death in HIV-infected patients. This, together with the accelerated course of hepatitis C with HIV coinfection, has led many experts to regard hepatitis C as an opportunistic infection.

**Course of HIV infection in HIV/HCV-coinfected patients**

Studies, that determined the influence of hepatitis C on HIV infection, yielded contradictory results at first. The Swiss Cohort Study identified hepatitis C as an independent risk factor for the more rapid progression of HIV infection to AIDS and death. This phenomenon could not be explained by less frequent use or poorer tolerability of HAART, but was due to a diminished rise in CD4+ T-cells in HIV patients with concurrent hepatitis C. However, long-term follow-up could not certify this difference further. In other studies (e.g. Johns Hopkins Cohort, EuroSIDA), hepatitis C did not influence the probability of progression of HIV infection, especially after correction for the use of and response to HAART (Rockstroh 2005). Taken together, extended follow-up of different cohorts could not show a significant influence of hepatitis C on the course of HIV infection.

**Course of hepatitis C with HAART**

The unfavorable course of hepatitis C in HIV infection can be improved by treatment of HIV infection with HAART. In addition, the development of liver failure can be delayed by the improved immune function under HAART. This is particularly true for patients who achieve a good immune recovery.

On the other hand, hepatitis C infection can aggravate the potential hepatotoxicity of several HAART regimens. Up to 10% of patients have to discontinue HAART due to severe hepatotoxicity. This risk is associated especially with the so-called “d-nucleosides” (ddI, ddC, d4T). These substances should be avoided in coinfected patients. Nevirapine and tipranavir should be used with caution.

In some coinfected patients, a temporary increase in transaminases is observed after initiation of HAART. This most likely corresponds to an increased inflammatory activity of hepatitis C as a result of the improved immune status. Nevertheless, long-term follow-up has shown that HAART improves the course of hepatitis C. Indications for HAART, according to current treatment guidelines, should be carefully checked in all coinfected patients.
Diagnosis

The diagnostic tests used in coinfected patients are no different from those used in patients with HCV monoinfection. Detection of HCV antibodies (anti-HCV) proves exposure to HCV, but does not distinguish between resolved and chronic hepatitis C. Chronic hepatitis C is diagnosed by the detection of HCV viremia (i.e. HCV RNA). It should be noted that HCV antibodies might be lost during the course of HIV infection as a result of the underlying immunosuppression, although nowadays this phenomenon has become rare, probably due to improved test kits. It may therefore be useful to determine HCV RNA levels, even if the anti-HCV test is negative, if there is clinical suspicion or advanced immunodeficiency. Similarly, determination of HCV RNA levels is indicated in cases of suspected acute (primary) HCV infection, as HCV antibodies usually only become detectable one to five months after infection.

Patients with HIV/HCV co-infection have significantly higher levels of HCV viremia than patients with HCV monoinfection (about 1 log). In parallel to an ongoing rise in viremia, the risk of perinatal or sexual transmission increases. However, the level of viremia does not have a prognostic value for the course of hepatitis C. Accordingly, regular testing of HCV-RNA as a routine clinical procedure is not necessary. However, it should be noted that some patients might lose HCV-RNA in parallel to progression of immune deficiency, but experience a flare up of hepatitis C together with clinical symptoms following immune reconstitution under HAART. Therefore, regular testing around the initiation of HAART seems to be prudent.

It is possible to predict a response to treatment from the level of the HCV viremia: if the concentration of HCV RNA is below 800,000 IU/ml, the probability of treatment success is significantly higher than at levels above 800,000 IU/ml (800,000 IU/ml equals about 2 million copies/ml dependent on the test used).

When considering the treatment of hepatitis C, genotyping is necessary before starting. Six genotypes with numerous subtypes are known to date, and are seen to have different regional distributions: genotypes 1 and 3 are predominantly found in Europe, whereas genotypes 4 and 5 are found in Africa, and genotype 6 in Asia. They are mainly of prognostic value with regard to the response to treatment. Genotypes 2 and 3 in particular are associated with significantly better responses to interferon therapy. Coinfection with several genotypes is possible.

Transaminases, the parameters of cholestasis, and markers of the synthetic capacity of the liver (CHE, albumin, total protein, and coagulation factors) should be determined. They provide the same indication and interpretation indices as in patients without HIV infection.

The importance of taking liver biopsies before the initiation of HCV therapy is controversial, and there are no consistent recommendations based on results from clinical studies. On the one hand, it is thought that HCV therapy should only be administered if there is a histologically confirmed “absolute” indication for treatment, as it may be associated with numerous side effects, possible interactions with HAART and relatively low efficacy. On the other hand, it must be assumed that HCV therapy is almost always justifiable in coinfected patients, as the course of hepatitis C is accelerated and past studies have shown that progression to fibrosis or cirrhosis occurs in approximately half of all patients. In addition, liver biopsies need
to be repeated every 2 to 3 years due to the accelerated course of disease, and not all patients are prepared to go through with this. If a liver biopsy is not available, current consensus recommendations suggest treatment of hepatitis in case of genotypes 2+3, or genotype 1 and low HCV viremia. If a liver biopsy has been performed that shows no significant fibrosis, immediate treatment is usually not required regardless of the underlying genotype.

There are several histological classifications used. In Europe the METAVIR-Score is used most often. It distinguishes five stages of fibrosis (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = significant septa without cirrhosis, 4 = cirrhosis). Hepatitis activity is graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). Treatment is recommended for grades F2-F4; it may be deferred for grades F0+F1.

Before performing a liver biopsy, contraindications must be carefully considered. This is particularly important for hemophiliacs, who often cannot be biopsied (risk of hemorrhage!).

Several methods for non-invasive assessment of liver fibrosis have become available and are being used increasingly. Of special interest is the Fibroscan® device that measures liver stiffness directly correlated to the degree of fibrosis with a novel technique (transient elastography). Scientific data and clinical experiences have so far been very promising. Recommendations on the need for liver biopsy will probably change in the near future.

If there is clinical suspicion requiring the detection or exclusion of extrahepatic manifestations (vasculitis, glomerulonephritis, systemic cryoglobulinemia), appropriate investigations may be necessary (skin biopsy, urine tests, kidney biopsy, detection of serum cryoglobulins).

The recommendations for autoantibody testing to exclude autoimmune disease vary and test results are difficult to interpret: up to 60% of all patients with hepatitis C have autoantibodies such as ANA, RF, anticardiolipin, SMA, and LKM1 antibodies as an accompanying autoimmune phenomenon without any clinical relevance. If the titers of these autoantibodies increase or appear for the first time during interferon therapy, treatment does not usually have to be discontinued, and so the need for routine testing of autoantibodies is arguable. In order to exclude autoimmune hepatitis, however, ANA, SMA, ANCA, and LKM1 antibodies should be determined before interferon therapy is initiated. Patients with positive results should be monitored closely for deterioration of liver function on interferon therapy as a sign of active autoimmune hepatitis. If liver function worsens, interferon should be discontinued. The need for immunosuppressive therapy can only be decided on a case-by-case basis.

Before treatment with interferon, TSH levels should always be determined to exclude thyroid disease. With normal thyroid function, it is sufficient to monitor TSH at 12-weekly intervals. In cases of hypothyroidism, substitution with levothyroxine is recommended, and thyrostatic treatment is similarly recommended for hyperthyroidism before initiation of interferon therapy. After adequate treatment, interferon therapy can usually be administered under close monitoring of TSH (every 4 weeks). Approximately 5% of patients develop thyroid dysfunction on interferon therapy. This generally manifests within the first 3 months of treatment. If hypothy-
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Hyperthyroidism is induced, interferon therapy can usually be continued in combination with substituted levothyroxine. The first manifestation of hyperthyroidism is enough cause for most authors to discontinue treatment, although even here it may be possible to continue interferon therapy in certain cases. In the majority of patients, thyroid dysfunction resolves after discontinuation of interferon. However, it may also persist, and therefore cases need to be considered individually.

Up to 12% of patients with hepatitis C have thyroid autoantibodies before treatment with interferon (antibodies against thyroid peroxidase = anti-TPO, antithyroglobulin antibodies and TSH receptor antibodies). In these patients, the risk of a deterioration in thyroid function on interferon is significantly higher than in patients without these antibodies. If possible, autoantibodies should be determined in all patients before beginning treatment, but at the very least in those patients with abnormal TSH levels, in order to have a baseline value to allow subsequent monitoring.

**Therapy**

The goal of hepatitis C treatment is to achieve permanently negative HCV RNA levels. This is generally referred to as a sustained response. It is defined as a negative HCV RNA six months after completion of treatment.

Negative HCV RNA at the end of the treatment period is described as an end of treatment response. If transaminases have normalized, this is referred to as a biochemical response. However, the latter does not correlate with the further clinical course of hepatitis C and is therefore no longer used today. Failure to respond to treatment is referred to as a non-response.

In the following text, response rates always refer to sustained responses. This is because only sustained responses have been clearly associated with the resolution of liver fibrosis and extrahepatic manifestations, as well as with the prevention of further transmission.

When HCV RNA becomes detectable again after having been negative, it is referred to as a relapse. The probability of a relapse is highest within the first months following completion of treatment and decreases steadily afterwards. Therefore, the success of therapy is usually determined and evaluated six months after the end of treatment. In individual cases, relapses may occur at later time points, sometimes after years. Therefore, regular monitoring is advisable even following successful treatment (monitoring of transaminases; HCV RNA if there is reason to suspect a relapse).

Hepatitis C is treated with interferons and nucleoside analogs. Interferons are glycoproteins that protect cells from viral infection by inhibiting viral mRNA translation and reducing viral penetration and release. In addition, the immune reaction is influenced via modulation of cytokine profiles. The guanosine analog ribavirin is used as a nucleoside analog. Liver transplantation may be a possible option for patients who have cirrhosis and cannot be treated with interferon therapy.

The treatment of hepatitis C in HIV-infected patients differs in two main points from the treatment of hepatitis C in monoinfected patients: the response rates are lower due to the underlying immunodeficiency, and discontinuation of treatment as a result of side effects is more frequent.
Interferon monotherapy and combination treatment with standard interferon-α and ribavirin are no longer relevant. Response rates varying from 13 to 40 % and discontinuation of treatment in approximately 30 % of cases due to side effects were not satisfactory. Pegylated interferons henceforth have replaced standard interferons. These are bound to polyethylene glycol (PEG), in contrast to conventional interferons (i.e. interferon-α 2a or interferon-α 2b). Pegylation shields the interferon-α protein from enzymatic degradation, and thereby considerably lengthens its half-life. As a result, absorption of interferon is slower (producing less peak concentrations, which are associated with side effects) and a consistently high plasma level (with less low trough levels, during which efficacy could be reduced). Pegylated interferons can therefore be administered only once instead of three times weekly.

The combination of pegylated interferon with ribavirin is regarded as standard therapy in coinfected patients. Initial encouraging results have been found by the APRICOT study (AIDS Pegasys™ Ribavirin International Coinfection Trial), which is the largest published study in HIV/HCV-coinfected patients to date (Torriani 2004). A sustained response was achieved in 40 % after a treatment period of 48 weeks. Only 12 % of participants had to discontinue therapy due to adverse events. Particularly genotype 1, which is associated with a poor prognosis, showed a better response to this treatment (29 %) compared to the conventional interferon/ribavirin therapy. The more favorable genotypes 2 and 3 reached response rates of 62 %. Overall response rates, as well as response rates according to different genotypes, were significantly better than in the other two treatment arms: standard interferon-2a plus ribavirin (total: 12 %, genotype 1: 7 %, genotypes 2+3: 20 %) or pegylated interferon with placebo (total: 20 %, genotype 1: 14%, genotypes 2+3: 36 %). All patients were treated over a period of 48 weeks regardless of the genotype. Of special interest is the finding that the relapse rate at week 72 was only 2 % for genotypes 2+3, whereas relapse-rates of up to 50 % were associated with the former treatment period of 24 weeks. Therefore, genotypes 2+3 should also be treated for 48 weeks.

The superiority of PEG-interferon/ribavirin was confirmed in subsequent trials with even better response rates (e.g. PRESCO). Currently, several trials are addressing the question of whether shorter treatment periods are possible in HIV-coinfected patients if early treatment response is achieved at week 4.

Detailed information on interferon, PEG-interferon and ribavirin can be found in the section on Drug Profiles.

Concerns that interferon treatment could have a negative effect on HIV infection have not been confirmed in any study. In fact, there is further suppression of detectable HIV viremia in the majority of patients as a result of the antiviral effect of interferon. Absolute CD4+ T-cell counts may drop slightly due to temporary leukopenia, but percentage values usually rise. No treatment study to date has shown a significant deterioration of HIV infection (Soriano 2002).

The treatment options remain inadequate for patients with a non-response or relapse. In patients treated earlier with interferon monotherapy, an attempt can be made using a combination of PEG-interferon and ribavirin. There are currently no standard recommendations for treatment of patients after failed PEG-interferon therapy. In single patients, a triple combination of PEG-interferon, ribavirin and amantidine (2 x 100 mg/day) has been used successfully, although reliable data are
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not available. HCV-specific protease inhibitors and polymerase inhibitors, as well as other new substances, will add new options in the next years.

The management of acute hepatitis C also remains unclear. In patients with HCV monoinfection, early treatment with interferon α-2b within the first six months has shown excellent response rates (98 %!) (Jaeckel 2001), although subsequent analyses found lower response rates (approx. 80 %). Retrospective analyses in HIV-infected patients revealed response rates of more than 80 % (Vogel 2005). These data support early treatment even in the presence of HIV coinfection. At the moment, we treat patients with asymptomatic acute hepatitis C immediately, whereas patients with symptomatic hepatitis are followed for 12 weeks in order to await possible spontaneous clearance. If not cleared, we recommend treatment for a period of 24 weeks with peg-interferon alone for genotypes 2+3, and peg-interferon plus ribavirin for genotypes 1+4. However, the optimal strategy is unclear at the moment. If possible, patients should be treated within prospective clinical studies.

Practical tips for management of treatment

The following treatment recommendations have been compiled for HIV coinfection:

**Indications and contraindications**

As HIV coinfection accelerates the course of hepatitis C and increases the risk of hepatotoxicity after initiation of HAART, the indication for treatment should be determined in every patient with diagnosed HIV/HCV coinfection. The algorithm in Figure 1 (see below) can be used as a guide.

In particular, treatment should be discussed for cases with a bioptically confirmed fibrosis of grade F2-F4. Extra-hepatic manifestations of hepatitis C are also an indication for treatment (vasculitis, glomerulonephritis, systemic cryoglobulinemia). The following factors are associated with a more favorable response to treatment:

- HCV RNA < 800,000 IU/ml (+ genotype 1)
- HCV genotype 2+3
- Age < 50 years
- Histologically, low grade of fibrosis
- Normal γ-GT
- Stable HIV infection
- Female sex (currently being discussed; possibly insufficient dose adjustment for weight in heavier men)

In addition, contraindications should be evaluated. The most important are:

- Decompensated liver cirrhosis or history of decompensation (but not compensated cirrhosis, i.e. CHILD A cirrhosis!)
- Leukopenia (<1,500/µl)
- Thrombocytopenia (< 50,000/µl)
- Anemia (< 10 g/dl)
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- Severe, as yet untreated thyroid dysfunction
- CD4+ T-cell count < 200/µl (relative contraindication, see below)
- Severe psychiatric illnesses
- Symptomatic cardiac disease
- Active opportunistic infections
- Active drug or alcohol abuse
- HIV treatment with ddI (AZT and d4T should be avoided too)

Methadone or polamidone substitution is not a contraindication if good monitoring can be ensured during the treatment phase. However, patients with active drug or alcohol abuse should first be introduced to the appropriate programs.

In addition, the immune status of the patient and current antiretroviral therapy must be considered (see below).

If possible, HCV should be treated before HIV. Reasons for this include the increased hepatotoxicity of HAART with concurrent hepatitis C; possibly, impaired immune reconstitution resulting from hepatitis C; better compliance; and finally, prevention of drug interactions. The following scheme is suggested:

**Patients without HAART**

If the CD4+ T-cell count is above 350/µl, treatment of hepatitis C can be started. It is unclear whether a high viral load (> 50,000/ml) requires initiation of HAART.

If the CD4+ T-cell count is between 200 and 350/µl, the patient might benefit from treatment of hepatitis C if HIV RNA is below 5,000 copies/ml. If it is higher, initiation of HAART should be considered.

A CD4+ T-cell count below 200/µl is a relative contraindication. HAART should be initiated first. When there is an adequate increase in the CD4 count, interferon therapy can be reconsidered.

**Patients on HAART**

If CD4+ T-cells are above 350/µl under stable HAART and the viral load is below the level of detection, treatment can be started.

If CD4+ T-cells are between 200 and 350/µl and the viral load is stable below the limit of detection, the decision should be dependent on the overall situation (with consideration of severity of hepatitis, HCV genotype and status of HIV infection).

A CD4+ T-cell count below 200/µl is a relative contraindication. It is a judgement call to decide whether to take the risk of a treatment attempt with interferon (with the likelihood of a poor response and the danger of a further decline in the CD4+ T-cell count as a result of interferon treatment).
Figure 1: Hepatitis C treatment algorithm

ALT, alanine aminotransferase; PEG-IFN, pegylated interferon; RBV, ribavirin; modified after Soriano 2002 and Rockstroh 2004
If necessary, antiretroviral treatment should ideally be modified several weeks before HCV therapy is initiated. ddI is contraindicated with concurrent HCV therapy (as it can lead to pancreatitis, mitochondrial toxicity, and more cases of liver decompensation). AZT and d4T should also be avoided if possible, in order to prevent additive toxicities (zidovudine: anemia and leukopenia; stavudine: mitochondrial toxicity). Before modifying HAART, it should be insured that the treatment success of HIV therapy is not going to be compromised. In such cases, HCV treatment should only be started if the overall clinical situation is stable, i.e. good viral suppression has been achieved and side effects have been evaluated or treated.

To detect a hepatocellular carcinoma (HCC), alpha-Fetoprotein (AFP) and sonography of the liver should be performed every 6-12 months in all patients with chronic hepatitis C. This is particularly relevant for patients with F3/F4-fibrosis. Some experts recommend shorter intervals that are not yet feasible in most circumstances. There is no urgent need to monitor HCV-RNA at every visit, as it has no prognostic value.

**Treatment practice**

The combination of PEG-interferon with ribavirin over a period of 48 weeks is recommended as the standard therapy (Soriano 2004) regardless of the genotype (Rockstroh 2004, Alberti 2005).

Two interferons are currently available as PEG-interferons: PEG-Intron™ and Pegasys™. PEG-Intron™ is administered subcutaneously and the dose is based on body weight at 1.5 µg/kg. Pegasys™ is injected subcutaneously at a fixed dose of 180 µg. Both substances are administered once a week, and must be kept refrigerated.

The dosage of ribavirin should be 800 mg daily for genotypes 2 and 3, whereas genotypes 1 and 4 need to be treated with 1,000-1,200 mg daily according to current consensus recommendations. The capsules can be taken once daily, or spread over the day.

Patients should be counseled extensively on the expected side effects before beginning treatment. Three main aspects should be explicitly addressed:

Almost all patients experience influenza-like symptoms or malaise when beginning treatment. As the severity of symptoms cannot be predicted beforehand, treatment should be initiated at a time when there are no important private or professional events pending (e.g. before a weekend). The administering physician should be readily available during the first days of treatment. In addition, paracetamol should be prescribed (dosage has to be adjusted individually; single dose = 1,000 mg). Symptoms usually improve within the first two to four weeks. A decision to stop treatment should therefore not be made before the end of the first month if possible.

Most patients tolerate treatment quite well and can continue their daily activities normally. However, it is possible that particularly in the initial stages of treatment, they may be unable to work for several days. In rare cases, the side effects may be so grave that patients are unable to work for the entire duration of treatment. This also needs to be discussed with the patient in advance.
Patients must be made aware of the fact that both interferon and ribavirin are potentially teratogenic. A reliable method of contraception for at least six months after treatment is therefore important.

All patients require regular clinical monitoring. This should initially take place every 2 weeks; later at least every 4 weeks. Laboratory monitoring should include:

- A complete blood count and transaminases every 2-4 weeks
- Thyroid function tests every 12 weeks (more frequently with pre-existing dysfunction)
- Immune status every 12 weeks
- Lactate levels every four weeks in patients on stavudine comedication

HCV RNA is the most important parameter for measuring the treatment response and is determined after 12 weeks to decide on the duration of treatment. In practice, it is often already determined after four or eight weeks - partly because it is a motivation for further treatment if there is a treatment response.

The evaluation of psychological side effects is made at every clinic visit. Observations made by others, such as family members, may also be very helpful.

The management of possible side effects is often the decisive factor for the success of treatment. A high discontinuation rate in numerous (older) clinical studies is likely also to have been due to a lack of experience with combination therapy. Proper management of side effects probably results in significantly better treatment success rates. It is often helpful to indicate to patients that side effects are reversible after stopping therapy.

Ribavirin causes hemolytic anemia in up to 20% of patients. This can be treated with epoetin alfa. Dose recommendations differ: usually approximately 100 IE/kg body weight are injected subcutaneously three times a week. 40,000 IE once a week also significantly improve ribavirin-induced anemia (Sulkowski 2005). Alternatively, halving the dose (hemoglobin below 10 g/dl) or discontinuing ribavirin altogether (hemoglobin below 8.5 g/dl) are possible options. However, dose reductions, frequently used in the past, should only be made if epoetin does not help. Newer studies have shown that the correct dosing of ribavirin is associated with a better treatment response. A daily 5 mg dose of folic acid is recommended to reduce hematotoxicity.

Treatment with granulocyte colony stimulation factor (GCSF) may ameliorate an interferon-induced leukopenia. Clinical experience is very limited so far. However, so that the required dose of interferon can be maintained in case of severe leukopenia (neutrophil count below 500/µl), this recommendation seems to be justified. Doses have to be adjusted individually. In most instances low doses are adequate, as hematopoiesis itself is not impaired (e.g. Filgrastim 30 Mio IE once a week).

Mild depression whilst on interferon can be treated with well-tolerated antidepressants (e.g. paroxetine 20 mg daily). Therapy should be stopped immediately in cases of severe depression or on development of suicidal thoughts.

The frequent occurrence of weight loss can be lessened with dietary counseling. It is important to ensure a regular diet that is tailored to the patient’s wishes (e.g. inpatients with drug addiction). It is possible that the weight loss is a form of lipoat-
Thyroid dysfunction may develop during treatment with interferon (see above), which might necessitate discontinuation of interferon therapy.

The duration of treatment depends on the treatment response. If HCV RNA is still positive after 12 weeks, treatment is discontinued irrespective of genotype, as a treatment response is unlikely even if therapy is continued. Earlier recommendations were to wait until week 24 because of delayed elimination kinetics in HIV patients compared to HCV-monoinfected patients. However, it is now possible to reach a decision after just 12 weeks, even in HIV patients.

If HCV RNA has dropped by at least 2 logs or is negative, treatment should be continued for another 36 weeks in patients with all genotypes. Earlier recommendations were to stop therapy after week 24 in patients with genotype 2 or 3. However, recent data from the APRICOT study showed a very low relapse rate after 48 weeks of treatment, whereas prior studies revealed relapse rates of up to 50% if patients were treated for only 24 weeks. Therefore, patients with all genotypes should receive treatment for at least 48 weeks. Continuation of treatment beyond this time point, especially in patients with genotypes 1 and 4, could possibly reduce relapse rates further.

Recommendations for treatment of hepatitis C are constantly evolving. Therefore an experienced treatment center should always be contacted if clarifications are needed.

Due to the complexities of HIV/HCV coinfection, patients should be treated within clinical studies wherever possible.

References

HIV and HBV coinfection

Introduction

The hepatitis B virus is one of the most common human pathogens worldwide. Up to 95% of all HIV-infected patients have been infected with hepatitis B, and approximately 10-15% have chronic hepatitis B, with considerable variation among geographical regions and risk groups. It is estimated that around 100,000 HIV-infected patients in the USA suffer from chronic hepatitis B. Sexual transmission is the most frequent route of contraction. Transmission via the bloodstream is more probable than for HIV: following a needlestick injury contaminated with HBV-infected blood, the risk of infection is around 30% (HCV approx. 2-8%; HIV approx. 0.3%). Primary HBV infection leads to chronic hepatitis in 2-5% of immunocompetent adults, whereas HIV-infected patients experience chronification about five times more often. A possible reason for this is the HIV-associated T-cell defect. A polarization to a Th2-type response could result in the inhibition of specific cellular defense mechanisms (e.g., cytotoxicity, production of interferon-γ and interleukin-2, and the T-cell proliferation rate). Genetic predisposition could also play an important role in the chronification of hepatitis B. Current data indicate that virus-specific factors, such as the extent of HBV viremia, genotype (A-H), or the emergence of escape mutants do not result in differences between HIV-infected and immunocompetent patients. It should be noted, that genotype A mainly affects homosexual men who tend to be positive for the hepatitis B antigen, whereas genotype D is predominantly seen among intravenous drug users in Southern Europe and seems to be associated more often with negative hepatitis B e antigen. Treatment response to interferon may be influenced by genotypes (with a possibly better response in patients with genotype A).

Hepatitis B and HIV have several common features, although hepatitis B is a double-stranded DNA virus. After entering the hepatocyte, viral DNA is integrated into the host genome. Viral RNA is translated by HBV reverse polymerase into new viral DNA and transcribed into viral proteins. Reverse transcription may be inhibited by nucleos(t)ides reverse transcriptase inhibitors. Integration of the virus into the host genome of hepatocytes and CD4+ T-cells prevents its eradication. Finally, the mechanisms for development of resistance are very similar for both viruses.

The diagnosis of HBV is established as in patients without HIV infection. Table 1 summarizes the interpretation of serological test results. Screening HIV-infected patients for HBV starts with HBsAg, anti-HBs, and anti-HBc. If a positive HBsAg is found, testing for HBeAg, anti-HBe, and HBV DNA should follow. There is debate about a so-called occult infection due to immune escape. This means patients lack HBsAg, but are positive for HBV DNA. Recent studies have not found evidence of such occult infection and the prevalence and impact in coinfection remains unclear.
Table 1: Interpretation of serological test results for HBV

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<th>anti-HBc</th>
<th>HBeAg</th>
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<td>–</td>
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<td>+ (IgM)</td>
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<tr>
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<td>+</td>
<td>+ (IgG)</td>
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¹Controversial. See text above.

In general, patients with chronic hepatitis B should be screened for hepatocellular carcinoma (HCC) every 6 to 12 months. Serum alpha fetoprotein and an ultrasound of the liver should be performed. This recommendation is independent of apparent cirrhosis, as 10 to 30% of patients who develop HCC do not have pre-existing cirrhosis.

Course of hepatitis B with concurrent HIV infection

In HIV-infected patients, chronic hepatitis B has an unfavorable course compared with monoinfected patients, and the risk of liver-associated mortality is significantly increased.

Data from the Multicenter AIDS Cohort Study have demonstrated the unfavorable influence of HIV infection on hepatitis B (Thio 2002a). In approximately 5,000 patients observed over a period of 14 years, the risk of liver-associated mortality was 8 times higher than in HBs antigen negative HIV patients (14.2/1,000 person-years vs. 1.7/1,000) and 15 times higher than in HBs antigen negative patients without HIV infection (14.2/1,000 vs. 0.8/1,000). Liver-associated mortality due to hepatitis B has increased significantly since the introduction of HAART in this cohort. Results from the EuroSIDA cohort confirmed the unfavorable course of hepatitis B resulting in increased liver-related mortality (Konopnicki 2005).

In addition to increasing mortality, HIV coinfection accelerates the progression of hepatitis B and increases the risk of cirrhosis. Histological analysis of a series of 132 homosexual men with chronic hepatitis B, of which 65 were HIV-coinfected, showed a higher prevalence of liver cirrhosis in HBV/HIV-coinfected patients (Colin 1999). No difference was observed in the extent of inflammatory activity. Interestingly, several patients developed severe fibrosis and cirrhosis, in the presence of only minimal inflammatory activity. This phenomenon has also been described in other immunocompromised patient populations (e.g. organ transplant recipients). HIV-positive patients possibly experience more frequent reactivation episodes of chronic hepatitis B than HIV-negative patients.

Despite the worsening described, initially the clinical course is usually more benign in HIV-positive patients, although viral replication is increased. This seems contradictory at first, but can be explained by the impairment of cellular immunity, which
may lead to an increase in viral replication, but at the same time also reduces hepatocyte damage. Therefore, transaminases in HBV/HIV-coinfected patients are frequently only mildly increased. In contrast, HBV DNA, as a marker for viral replication, is higher than in immunocompetent patients. Accordingly, despite less inflammatory activity, liver fibrosis and cirrhosis are more common.

There is a direct correlation between the extent of immunosuppression and the control of viral replication of HBV: patients with AIDS more frequently show signs of active viral replication (HBs- and HBe antigen positive, HBV DNA detectable) than patients without AIDS. Even in cases with apparently resolved hepatitis B (anti-HBe positive, HBV DNA negative, even anti-HBs positive), increasing deterioration of the immune system may result in reactivation of the HBV infection. Notably, some cases of reactivation of hepatitis B have been described following immune reconstitution after initiation of HAART.

Most studies on the influence of hepatitis B infection on the course of HIV disease have not been able to determine a shorter survival time. HBV infection neither leads to a more rapid decline of CD4+ T-cells nor to an increased frequency of AIDS-defining events. However, the reduction in HIV-associated mortality has led to an increase in mortality resulting from liver-related complications. In addition, HAART-related hepatotoxicity develops about three times more frequently in patients with chronic hepatitis B. Whether or not the prognosis of HBV/HIV-infected patients is changed by HAART and HBV-effective therapies, remains to be seen.

**Prevention**

All patients infected with HIV but with negative hepatitis B serology should be vaccinated! The vaccine may, however, be less effective due to immunosuppression. Approximately 30 % of HIV-infected patients have a primary non-response (only 2.5 % in immunocompetent individuals). This is particularly true for patients with CD4+ T-cell counts less than 500/µl whose response rate is only 33 %. Therefore, a conventional dose is administered to patients with CD4+ T-cell counts greater than 500/µl (20 µg at months 0, 1, and 12), whereas an intensive schedule is recommended for patients with CD4+ T-cell counts less than 500/µl (20 µg at months 0, 1, 2, and the last dose between month 6 and 12). In case of non-response (checked 12 weeks after each cycle), vaccination is repeated at double the dose in four steps (40 µg at months 0, 1, 2, and 6-12). Patients with CD4+ T-cell counts less than 200/µl, who are not on HAART, should receive HAART first and HBV immunization thereafter.

Loss of protective immunity is seen in up to 30 % during each year following seroconversion. Therefore, anti-HBs should be monitored once a year and consideration should be given to booster doses if anti-HBs-antibody levels are less than 100 IU/l. HIV patients, who are not adequately immunized against HBV, should be screened yearly to look for newly acquired infection.

HIV/HBV-coinfected patients who are seronegative for hepatitis A should be vaccinated against hepatitis A (months 0, and 6), as there is an increased rate of severe or fulminant hepatitis in case of acute hepatitis A. Patients who are susceptible to both hepatitis A and B can be vaccinated with a bivalent vaccine (months 0, 1, and 6).
Following immunization, patients should be counseled about common measures to prevent further transmission and transmission of other viruses such as hepatitis C (safer-sex practices, avoidance of needle-sharing and others). They should be educated about strategies to prevent progression of liver disease such as avoidance of alcohol consumption, tobacco use (controversial), or herbal supplements, many of which are hepatotoxic. The application of hepatotoxic drugs (e.g. anti-tuberculocidal agents) should be carried out cautiously.

Newborns of mothers with chronic hepatitis B should receive hepatitis B-immunoglobulin and active immunization.

**Treatment**

Treatment of chronic hepatitis B is problematic in coinfected patients because of the impaired immune function. As HBV persists in infected cells even after successful treatment, eradication of HBV seems not possible with current treatment strategies. Similar, development of protective anti-HBs-antibodies with subsequent loss of HBsAg is difficult to achieve because the integrated HBV pool escapes the direct antiviral effect of most anti-HBV drugs. Current treatment goals are seroconversion from HBeAg to anti-HBe, a complete suppression of HBV DNA, normalization of transaminases, improvement of liver histology, and prevention of hepatocellular carcinoma. Other benefits of HBV therapy include the reduction in the risk of transmission and possibly in the risk of HAART-induced hepatotoxicity.

**Drugs with HBV activity**

Studies with interferon from the pre-HAART era showed almost no response (response most often 0%). Immune reconstitution with HAART and the introduction of pegylated interferons will change and newly define the role of interferons in treatment. In general, the efficacy of IFN-α therapy is higher in HBeAg-positive than in HBeAg-negative chronic hepatitis B. Patients with high ALT levels and low HBV DNA titers show the best responses. In HBV-monoinfected patients, positive for HBeAg, the rate of seroconversion is higher with interferon than with nucleos(t)ides. This raises the question whether treatment with interferon should be offered to the particular subset of coinfected patients with several positive predictors of treatment response (HbeAg-positive, high CD4+ T-cell counts, elevated ALT levels) and no need for HAART. Results on PEG-interferon are currently being awaited. However, data are limited at the moment and the inclusion of patients in prospective clinical trials is highly recommended. Treatment with interferon is limited by its toxicity. In patients with decompensated liver disease, IFN-α is contraindicated. It should be used cautiously in patients with advanced liver disease. Detailed information on the use of interferons can be found in the sections on Hepatitis C and on Drugs.

In patients with low CD4+ T-cell counts, the response to IFN-α is much lower. Two drug classes are available for these patients: nucleoside and nucleotide analogs, both of which inhibit the HBV polymerase.

Lamivudine was the first nucleoside analog licensed for the treatment of chronic hepatitis B. It has excellent activity against HBV in addition to its antiretroviral efficacy. It can improve both markers of viral replication and histological activity. The rate of seroconversion in coinfected patients is about 22 to 28% (Benhamou
The optimal duration of treatment is unclear. 6 to 12 months of treatment are recommended for HBV-positive patients without HIV infection. Longer periods of treatment are associated with better response rates. In HIV-infected patients, the treatment duration with lamivudine is usually determined by the underlying HIV infection. Long-term treatment with lamivudine is limited by the development of resistance. This is conferred by a mutation in the YMDD motif in the HBV DNA polymerase gene. Similar to a pre-core-mutant, HBeAg production may stop in case of mutations in this motif. The frequency of resistance development has been reported to be at least 20% of patients per year. The effect of continuing lamivudine treatment on the course of hepatitis B in case of resistance is unknown. If lamivudine treatment is discontinued, the clinical picture of acute hepatitis may develop as a result of a reactivation.

Emtricitabine (FTC) has added new options for the treatment of hepatitis B. Seroconversion occurs in up to 30% of patients after 2 years. FTC, like 3TC, is a cytosine analog licensed for the treatment of HIV infection. It should be considered interchangeable with 3TC, as both substances share cross-resistance and are very similar in terms of characteristics and tolerability. The effective dose is 200 mg once daily. FTC is well tolerated with no dose-limiting adverse events. Preliminary results suggest that resistance to FTC may occur less frequently than with 3TC.

The nucleotide analog adefovir is an alternative treatment. It has been licensed for the treatment of chronic hepatitis B since the end of 2002 in the USA and since 2003 in Europe. The in vitro efficacy of adefovir against HBV is excellent. Loss of HBeAg occurs in about 27% of patients treated, seroconversion in 12%. For a long time, no significant development of resistance to adefovir was observed. After 2 years of treatment, about 2.5% of patients develop resistance, after 3 years about 6% (Angus 2003, Xiong 2003, Hadziyannis 2005), although there seems to be no cross-resistance to lamivudine. Therefore, adefovir is still an option even after development of resistance to lamivudine. It is unclear whether it should be added to lamivudine therapy or given sequentially. Neither HIV resistance mutations nor an effect of adefovir on HIV have been observed to date. Nevertheless, more data are still needed to ensure adefovir does not select resistance mutations in HIV at low doses, which might compromise the future activity of tenofovir. A clinical picture of acute hepatitis may develop after discontinuation of adefovir, similar to stopping lamivudine.

The standard dose of adefovir is 10 mg once daily. Dose adjustment is necessary in cases of renal insufficiency. Several placebo-controlled studies have shown no increase in side effects when compared to placebo. In particular, the nephrotoxic effects that were observed at a dose of 120 mg have been reported with an incidence of less than 1% after 96 weeks of observation on the lower dose.

Tenofovir is a further possibility. It is actually only licensed for treatment of HIV infection and not for treatment of hepatitis B. Several pilot studies have shown excellent effectiveness of tenofovir against hepatitis B in HIV-coinfected patients, with 70% of patients showing undetectable HBV DNA levels after 2 years and 15% of patients showing HBeAg seroconversion. Tenofovir is also effective in the presence of lamivudine resistance. Due to the potential (rare!) development of nephrotoxicity, creatinine and phosphate levels should be monitored regularly. Interestingly, tenofovir seems to be active if failure of adefovir therapy occurs.
Entecavir (Baraclude™) is the substance licensed most recently for HBV treatment. As it has no activity against HIV, it seems to be particularly suited for patients who do not need HAART. Activity against HBV appears to be excellent, even in patients pretreated with lamivudine. Patients naïve to 3TC are given 0.5 mg entecavir per day; 3TC-experienced patients receive 1 mg entecavir per day.

In the light of the lesson learned from HIV and the high resistance rate of HBV on lamivudine therapy, combination of at least two drugs seems prudent. However, studies on combination therapy found divergent results. Nevertheless, it is reasonable to assume that combination therapy enhances antiviral activity and delays the selection of HBV resistance. At present, combination therapy with one nucleoside and one nucleotide analog should be preferred to monotherapy if feasible.

Finally, liver transplantation may be an option for selected patients who have cirrhosis and/or develop hepatocellular carcinoma.

Treatment guidelines

Several treatment guidelines have since been published (Murphy 2004, Alberti 2005, Soriano 2005, Brook 2005). In principle, due to accelerated progression and increased mortality in coinfection, treatment possibilities should be examined for every patient. Treatment is recommended if:

- ALT is consistently > 2-fold above the norm (high pre-treatment ALT values correlate with better treatment responses to interferon and lamivudine);
- HBeAg is positive;
- HBV DNA > 20,000 IU/mL, if HbeAg+; > 2,000 IU/mL, if HbeAg- (the optimal threshold is unknown; 20,000 IU correspond to approximately 10^5 copies/mL depending on the assay used);
- Significant inflammation or liver fibrosis has been detected biotically.

The role of liver biopsy in coinfected patients has been discussed controversially. Currently, the indication for HBV therapy is based on serological markers alone. Indeed, liver biopsy is seen as desirable, as knowledge of the severity of liver damage may influence the choice or length of treatment, and other causes of liver disease may be excluded. Liver biopsy is recommended particularly for patients with the inactive carrier state (positive for HBsAg, but no other marker of replication). Non-invasive assessment of liver fibrosis can also be considered (e.g. Fibroscan™, see above).

There are several histological classifications used. In Europe the META VIR-Score is used most often. It distinguishes five stages of fibrosis (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = numerous septa without cirrhosis, 4 = cirrhosis). Hepatitis activity is graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). Treatment is recommended for grades F2-F4, it may be deferred for grades F0+F1.

The following non-binding treatment recommendations may be suggested, but need to be confirmed in further studies (figures 1 and 2). An effective treatment of HIV infection must not be put at risk. Accordingly, 3TC, FTC and tenofovir, which are effective against both HIV and HBV, have to be combined with other substances effective against HIV in order to ensure an adequate HAART. On the other hand,
Adefovir is not effective for treatment of HIV and must not be considered as part of the HAART regimen.

**Figure 1: Treatment recommendations for HIV-HBV coinfected patients without indication for HAART (modified after Alberti 2005)**

* HBV-DNA > 20,000 IU/ml in HBeAg+ patients; > 2,000 IU/ml in HBeAg- patients  
** Metavir < A2 and/or < F2; ***Metavir ≥ A2 and/or F2 (for Metavir-Score refer to text)  
Monitoring means: transaminases every 3 months, INR/HBV-DNA every 6 months

The main consideration is the need for HAART:  
- If there is no need for HAART, the use of drugs without HIV activity seems the best choice (i.e. adefovir, entecavir or IFN-α; see figure 1). Lamivudine, emtricitabine, and tenofovir should be avoided.  
- If the patient is under HAART or needs HAART due to low CD4+ T-cell counts, drugs with both HIV- and HBV-activity should be included in the HAART regimen (see figure 2). In treatment naïve patients who start therapy, the combination of FTC (or 3TC) and tenofovir is preferred as nuke backbone.

The drugs currently available and their dosages used are summarized in Table 2.
**Figure 2: Treatment recommendations for HIV-HBV coinfected patients with indication for HAART (modified after Alberti 2005)**

* If compatible with treatment of HIV infection. As an alternative, a substance without HIV-activity may be added (preferably entecavir).

Initial normalization of ALT and significant reduction of HBV DNA will be achieved in most cases by any anti-HBV agent. ALT levels do not correlate well with inflammatory activity and are influenced by many other factors such as hepatotoxicity of HAART or other drugs, alcohol consumption, and immune reconstitution. Therefore, their value for monitoring treatment is limited. HBeAg seroconversion will occur in as many as 25% of patients. The most desirable endpoint of HBsAg loss is observed in only 5-10% of patients within one year of the start of treatment with IFN-α, but occurs less frequently with nucleos(t)ide analogs.

Data on the durability of treatment responses are heterogeneous. HBeAg loss induced by IFN-α is durable in more than 80% of the patients for more than 5 years. Durability after 3TC treatment is not as good, and relapses often occur when lamivudine is discontinued. Therefore, 3TC should be continued for at least 6 months after HBeAg seroconversion.

The optimal duration of treatment is not clear at the moment. Recommendations for HBV-monoinfected patients: after seroconversion (loss of HBs antigen) or loss of HBs antigen, treatment should continue for at least another 4 to 6 months. Seroconversion should be determined on two occasions 3 months apart. For HBs-negative mutants, the parameters for treatment success are transaminases and HBV DNA (< 2,000 IU/ml) or loss of HBs antigen. Otherwise treatment should be discontinued with loss of efficacy.
Table 2: Current therapeutic options for chronic hepatitis B in HIV/HBV coinfection.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Length of therapy</th>
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<tbody>
<tr>
<td>Interferon-α</td>
<td>5 MU per day or 10 MU 3 days per week</td>
<td>4-6 months in HbeAg-positive patients</td>
</tr>
<tr>
<td></td>
<td>axios 180 µg once a week</td>
<td>12 months in HbeAg-negative patients</td>
</tr>
<tr>
<td>PEG-Interferon</td>
<td>Pegasys™ 180 µg once a week</td>
<td>Only Pegasys™ is licensed for hepatitis B in monoinfected patients. Here, length of therapy is 12 months.</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>300 mg QD</td>
<td>Minimum of 12 months in HbeAg-positive patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indefinite in HbeAg-negative patients</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200 mg QD</td>
<td>Undefined</td>
</tr>
<tr>
<td>Adefovir</td>
<td>10 mg QD</td>
<td>Minimum of 12 months, possibly lifelong</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300 mg QD</td>
<td>Undefined</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5 mg, if 3TC naïve</td>
<td>Undefined</td>
</tr>
<tr>
<td></td>
<td>1.0 mg, if 3TC experienced</td>
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Treatment of HBV may have to be continued indefinitely after seroconversion due to the persistence of HBV. This may at least be the case in patients with ongoing immunosuppression.

A transient elevation of transaminases – which is usually moderate and soon resolves – may be observed after initiation of HBV therapy. It is caused by immunoreconstitution and subsequent increased inflammatory activity. In case of marked and/or ongoing elevation of transaminases, alternative explanations have to be considered (e.g. increasing HBV replication, resistance of HBV, lactic acidosis, hepatotoxicity of antiretroviral drugs, superinfection with hepatitis viruses other than hepatitis B).

As most cases of acute hepatitis B even in HIV-infected patients resolve spontaneously, only supportive treatment is recommended. In addition, data on this situation are sparse (e.g. danger of resistance in case of early therapy with no more options afterwards).

Two main issues will dominate the further development of HBV therapy in the near future. Firstly, combination therapies, including the combination with new compounds, are being investigated further and could significantly influence the development of resistance. Secondly, there are numerous new drugs with specific HBV activity that are still being developed and that will enable further progress (e.g. chloroquine and telbivudine).

References


