

Chapter 18: Management of HCV/HIV coinfection

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Epidemiology of HIV and HCV coinfection

HIV and HCV share transmission pathways, which explains the high rate of coinfection with both viruses. Of the 33.4 million HIV-infected persons worldwide in 2008 it is estimated that at least 5 million of them have concomitant hepatitis C virus infection. Whereas both viruses are transmitted with high efficacy via blood-to-blood contact, HCV is less easily transmitted sexually. Thus, the prevalence of hepatitis C coinfection within different countries, regions and populations is closely related to the prevalence of blood-borne transmission (mainly intravenous drug use) of HIV. Among HIV-infected patients in Europe, Australia and the US, at least one out of four is coinfecting with hepatitis C (Rockstroh 2004). Hepatitis C coinfection rates as high as 70% can be seen in Eastern European countries like Belarus and the Ukraine where intravenous drug use (IVDU) is the main route of HIV transmission. On the other hand, in Central European countries such as Belgium, Austria or Germany, where sexual intercourse dominates as mode of HIV transmission, hepatitis C coinfection rates are rather low, between 10 and 15% (Rockstroh 2005). Similar rates can be found in HIV-positive patients in Australia (Jin 2009) and the UK (Turner 2009). Interestingly, recent data from the US indicate that 25% to 35% of patients with HIV are coinfecting with HCV (Singal 2009) reflecting the contribution of at-risk populations such as prison inmates to the overall numbers. 65-70% of HIV-positive prisoners in the US are coinfecting with hepatitis C, in contrast to 18-25% within the general US HIV-positive population (Weinbaum 2005). In Asia, coinfection rates of up to 85% have been observed among Chinese plasma donors whereas in countries with predominantly heterosexual HIV transmission like Thailand coinfection rates are around 10% (Qian 2006). In sub-Saharan Africa, where again the primary route of transmission of HIV is sexual, HCV coinfection rates so far have been reported to be relatively low.

Although the traditional route of HCV transmission is blood-borne and includes IVDU, snorting drugs, sharing toothbrushes/razors, and tattooing (Bollepalli 2007), recent epidemic outbreaks among HIV-positive men who have sex with men (MSM) from several major European cities such as London, Paris, Amsterdam, and Berlin as well as more recent reports from the US and Canada, document that HCV may well be sexually transmitted and should therefore also be taken into account at regular STD screenings (Gotz 2005; Danta 2007; Vogel 2009; Vogel 2010).

HCV is detected in 4-8% of infants born to HCV-infected mothers (Bevilacqua 2009). Dual HCV/HIV infection increases the risk for transmission of both viruses and high levels of HCV viremia in the mother increases the risk of perinatal HCV transmission (Zanetti 1995). However, in HIV/HCV-coinfecting mothers receiving HAART and undergoing cesarean section the risk of HCV transmission is strikingly reduced to less than 1%.

In summary, the prevalence of hepatitis C within the HIV-infected population is far higher than in the general population where the global burden of hepatitis C is estimated to be roughly 2%. This highlights the importance of preventing further spread of hepatitis C infection as one of the major co-morbidities in HIV-infected individuals. The average estimated risk of transmission for hepatitis C in HIV is depicted in Table 1. Although they share common routes of infection, the viruses are transmitted with varying efficacy depending upon the mode of transmission.

Mode of transmission	HIV	HCV	HCV / HIV coinfection
Perinatal	7-50%	1-7%	1-20%
Sexual contact*	1-3%	<1%	<4%
Needle stick injury	0.3%	<1%	Unknown

* With sexual contact the risk refers to cumulative exposure.

Table 1. Average estimated risk of transmission for HIV, HCV and HCV/HIV coinfection.

Specifics regarding the diagnosis of HCV in HIV coinfection

The presence of HCV can be confirmed serologically by the detection of antibodies to the virus via ELISA testing. Loss of HCV antibodies observed in rare cases in very advanced immune deficiency in HIV/HCV coinfection does not necessarily indicate viral clearance (Cribier 1999). Therefore, a single negative HCV antibody ELISA does not necessarily exclude HCV infection in HIV-positive patients, especially in severe immune deficiency. Additionally, a rise of liver transaminases has been proven to be more sensitive in the detection of acute HCV infection in HIV-positive patients than repeated testing for the presence of antibodies against HCV (Thomson 2009). However, in more than 80% of HIV-positive individuals with positive HCV antibodies, HCV RNA is detected in the blood. Higher concentrations of HCV RNA are found in HIV-positive individuals than in HIV-negative patients with hepatitis C (Perez-Olmeda 2002). Interestingly, recent data from a cross-trial comparison showed that HIV-positive patients were less likely to present with elevated serum ALT and clinical signs or symptoms of hepatitis than HIV-negative patients (Vogel 2009). In observations from hemophiliac patients the mean concentrations of HCV RNA increase by 1 log over the first two years after HIV seroconversion (Eyster 1994). The levels of HCV viremia increase eight times faster in HIV-positive individuals than in patients with hepatitis C who are not infected with HIV. The highest concentrations for HCV viremia have been reported in patients who subsequently develop liver failure.

Interestingly, spontaneous clearance of HCV RNA has been observed in some HIV/HCV-coinfected patients experiencing significant immune reconstitution following HAART initiation (Fialaire 1999; Thomson 2009). In contrast, there are also patients with positive HCV antibodies and negative HCV RNA, where after initiation of

HAART, HCV RNA was noted to reemerge frequently in combination with a flare of liver transaminases. Therefore, regular monitoring of HCV RNA levels is warranted in HIV/HCV-coinfected patients.

The distribution of HCV genotypes in HIV-positive patients reflects the route of transmission. Genotype 1b accounts for 2/3 of post-transfusion HCV infections and is the predominant genotype in hemophiliacs. In contrast, genotypes 1a and 3a are more common in intravenous drug users (Pol 1994).

The natural history of hepatitis C in HIV-positive patients

Various studies have demonstrated that underlying HIV infection weakens the immune response to hepatitis C, thereby diminishing the chance of spontaneous viral clearance of HCV infection. Interestingly, data from the European epidemic of sexually transmitted acute hepatitis C infection in HIV-positive individuals suggest that despite underlying HIV infection spontaneous resolution of HCV may occur in up to 20-30% of newly infected patients (Vogel 2010).

Numerous large cohort studies have demonstrated that once chronic hepatitis C is established the presence of HIV leads to a faster HCV clinical progression due to the lack of critical CD4-positive T cell responses against HCV (Danta 2008). In the American multicenter Hemophiliac Cohort Study liver failure occurred in 9% of multi-transfused HCV/HIV-coinfected adult hemophiliacs without an AIDS-defining opportunistic infection or malignancy (Eyster 1993). In the same time period, no case of liver failure was observed in HCV-positive HIV-negative hemophiliacs. Subsequently, several studies have confirmed the unfavorable course of hepatitis C in HIV-coinfected hemophiliacs, particularly in the setting of progressive immunodeficiency and lower CD4 counts (Rockstroh 1996; Puoti 2001).

In addition, the time interval between HCV exposition and development of cirrhosis was found to be shortened in coinfecting subjects. Indeed, within 10-15 years of initial HCV infection, 15-25% of HIV-coinfected patients develop cirrhosis compared with 2-6% of HIV-negative patients (Soto 1997). Importantly, mortality due to advanced liver disease happens ten years earlier in coinfecting hemophiliacs than in HIV-negative hemophiliacs with hepatitis C (Darby 1997). The incidence of hepatocellular carcinoma is also higher in coinfecting patients (Giordano 2004).

Effect of hepatitis C on HIV infection

As clear as HIV's influence on the accelerated disease progression for HCV-associated liver disease is, HCV's influence on the course of HIV disease is conflicting. The Swiss Cohort first revealed a blunted CD4 cell response associated with a faster progression to AIDS after initiation of HAART in HIV/HCV-coinfected patients (Greub 2000). Interestingly, four-year follow-up data from the same cohort study did not see significant differences with regard to CD4 cell count recovery between HCV-positive and HCV-negative HIV-positive patients (Kaufmann 2003). Subsequent studies have indeed found that after adjusting for use of HAART, no difference in CD4 cell count recovery can be observed (Sulkowski 2002). Updated information from an analysis of

the large EuroSIDA cohort, after taking into account ongoing chronic (persistent HCV replication) and resolved (positive HCV antibodies but negative HCV RNA) hepatitis C infection, confirm that no difference in CD4 cell count recovery is observed in patients with chronic hepatitis C infection and detectable HCV RNA in comparison to HIV-monoinfected patients (Rockstroh 2007). In addition, recent data from the same cohort revealed that CD4-positive T cell recovery in HIV-positive patients with maximal suppression of HIV replication is not influenced by HCV serostatus in general or HCV genotype or level of HCV in particular (Peters 2009).

Effect of HAART on hepatitis C

In HIV/HCV-coinfected patients starting antiretroviral therapy a transient increase in HCV RNA levels may occur at week 4 but thereafter no significant changes in concentrations of HCV RNA happen over the first six months of treatment (Rockstroh 1998). However, a 1 log decrease of HCV RNA has been reported in HIV/HCV-coinfected individuals receiving more than 12 months of HAART and having significant immune reconstitution. Other investigators, however, have not observed this decrease in HCV RNA. Moreover, eradication of HCV has been reported in individual patients receiving HAART following CD4 count recovery.

There is increasing evidence that HAART-induced immune reconstitution might reverse the unfavorable accelerated course for hepatitis C in patients with severe HIV-associated immune deficiency (Verma 2006; Vogel 2009). Taking into account that liver disease progresses especially in patients whose CD4 count drops below 200/ μ l it is appealing to think that CD4 increases on HAART may impact the further course of liver disease. In an early study of 162 individuals with HIV/HCV coinfection who underwent liver biopsy, the use of protease inhibitors as part of their HAART regimen was associated with significantly lower rates of progression of liver fibrosis that could not be explained by other cofactors (Benhamou 2000). These findings were then reinforced by several cohort analyses which showed that HIV/HCV-coinfected individuals on HAART had significantly lower liver-related mortality than patients receiving either suboptimal (one or two nucleoside reverse transcriptase inhibitors) or no antiretroviral therapy (Qurishi 2003).

One paper also addressed the amount of immune reconstitution achieved on HAART and the subsequent risk for developing hepatic decompensation in HIV/HCV-coinfected individuals commencing HAART (Pineda 2007). Those patients who experienced the highest CD4 cell count gain on HAART were the least likely to develop further complications of liver disease, again highlighting a favorable impact of HAART-induced immune reconstitution on the course of liver disease. As a consequence, the recently updated antiretroviral treatment guidelines of the European AIDS Clinical Society recommend earlier initiation of antiretroviral therapy in HIV patients with HCV coinfection (CD4 T cell count between 350-500/ μ l in asymptomatic patients).

Short-term and long-term virologic success rates of HAART in HIV/HCV coinfection are, however, limited by an increased risk of hepatotoxicity. Various studies have shown that the presence of HCV was independently associated with an increased risk of rises in serum aminotransferases (Lichterfeld 2004) highlighting the need for close monitoring.

Therapy

The most important reason to treat hepatitis C in HIV-coinfected individuals is the unfavorable course of hepatitis C in the setting of HIV coinfection particularly with the increased life expectancy gained by successful HAART. An increased risk of hepatotoxicity after HAART initiation in HIV/HCV-coinfected patients, possibly limiting the long-term benefit of HAART in this particular patient group, further underlines the need for successful treatment of hepatitis C (Sulkowski 2000). Several studies have been able to demonstrate that successful treatment of hepatitis C dramatically reduces subsequent complications of preexisting liver disease. This implies that once viral clearance is achieved with hepatitis C combination therapy the prognosis of liver disease dramatically improves (even in the presence of already developed liver cirrhosis) and once HCV infection is eradicated further liver complications are very unlikely.

The goal of hepatitis C treatment is to achieve persistently negative HCV RNA levels. This is generally referred to as a sustained virologic response (SVR). It is defined as negative HCV RNA six months after completion of HCV therapy. Negative HCV RNA at the end of the treatment period is described as an end-of-treatment response (EOT). Negative HCV RNA after four weeks of HCV treatment initiation is referred to as rapid treatment response. Failure to respond to treatment is referred to as non-response.

The combination of pegylated interferon and ribavirin is regarded as standard therapy in coinfecting patients. Table 2 summarizes the main results from randomized clinical trials investigating the efficacy of pegylated interferon and ribavirin in HIV/HCV-coinfected individuals. Recently published data from the GESIDA study show similar efficacy and safety for both pegylated IFN α -2b and pegylated IFN α -2a in the treatment of chronic HCV infection in HIV-infected patients (Berenguer 2009).

	ACTG5071	APRICOT	RIBAVIC	Laguno	PRESCO
Number of Patients	66	289	194	52	389
PEG-INF α	2a	2a	2b	2b	2a
IV drug use	-	62%	80%	75%	90%
Liver cirrhosis	11%	15%	39%		
(F3-F4)	19%	28%			
(F3-F4)					
Genotype 1,4	77%	67%	61%	63%	61%
Normal ALT	34%	0%	16%	0%	0%
Mean CD4+	495	520	477	570	546
HAART	85%	83%	83%	94%	74%
Discontinuation rate due to AE*	12%	25%	17%	17%	9%
Discontinuation rate due to other reasons	-	31%	39%	23%	7%
EOT (ITT)**	41%	49%	35%	52%	67%
SVR (ITT)***	27%	40%	27%	44%	50%

*adverse events, **end-of-treatment response, intent-to-treat analyses, *** sustained virological response, intent-to-treat analyses

Table 2: Results from randomized clinical trials investigating the efficacy of pegylated interferon and ribavirin in HIV/HCV-coinfected individuals.

Overall, SVR rates of up to 50% can be achieved (Torriani 2004; Nunez 2007). The difference in rates of SVR in various studies can be explained mainly by differences in ribavirin dosages used. In the initial HCV treatment trials in HIV-coinfected individuals, due to the fear of interactions between ribavirin and commonly used NRTIs for HIV treatment, an 800 mg daily dose of ribavirin was chosen for most patients independent of the prevailing genotype. This led to suboptimal SVR rates. However, in the PRESCO trial, where weight-adjusted daily ribavirin dosages of 1000-1200 mg were used independent of genotype, SVR rates almost doubled in comparison to some of the earlier studies such as APRICOT, most likely due to the higher ribavirin levels. In spite of this, very recently presented data from the PARADIGM trial, a double-blind, multicenter study comparing 800 vs 1000/1200 mg of ribavirin plus PEG-IFN in HCV/HIV coinfecting patients showed no significant differences in the rates of SVR (Rodriguez-Torres 2009).

In the current guidelines, daily administration of ribavirin 1000 mg (<75 kg body weight) and 1200 mg (>75 kg body weight) split into 2 doses (BID) is recommended for HCV therapy in HIV coinfection for all genotypes in combination with pegylated interferon.

The standard dosage for PEG-IFN α -2a is 180 mg/kg body weight once weekly and for PEG-IFN α -2b it is 1.5 mg/kg body weight once weekly. Duration of therapy is individualized taking into account factors for HCV treatment response such as genotype, baseline viral load and time to reach HCV undetectability (see Figure 1). Results from the PRESCO trial indicate that at least some patients may benefit from a longer duration of HCV combination therapy, of up to 72 weeks (see Figure 1). This mainly refers to patients infected with HCV genotypes 1 and 4 (Núñez 2007) for whom poorer response rates have been extensively shown when compared with genotypes 2 and 3.

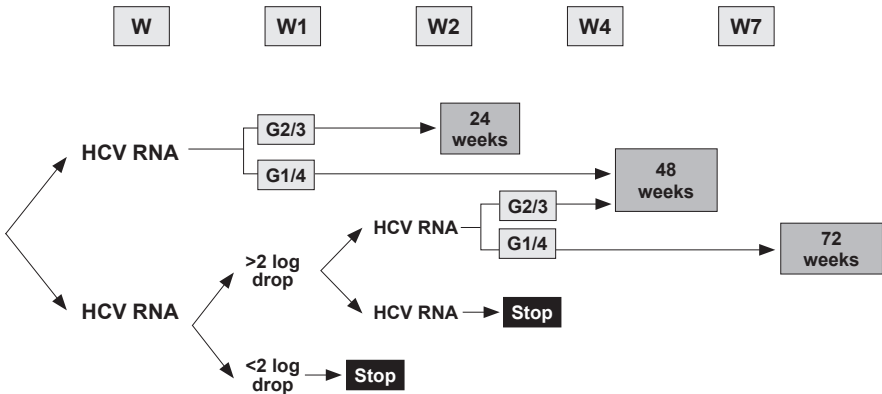


Figure 1: Algorithm for management of hepatitis C in HIV coinfection.

Proposed optimal duration of hepatitis C virus (HCV) therapy in HIV/HCV-coinfecting patients (w: week; G: genotype) (modified according to Rockstroh 2009). *In patients with low baseline viral load (<400,000 IU/l) and minimal liver fibrosis.

Unlike HAART, HCV treatment offers the possibility of eradicating HCV within defined treatment periods and this clearly appears potentially advantageous for the subsequent management of the patient's HIV infection. Every patient should be considered for HCV treatment when the benefits of therapy outweigh the risks. Benefits of therapy also need to be seen in the context of rapid liver fibrosis progression in HIV/HCV coinfection and improved HCV treatment outcome under optimized management in these patients. Information on liver fibrosis staging is important for making treatment decisions in coinfecting patients. However, a liver biopsy is not mandatory for decisions on treatment of chronic HCV infection. Recently introduced noninvasive markers such as blood tests or transient elastography constitute new and exciting means of assessing liver disease in HIV and hepatitis-coinfecting individuals (Rockstroh 2009). When liver biopsy or non-invasive tests for assessing hepatic fibrosis (e.g., elastometry by Fibroscan[®], Echosense, France) demonstrate lower grades of liver fibrosis (F0-F1) regardless of HCV genotype, treatment can be deferred. Assessment of fibrosis should be repeated frequently to monitor progression in these cases. It is especially important to perform a liver disease stage assessment in patients with a low likelihood of achieving SVR.

Diagnosis of hepatitis C

HCV Ab (positive 1-5 months after infection, may rarely be lost with immunosuppression)
HCV RNA level* (while not prognostic for progression, it is for response to treatment)

Status of liver damage

Grading of fibrosis (e.g., Fibroscan[®], liver biopsy, serum fibromarkers**)
Hepatic synthetic function (e.g., coagulation, protein, 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
Auto-antibodies (ANA, SMA, ANCA and LKM1***)
TSH, thyroid autoantibodies if applicable

Monitoring of HCV treatment

Differential blood count and liver enzymes every 2-4 weeks
HCV RNA at week 4 (to evaluate rapid virological response), week 12, 24, 48, (72 if applicable) and 24 weeks after stopping HCV therapy
CD4 count every 12 weeks
TSH every 12 weeks

**Low viral load defined as less than 400,000 IU/l when using PEG-IFN+RBV; there is no standard conversion formula for converting the amount of HCV RNA reported in copies/ml to the amount reported in IU. The conversion factor ranges from about one to five HCV RNA copies per IU.*

***Serum fibromarkers 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 more accuracy in predicting liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.*

****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.*

Table 3. Diagnostic procedures for hepatitis C in HIV coinfection (adapted from Rockstroh 2008).

In addition to this, insulin resistance (which can be determined using the homeostasis model assessment of insulin resistance (HOMA-IR) score) has been reported as a negative predictor of achieving SVR and therefore may also be considered during evaluation.

Current therapy is particularly recommended in all those patients with a high likelihood of achieving an SVR, i.e., patients infected with genotype 2 or 3 and those infected with genotype 1 if the viral load is low (<400,000-500,000 IU/ml) (Rockstroh 2008 and 2009). If chronic hepatitis C is detected early in the course of HIV infection (before the initiation of HAART) treatment for chronic HCV is advised. However, if a coinfecting patient has severe immune deficiency (CD4 count <200 cells/ml), the CD4 count should be improved using HAART before beginning HCV treatment. Patients with a CD4 relative percentage of >25% are more likely to achieve SVR than those with lower CD4 percentages (Opraval 2007). If an early virological response of at least 2 log₁₀ reduction in HCV RNA compared with baseline is not achieved by week 12, treatment should be discontinued as an SVR is unlikely. The current European recommendations for treatment initiation of PEG-IFN and ribavirin for HIV/HCV coinfecting patients are shown in Figure 1. The procedures for diagnosis of hepatitis C, assessment of liver disease stage and control examinations before and during HCV therapy are summarized in Table 3.

The choice of antiretrovirals while on HCV therapy

The choice of the best-tolerated HIV drugs appears crucial for completing the planned treatment duration of hepatitis C therapy of 24-72 weeks. ddI use has been independently associated with increased adverse event rates including lactic acidosis and hepatic decompensation in patients who have liver cirrhosis prior to commencement of PEG-IFN/RBV therapy (Mauss 2006). Apparently, ribavirin enhances the phosphorylation of ddI and thereby leads to an increased risk of pancreatitis and mitochondrial toxicity in subjects receiving concomitant ribavirin and ddI therapy (Moreno 2004). ddI use is therefore contraindicated in combination with ribavirin, especially in patients who have already developed liver cirrhosis. The use of HIV antiretrovirals such as AZT and d4T are also discouraged whenever possible, as increased toxicity can be expected. RBV + AZT is associated with enhanced anemia (Alvarez 2006) while RBV + d4T is associated with increased mitochondrial toxicity and weight loss and a high potential to worsen pre-existing lipodystrophy. Patients on atazanavir-containing HAART may develop jaundice due to an increase in total serum bilirubin levels following initiation of ribavirin (Rodriguez-Novoa 2008). The role of abacavir is uncertain at this point but cohort data suggest lower SVR results in patients on abacavir-containing HAART (Bani-Sadr 2007). As abacavir and ribavirin are both guanosine analogues it is speculated that there may be interference or competition in the phosphorylation pathway. Interestingly, in the presence of therapeutic ribavirin levels no difference was observed between abacavir and other nucleosides in achieving SVR in HIV/HCV-coinfecting patients receiving PEG-IFN/ribavirin therapy and concomitant HAART (Laufer 2008).

Treatment of HCV for relapsers or non-responders

Patients with a history of previous HCV therapy who were either non-responders or who relapsed while on previous HCV therapy need to be reassessed with regard to a new HCV treatment optimizing the dose and duration as well as the best supportive therapy. Recent results from the SLAM-C trial (ACTG 5178) have attenuated hopes that maintenance therapy with PEG-INF might be beneficial for non-responders. In the meantime, data from the ENDURE trial comparing half-doses of PEG-IFN α -2b vs. placebo in coinfecting, pre-treated patients with compensated liver cirrhosis are eagerly awaited. Table 4 summarizes possible interventions for HCV/HIV-coinfecting non-responders and relapsers to previous interferon-based therapies (Rockstroh 2008 and 2009).

Category	Subgroup	Recommended intervention
Suboptimal treatment	Suboptimal schedule <ul style="list-style-type: none"> • Interferon monotherapy • Low doses of ribavirin • Short length of therapy Limiting toxicities & poor adherence	Re-treatment using combination therapy of PEG-IFN plus weight-based dose of ribavirin
		Optimal support (SSRI, paracetamol/NSAID*, adherence support, use of hematopoietic growth factors**)
Optimal treatment with virologic failure	Relapse (HCV RNA negative at the end of treatment)	Re-treatment using combination therapy of PEG-IFN 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 upon licensure

**NSAID, non-steroidal anti-inflammatory drugs; PEG, polyethylene glycol; SSRI, selective serotonin reuptake inhibitors.*

***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.*

Table 4: Classification of and interventions for HCV/HIV-coinfecting patients who are non-responders/relapsers to prior IFN-based therapies.

Treatment of acute HCV in HIV

In patients with acute HCV infection HCV therapy is recommended if the 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. Uncontrolled pilot studies of treatment of acute HCV infection in HIV-coinfected patients demonstrate SVR rates above 60% mostly with combination therapy of PEG-IFN/RBV for 24-48 weeks. Unfortunately, clear guidance is difficult at this point due to the lack of controlled data. HCV RNA levels at weeks 4 and 12 may help to guide treatment duration.

Liver transplantation in HIV/HCV coinfecting patients

In general, HIV/HCV-coinfecting individuals develop more rapid HCV-related hepatic injuries such as liver fibrosis and cirrhosis. Additionally, HIV/HCV coinfection is associated with an increased rate of hepatocellular carcinoma (HCC). Typically HCC occurs in HIV/HCV-coinfecting patients at an earlier age and the course is more aggressive with a shorter survival compared to HCV-monoinfecting individuals. Therefore, the presence of esophageal varices using upper-gastrointestinal endoscopy should be monitored in patients with liver cirrhosis every 1-2 years, and an ultrasound of the liver and a serum alpha-fetoprotein determination should be performed at least every 6 months in patients with F3/F4 fibrosis according to the recommendations of the European Consensus Guidelines (Alberti 2005).

Liver transplant should be considered in patients with decompensated liver cirrhosis, as this is a contraindication for HCV treatment. To fulfill the selection criteria for a liver transplant in HIV/HCV-coinfecting individuals the CD4+ count has to be at least 100 cells/ μ l. Additionally, the patient has to have either undetectable HIV viremia (<400 copies/ml) or at least rational treatment options to control HIV infection successfully after liver transplantation. Further contraindications for transplantation are opportunistic diseases, ongoing alcohol or drug abuse, HCC metastasis in other organs, a second malignant disease, cardiopulmonary disease or older age with an elevated risk of mortality related to the operation. Recent data from a large US cohort sheds light on survival rates after liver transplantation (Mindikoglu 2008). The estimated 2-year survival rate was found to be somewhat lower in HIV-positive patients (70%) compared with HIV-negative patients (81%). This was mostly attributable to HBV or HCV coinfection. Other studies have shown good outcome results in the setting of HBV/HIV coinfection when compared to HIV mono-infection (Vogel 2005). This highlights the major problem in HCV/HIV-coinfecting transplant recipients: HCV re-infection of the transplanted organ. Re-infection with HBV can be prevented with anti-HBs immunoglobulin and HBV antivirals.

In the context of post-transplant immunosuppression, it is important to point out that there are crucial pharmacokinetic drug-drug interactions on the level of the cytochrome P450 metabolism and p-glycoprotein induction between the key immunosuppressive drugs tacrolimus or cyclosporine A and the antiretroviral agents used for HIV therapy. Determinations of the plasma levels of the antiretroviral drugs are necessary. Furthermore, the doses of cyclosporine A or tacrolimus usually need to be reduced when the patient is treated concomitantly with a protease inhibitor, especially if boost-

ed with ritonavir (Vogel 2004). By contrast, NNRTIs can lower the concentrations of immunosuppressive drugs.

Recurrence of chronic hepatitis C in the liver graft is frequently observed in HIV-positive patients and a more rapid progression to graft cirrhosis and liver disease related mortality compared to HCV-monoinfected patients has been reported. Therefore, combination therapy with pegylated interferon plus ribavirin seems to be the best management option 1-3 months after liver transplantation and after re-infection with hepatitis C virus is detected.

Conclusion

HIV has been shown to accelerate the progression of hepatitis C and to result in higher liver disease-related mortality and morbidity in HIV/HCV-coinfected patients compared to HCV- or HIV-monoinfected individuals. Enhanced hepatotoxicity of HAART as well as drug-drug interactions between HAART and ribavirin clearly underline the need for specific treatment strategies in these patients. A number of important clinical studies have established PEG-IFN plus ribavirin combination therapy as the current gold standard allowing sustained virologic response rates of almost 50% in HIV/HCV-coinfected individuals under optimized management conditions (weight-based ribavirin 1000-1200 mg daily and individualized treatment duration).

Nevertheless, the proportion of patients not treatable or those who relapse, especially in patients with genotype 1 infection, remains high. In addition, only one treatment modality is currently available. Luckily, analogous to antiretroviral therapy in HIV patients, new HCV polymerase and protease inhibitors are being developed and investigated in clinical trials, and results are impatiently awaited.

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