HEPATOLOGY

A clinical textbook

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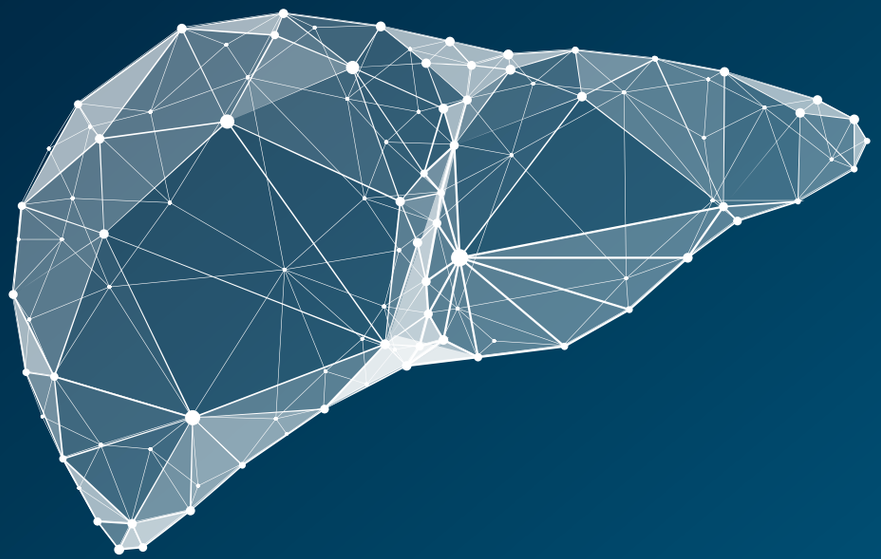

6. Viral hepatitis and HIV coinfection

6.2 Hepatitis C virus and HIV coinfection

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Short history of HCV/HIV-coinfection

In the beginning of the HIV epidemic co-infection with the hepatitis C virus (HCV) was usually caused by contaminated blood products or blood in particular in patients with hemophilia or intravenous drug use (Darby 1997, Nelson 2011). As there were at best limited treatment options for HIV most patients died due to AIDS. With the substantial improvement of efficacy of antiretroviral therapy chronic hepatitis C gained increasing clinical importance. Liver related death due to decompensated liver cirrhosis and hepatocellular carcinoma became one of the most frequent causes of death in Western cohorts of HIV patients (Rosenthal 2003, Klein 2016). Immunodeficiency due to HIV co-infection promotes fibrosis progression and the development of hepatocellular carcinomas (Eyster 1993, Rockstroh 1996, Darby 1997, Puoti 2000, Puoti 2000, Giordano 2004, Pineda 2007, Danta 2008). In addition, immunodeficiency decreased the efficacy of interferon-based therapy of HCV leading to an accumulation of HCV/HIV-coinfected patients in clinical cohorts with a history of often multiple unsuccessful interferon-based therapies and advanced liver fibrosis.

On the other hand, due to HIV and HCV testing of blood products, the approval of genetically produced clotting factors, the transmission of these viruses by medical procedures or blood products was drastically reduced. In addition, the broad acceptance of opioid maintenance therapies and safer use as harm reduction in people with intravenous drug use also had a marked effect on the incidence of HIV and HCV. However, in particular in Russia and some of the countries formerly belonging to the Soviet republic, such as Belarus, Ukraine and Georgia the incidence of HIV and HCV infections increased in the last twenty years mainly through exposure to intravenous drug use, sexual contacts and unsafe procedures associated with blood contacts (Nelson 2011, Platt 2016). In Asia, coinfection rates of up to 85% have been reported 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 the primary route of transmission of HIV is sexual, HCV coinfection rates have so far been reported to be low.

In Western countries after the start of the next millennium an epidemic in men having sex with men (MSM) turned HCV into a sexually transmitted disease (Gotz 2005, Danta 2007, Vogel 2009, Jin 2010, Vogel 2010, CDC 2011, Matthews 2011, Schmidt 2011, Boesecke 2015). The main risk factors for transmission are traumatic sex practices associated with bleeding such as fisting or sharing sex toys and sex parties using recreational drugs (chemsex) – often intravenously (slamsex) (Van de Laar 2009, Schmidt 2011, Jin 2017, Mata-Marin 2022). This still ongoing epidemic was first observed in Europe and the US soon becoming a worldwide phenomenon. In the HIV population HCV as a sexually transmitted disease in MSM passed HCV transmitted by intravenous drug use in incidence in Western cohorts (Danta 2011, Peters 2014).

In the initial period (pegylated) interferon plus ribavirin was the only available therapy and efficacy remained far from optimal in chronic hepatitis C (Berenguer 2009). In contrast, when administered in recently acquired hepatitis C the efficacy of interferon and ribavirin was much higher. Despite the lack of a formal approval of interferon-based therapies for acute hepatitis C, early treatment was recommended by guidelines to improve treatment outcomes.

The introduction of direct acting antivirals changed the treatment paradigm radically. A brief transition period with boceprevir and telaprevir in combination with pegylated interferon and ribavirin increased antiviral efficacy, but at the expense of even more toxicities.

Finally, in 2014 the broad introduction of interferon-free antiviral combination therapy with excellent tolerance and efficacy lead to the demise of interferon-based therapies. The main concern remaining was their high costs. In some regions of the world the production of generic substances or special pricing negotiations helped to overcome this challenge (Hill 2014, Hézode 2017).

In patent protected markets due to the pricing politics only combination therapies under exclusive control of a single manufacturer survived. However, in generic markets other highly effective combination therapies may be available.

Specifics of the clinical course of hepatitis C in HIV coinfected patients

The natural course of chronic hepatitis C is characterised by a negative effect of HIV induced cellular immunosuppression on the progression of liver fibrosis compared to HCV monoinfected individuals (Eyster 1993, Rockstroh 1996, Soto 1997, Benhamou 2001, Puoti 2004, Danta 2008). This effect was shown to be partially reversible by immune-restoration due to highly active antiretroviral therapy (Qurishi 2003). A negative impact of antiretroviral therapy on the development of liver fibrosis due to liver toxicity could not be demonstrated (Rockstroh 1998, Sulkowski 2000, Rockstroh 2005, Jones 2011).

In cohort data an increased incidence of hepatocellular carcinoma compared to HCV monoinfected individuals was reported. In addition, the progression of hepatocellular carcinoma is thought to be more aggressive (Giordano 2004, Salmon-Ceron 2009, Bourcier 2012, Klein 2016).

A negative impact of HCV infection on the clinical course of HIV infection was not observed in several cohort studies (Sulkowski 2002, Peters 2009). However, a decreased CD4+ cell count was reported in patients with HCV/HIV-coinfection, which may have been due to lymphopenia in patients with splenomegaly (Greub 2000).

Vertical transmission of HCV is a further concern. HCV is detected after birth in 4 to 8% of infants born to HCV positive mothers (Bevilacqua 2009). HCV/HIV coinfection increases the risk for transmission of both viruses and high levels of HCV viraemia in the mother increases the risk of perinatal HCV transmission (Zanetti 1995). However, the risk of HCV transmission is reduced to less than 1% in mothers with HCV/HIV coinfection receiving antiretroviral therapy (ART) and undergoing caesarean section.

Treatment of hepatitis C in patients with HIV coinfection

In general, treatment of HCV in patients with HIV coinfection follows the rules of patients with HCV monoinfection. Efficacy of HCV therapy is comparable to HCV monoinfected patients which is a marked change compared to the interferon era (Molina 2015, Rockstroh 2015, Wyles 2015, Ingiliz 2016, Rockstroh 2018, Buggisch 2018). In contrast to interferon-based therapy, cellular immunosuppression has little influence on treatment efficacy with direct acting antivirals (Opravil 2008, Berenguer 2018). No specific recommendations concerning dosing or duration of HCV therapy exist for HCV/HIV-coinfected patients.

However due to the presence of concomitant antiretroviral therapies and a higher number of comedications in HIV coinfected patients the assessment of drug-drug interactions is important before initiation of HCV therapy.

Aspects to be considered before the start of therapy

As a general rule, the simultaneous administration of cobicistat or ritonavir in combination with a HCV protease inhibitor, i.e. glecaprevir, grazoprevir or voxilaprevir should be avoided due to an increase in drug levels of the latter.

The second rule concerning drug-drug interactions is to avoid any other strong inducers of the cytochrome P 450 3A enzyme family or inducers of p-glycoprotein. Antiretroviral drugs such as efavirenz, nevirapine or rifampicin, rifabutin, rifapentine, carbamazepine and phenytoin should also be avoided (Kaur 2015, Kempker 2019). This may lead to prioritising one treatment over the other in the case of concurrent tuberculosis. In patients without liver cirrhosis completion of tuberculostatic therapy may be preferred before initiating HCV therapy.

The third rule is to avoid the potentially fatal interaction of sofosbuvir with antiarrhytmics. In particular amiodarone should be avoided taking into account the very long half-life of the drug of more than 3 months (Back 2015, Boglione 2019).

For specific information on drug-drug interactions consultation of the website https://www.hep-druginteractions.org/ is highly recommended.

Another important aspect is that HCV protease inhibitors such as glecaprevir, voxilaprevir or grazoprevir are not recommended in patients with decompensated liver cirrhosis due to marked increases in drug levels (summary of product characteristics EMEA). This may cause a problem in case of antiviral failure in patients with decompensated liver cirrhosis as voxilaprevir is contraindicated. In this situation the patient should be registered with a transplant centre as treatment may be completed after liver transplantation.

Treatment of HCV in HIV coinfection

In most countries pangenotypic regimen such as sofosbuvir/velpatasvir (12 weeks) or glecaprevir/pibrentasvir (8 weeks) are the current standard therapy for treatment-naïve HCV patients. Ribavirin may be added to sofosbuvir/velpatasvir in case of liver cirrhosis. As re-treated patients from the interferon era are disappearing, prolonging therapy of glecaprevir/pibrentasvir to 12 weeks in genotype 3 patients is of little relevance. With these regimens tolerance is very good and efficacy of >98% in non-cirrhotic patients is achieved *(see Chapter 3.4)*.

In case of treatment failure sofosbuvir/velpatasvir/voxilaprevir is the treatment of choice with an efficacy of 95% SVR12 (Bourlière 2019). In case of re-infection standard treatments can be used.

Treating patients with failure to sofosbuvir/velpatasvir/voxilaprevir is more complex and requires adherence assessments and resistance testing leading to individual treatment decisions in specialised care centres (Dietz 2021).

In countries with a generic environment sofosbuvir/daclatasvir for 12 weeks is an alternative treatment option except for genotype 2 patients (Rockstroh 2017). Alternatively, sofosbuvir/ravidasvir for 12/24 weeks is another option in particular in Asia as this drug combination was developed with financial support from Thailand and Malaysia (Andrieux-Meyer 2021).

Treatment of recently acquired HCV in HIV

In the past, interferon-based regimens were more efficacious when used in the acute phase of HCV infection, but given the SVR rate of >90% with most DAA regimens in chronic HCV this advantage is no longer important. Nevertheless, some trials assessed the option of shortening treatment with direct acting antivirals in patients with recently acquired hepatitis C with mixed results (Naggie 2017, Rockstroh 2017, Matthews 2021, Martinello 2023). As a consequence, no shortened treatment duration is recommended for patients with acute or recently acquired hepatitis C.

Treatment is recommended in PLWH without a decrease of 2 log of HCV RNA at 4 weeks compared with initial HCV RNA due to the very low probability of spontaneous clearance and in persons with persistent serum HCV RNA 12 weeks after diagnosis of recently acquired HCV (Vogel 2009, NEAT 2011, Thomson 2011, Monin 2023). HCV treatment immediately after diagnosis may be considered in PLWH with ongoing risk behavior to reduce onward transmission. However, counseling strategies to change the risk behavior are also an essential part of the prevention measures (Braun 2021).

Data assessing the effect of early HCV therapy on the incidence of recently acquired hepatitis C in HIV-infected patient populations are conflicting and in 2020-2022 were over-shadowed by lockdown efforts and social distancing due to the COVID-19 pandemic (Smit 2021, Chromy 2022, Kusejko 2022, Popping 2022). However, at least some cohort studies are suggesting a regional effect of DAA therapy on the incidence of acute HCV infection in particular in MSM communities. Nevertheless, reinfection in successfully treated patients is not infrequent and remains a challenge (Berenguer 2019, Ingiliz 2020). Chemsex is an addiction with all the associated psychological aspects and is not easy to modify (Künzler-Heule 2021).

Management of liver cirrhosis and liver transplantation in people with HCV/HIV coinfection

In general, compared to HCV monoinfection, individuals with HCV/HIV coinfection develop more rapid HCV-related hepatic injuries such as liver fibrosis and cirrhosis. Additionally, HCV/HIV coinfection is associated with an increased rate of hepatocellular carcinoma (HCC). Typically, HCC occurs in coinfection at an earlier age and the course is more aggressive, with a shorter survival compared to HCV mono-infection (Giordano 2004, Salmon-Ceron 2009, Bourcier 2012, Klein 2016). An ultrasound of the liver should be performed every six months for HCC surveillance in patients with F3/F4 fibrosis, according to EACS guidelines (EACS 2022). Alternative imaging procedures (MRI, CT) should be considered in case of low-quality ultrasound results. It is important to note that HCC screening and monitoring of decompensation is upheld in patients with cirrhosis even after HCV cure has been achieved as improvement in liver stiffness may occur but not complete reversal (Berenguer 2024).

As upper gastrointestinal bleeding is another important complication, the presence of oesophageal varices using upper-gastrointestinal endoscopy should be monitored in patients with liver cirrhosis every year. Liver transplantation should be considered in patients with decompensated liver cirrhosis. Clinical experience is encouraging in patients with well-controlled HIV infection (Mindikoglu 2008, Baccarini 2011, Anadol 2012). To fulfil the selection criteria for a liver transplant in individuals with HCV/HIV coinfection, the CD4+ T cell count has to be at least 100 cells/µl. Additionally, the patient has to have either undetectable HIV viraemia (<50 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 use, large multilocular HCC or HCC metastasis in other organs, a second malignant disease, advanced cardiopulmonary disease or older age with an elevated perioperative mortality risk (EACS 2022).

The possibility to eradicate HCV in virtually all patients posttransplant due to the high efficacy of DAA regimen will positively affect transplant survival. On the other hand, the need for liver transplantation due to chronic HCV will be substantially reduced over the years to come in countries with large scale access to DAAs.

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