Hepatitis C virus infection in the human immunodeficiency virus infected patient

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Abstract

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) share the same transmission routes; therefore, coinfection is frequent. An estimated 5-10 million individuals alone in the western world are infected with both viruses. The majority of people acquire HCV by injection drug use and, to a lesser extent, through blood transfusion and blood products. Recently, there has been an increase in HCV infections among men who have sex with men. In the context of effective antiretroviral treatment, liver-related deaths are now more common than Acquired Immune Deficiency Syndrome-related deaths among HIV-HCV coinfected individuals. Morbidity and mortality rates from chronic HCV infection will increase because the infection incidence peaked in the mid-1980s and because liver disease progresses slowly and is clinically silent to cirrhosis and end-stage-liver disease over a 15-20 year time period for 15%-20% of chronically infected individuals. HCV treatment has rapidly changed with the development of new direct-acting antiviral agents; therefore, cure rates have greatly improved because the new treatment regimens target different parts of the HCV life cycle. In this review, we focus on the epidemiology, diagnosis and the natural course of HCV as well as current and future strategies for HCV therapy in the context of HIV-HCV coinfection in the western world.

Core tip: Hepatitis C virus (HCV) infection incidence has increased among men who have sex with men. Additionally, mortality and morbidity from chronic HCV infection has increased and liver-related deaths are now more common than Acquired Immune Deficiency Syndrome-related deaths. Several new direct-acting antiviral agents have been developed or are under development, and therapy strategies change faster than guidelines can be updated. This review focuses on the epidemiology, diagnosis, natural course and treatment of HCV infection in human immunodeficiency virus infected patients.

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INTRODUCTION

A hallmark feature of hepatitis C virus (HCV) infection is its propensity for lifelong chronic infection. The majority (65%-80%) of all infected individuals remain chroni-
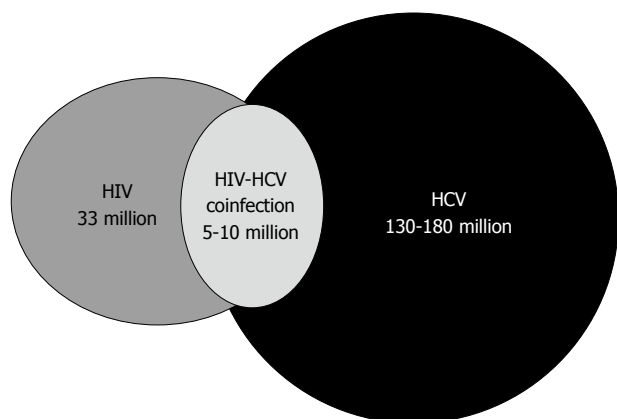
Figure 1 Worldwide numbers of human immunodeficiency virus infected, hepatitis C virus infected or human immunodeficiency virus - hepatitis C virus coinfected individuals. HIV: Human immunodeficiency virus; HCV: Hepatitis C virus.

cally infected and at risk of severe liver disease (cirrhosis, end-stage liver disease and liver cancer); however, the remaining 15%-40% spontaneously resolve their infections[1]. Worldwide, this has resulted in more than 130 million chronically infected individuals. We conducted a narrative review to provide an overview of human immunodeficiency virus (HIV)-HCV coinfection. A comprehensive computerized literature search was carried out with PubMed and ClinicalTrials.gov to collect relevant articles. This review describes the epidemiology, diagnosis and the natural course of HCV as well as guidelines for HCV therapy in the context of HIV-HCV coinfection in the western world.

EPIDEMIOLOGY

HCV and HIV share the same routes of transmission; therefore, coinfection with both viruses is frequent with an estimated 5-10 million coinfected individuals[2] (Figure 1). Contaminated blood product transmission used to be an important route of exposure, which explains why many hemophiliacs are coinfected with HIV-HCV. However, with the introduction of HIV and HCV screening, the blood product transmission rate has decreased in the western world[3]. Now, the primary routes of parenteral exposure are through injection drug use and, to a minor extent, through tattooing and piercing. The HIV and HCV transmission efficiency varies and transmission through percutaneous blood exposure is 10-fold higher for HCV compared with HIV[4]. As a consequence of this the incidence rate of HCV infection is higher than HIV among people who inject drugs (PWID)[5], and it is estimated that 50%-90% of all PWIDs are infected with HCV[6-10]. PWIDs with HIV-HCV coinfection are a population with behavioral and psychosocial problems, which together with clinical challenges, impacts not only the HIV and HCV infection course but also its treatment with antiviral therapy[11].

HCV also occurs through sexual transmission. Over

the last decade, an increase in the HCV incidence rate among men who have sex with men (MSM) has emerged[12-15]. The background for the increased sexual transmission appears complex[16]. Sexual transmission has traditionally been considered inefficient, and truly, heterosexually HCV transmission is inefficient. Hence, the few prospective studies performed in heterosexual monogamous couples reported incident transmission rates of 0%-0.6% per year[17-19]. However, the increased transmission among MSM may be explained by changes in sexual behavior due to the expanded antiretroviral treatment (ART) availability and the lowered risk of HIV transmission, therefore, leading HIV infected individuals to engage in unprotected sexual activity with individuals with the same HIV status (termed serosorting)[8-10,16]. Further, traumatic sexual practices and substance abuse may increase bleeding during sexual activity and thereby increase the HCV transmission risk[16]. Finally, an increase in sexually transmitted diseases has been associated with serosorting and increased HCV transmission[14,20,21].

Transmission from mother-to-child is estimated at 4%-7% per pregnancy in women with HCV viremia (reviewed in[22]). Coinfection with HIV increases the transmission rates 4-5-fold; however, transmission is associated with levels of HCV and HIV viremia. Additionally, in a cohort of coinfected women who all received ART, no HCV transmission occurred[23]. The actual time and mode of transmission is unknown.

ACUTE HCV INFECTION

Acute HCV infection is defined as the first 6-mo period after HCV infection. The definition is arbitrary as the determination of when an acute infection becomes chronic is uncertain and no serological tests are available to distinguish between the two. Initial HCV infection is characterized by the detection of HCV RNA in the blood 2-14 d post exposure, increasing levels of liver-associated plasma enzymes and the gradual appearance of HCV antibodies[24]. In HIV infected individuals, the appearance of HCV antibodies may be delayed or absent, hypothetically, due to immunosuppression, with failure to mount or maintain HCV antibody titers for detection by standard serodiagnostic tests. The few studies conducted to assess the incidence of seronegative chronic HCV infection reported an incidence between 0%-13%[25-27].

Acute HCV clinical diagnosis has a low sensitivity as 75%-80% of cases are asymptomatic and are diagnosed based on risk history [*e.g.*, needle stick injury or injection drug use (IDU)] or elevated liver-associated enzymes. Symptomatic acute HCV is often mild and involves nonspecific symptoms, such as lethargy and myalgia; however, jaundice might also be observed[28,29]. Little is known about the natural history of early HCV infection in HIV-positive individuals. Its clinical presentation has been described as being similar in HIV infected and HIV uninfected patients[14,30] as well as having less pronounced clinical symptoms with HIV infection[31].

FACTORS ASSOCIATED WITH HCV RESOLUTION

The spontaneous HCV resolution rate is considered to be lower in HIV infected individuals than in HCV infected individuals without HIV, with estimates varying between 5% and 25%[4,32-34].

Several factors affect the HCV resolution rate. There is an overall consensus that female sex, younger age at infection, Caucasian race[33], coinfection with hepatitis B virus (HBV)[32,35-37] and symptomatic acute hepatitis[34,38-40] are associated with resolution. A strong genetic association with spontaneous HCV resolution has been mapped to a single nucleotide polymorphism (SNP) located approximately 3 kb upstream of interleukin 28B (*IL28B*; rs12979860)[41-46]. The genetic variations in SNPs marking *IL28B* explained approximately 10% of spontaneous HCV resolution cases[47]; however, the effect of *IL28B* on HCV may vary between HCV genotypes[48].

Both innate and adaptive immunity is believed to make important contributions to spontaneous resolution. HCV resolution has been associated with a rapid production of broadly neutralizing antibodies and a strong, broadly targeted T cell response. The innate immune response is induced upon recognition of viral pathogen-associated molecule patterns that are sensed by pathogen-recognition receptors. The sensing of HCV, which occurs through interaction with toll-like-receptors (TLR) and retinoic acid-inducible gene-I (RIG-I), leads to an intracellular signaling cascade that activates interferon (IFN) regulatory factors and ultimately induces production of IFNs. The production of IFNs leads to transcription of hundreds of IFN- stimulated genes (ISG) through the JAK-STAT signal pathway, which results in an antiviral state in the liver[49].

Individuals who resolve HCV infection have a broader and more sustained CD4 and CD8 T-cell response (reviewed in[50]) than individuals with chronic HCV. The detection of fully functional HCV-specific CD4 T lymphocytes during acute infection is associated with subsequent HCV resolution[51]. Further, a temporal association between the detection of HCV-specific CD8 T-cell responses indicates that CD8 T-cells are also important in HCV resolution. Hence, both CD4 and CD8 T-cell responses are required to achieve HCV resolution. The importance of CD4 T lymphocytes in resolution is further underscored by the lower resolution rate found with HIV coinfection, which may in part be due to CD4 T lymphocyte depletion.

Genetic associations with spontaneous HCV resolution have been investigated in many different parts of the human immune response. In the innate immune response, associations have been reported in killer immunoglobulin-like receptors (KIR)[52], inhibitor of NF-kB ε (*IkBε*)[53], TLR-7[54] and in the three main effector pathways of the IFN-mediated antiviral response, which include MxA, 2'5'-oligoadenylate-synthetase-directed ribonuclease L (OAS-1) and protein kinase R (PKR)[55].

In the adaptive immune response, the human-leukocyte-antigen (HLA) class II loci DQ and DRB1 are the loci with the most consistently association with spontaneous HCV resolution[40,56-63]. Further, regarding HLA class I, HLA-B57 and B27 have been associated with resolution[64-66]. The association with B57 is interesting because B57 has also been reported to be associated with slower HIV disease progression[67-70].

CHRONIC HCV INFECTION

The risk factors for progression to chronic HCV infection include asymptomatic acute infection, male sex, older age at infection, black ethnicity, HIV co-infection and non-CC *IL28B* genotypes[9,33,71].

Chronic HCV infection in HIV infected individuals differs from that in individuals without an HIV infection in several ways. Coinfected individuals have a higher HCV viral load[72] and thereby have higher transmission rates. Coinfection is also associated with more rapid progression of fibrosis[73], cirrhosis[74], end-stage liver disease (ESLD) and hepatocellular carcinoma[75-79]. Recently, Kirk *et al*[77] reported that even after an adjustment for HCV viral load (VL) levels, HBV chronicity, sex, race and alcohol use, HIV-HCV coinfection was associated with liver fibrosis as advanced as those without HIV who were 10 years older.

The improvement of ART in the mid-1990's led to greatly improved survival from HIV infection. With the decline in Acquired Immune Deficiency Syndrome (AIDS)-related deaths, non-AIDS causes of morbidity and mortality have become prevalent[80] and for HIV-HCV coinfected individuals, the burden of disease is largely related to their HCV disease[81-86]. A recent study of mortality from 2005-2009 in the Swiss HIV Cohort Study reported that 32% of deaths among individuals coinfected with HIV-HCV were caused by liver failure, including hepatocellular carcinoma[86]. HCV viral load[72,76,87-89], HCV genotype 3[87,89-93], ART[94], HCV treatment[95], CD4 T lymphocyte nadir[96], age, and drug use[97] have been shown to be associated with mortality in HIV-HCV coinfected individuals.

The differences in the causes of mortality among HCV infected individuals with and without HIV may reflect the differences in life-style-related risks for disease, drug use; the lasting chronic inflammation state, late presentation, treatment failure, prolonged immunodeficiency prior to treatment or no access to care or ART[80,98]. As a consequence of the high HCV prevalence in the HIV infected patient populations and accelerated disease progression, HCV-related morbidity and mortality is a substantial concern in HIV infected patients.

DIAGNOSIS

All HIV-infected patients should be tested for HCV infection. Initial screening for HCV should be performed by testing for anti-HCV antibodies; however, chronic

HCV infection diagnosis is based on the presence of both anti-HCV antibodies (detected by enzyme-immuno-assays) and HCV RNA (detected by molecular assays)[99].

False negative anti-HCV results may occur in HIV-infected persons with advanced immuno-suppression (CD4 < 100/mm^3). Additionally, true negative anti-HCV results are common during acute HCV infection prior to seroconversion[26,100]. Different estimates of the duration from infection to seroconversion are specified and vary from 20-150 d. Most authors agree, however, that anti-HCV antibodies are expected to be detectable within the first 12 wk after exposure[24]. If anti-HCV is negative and HCV infection is still suspected due to elevated liver enzyme levels or risk factors, such as IDU or high-risk sexual behavior, HCV RNA testing should be performed.

HCV RNA is detectable in the plasma of most patients within 2 to 14 d following infection[24]. During the transition from an acute to a chronic infection, HCV RNA and serum alanine and aspartate aminotransferase (ALT and AST) levels may fluctuate, and some patients may have periods with undetectable HCV RNA and normal ALT levels[1]. While a single detectable HCV RNA result is sufficient to confirm the diagnosis of an active HCV infection, a single negative result cannot exclude active viremia because RNA levels might transiently decline below the detection limit; therefore, repeated testing is advised[1]. After the establishment of a chronic HCV infection, the HCV RNA levels stabilize and vary less than 1 log in the majority of cases[101]. The most recent HCV RNA assays are based on the use of the polymerase chain reaction and can detect HCV RNA between 10 IU/mL to 10^7 IU/mL[102,103]. Serum ALT and AST levels often fluctuate, and prolonged periods of normal serum liver enzyme levels may be observed. Although higher serum ALT and AST levels are clearly predictive of a more rapid disease progression and calls for an additional assessment of liver parenchymal changes, significant liver disease may be present even in the case of persistently normal ALT levels[104].

HCV has six clinically relevant genotypes that can be subdivided into multiple subtypes. HCV genotyping is essential when considering HCV treatments. It predicts the response to treatment and influences the decision to start a treatment and/or perform a liver biopsy. Several tests are available to determine HCV genotypes, and the most accurate method is to sequence an appropriate region that is divergent enough to discriminate subtypes and genotypes. Most assays target the highly conserved 5' untranslated region (5'UTR) as well as the E1 and NS5B regions of the HCV genome[105,106].

Hepatic parenchymal change severity assessments can be done by liver biopsy, liver transient elastography (TE) or by serum biomarker evaluation. Liver biopsy is considered the gold standard; however, its use is limited by the fact that its invasiveness carries the risk of rare but potentially lethal complications as well as the possibility of sampling error and intra- and inter-observer variability[107]. In contrast, liver biopsies provide histological fi-brosis staging and the simultaneous evaluation of necro-inflammation, which enables for an assessment of the current fibrosis stage and activity level[108].

TE is non-invasive, painless, rapid and easy to perform at the bedside or in the outpatient clinic. The results are immediately available. TE reproducibility has been shown to be excellent in both inter- and intra-observer agreements[108,109]. One limitation of TE is that overestimation of liver stiffness may occur in patients with pronounced liver inflammation[110]. TE is obviously not capable of giving a direct histological liver description. The diagnostic accuracy of TE is high for cirrhosis, but poor for significant fibrosis[111].

Blood parameters combined with other biochemical factors have been validated to non-invasively predict the extent of liver fibrosis in a variety of liver diseases. Some tests are based on laboratory markers that are routinely available for most HIV-HCV coinfected individuals [*e.g.*, the AST-to-Platelet-Index (APRI), FIB-4 ((Age × AST)/{Platelets × [sqr (ALT)]}), Forns {7.811 - 3.131 × ln [number of platelets (10^9/L)] × 0.781 ln [GGTP (U/L)] + 3.467 × ln [age (years)] - 0.014 [cholesterol (mg/dL)]}]. The tests have mostly been validated in chronic HCV infected individuals without HIV. In HIV-HCV coinfected individuals, APRI, Forns and FIB-4 were found to be accurate for cirrhosis diagnoses but relatively inaccurate for significant and advanced fibrosis diagnoses[112,113].

ANTIVIRAL THERAPY

ART has been strongly associated with a slower fibrosis progression, decline in liver inflammation and decreased liver-associated mortality risk in HIV-HCV coinfected patients[73,114-118]. ART is, thus, indicated for every individual coinfected with HIV and HCV. However, the adverse impact of HIV coinfection on HCV disease is not entirely ameliorated by ART[76,119] and treatments aimed at chronic HCV infection eradication has been associated with a significantly lower risk of clinical events, as measured by ESLD, hepatocellular carcinoma or death rates. Interestingly, in a study by Limketkai *et al*[76], individuals who achieved viral suppression with either sustained (negative HCV RNA 24 wk after stopping therapy) or transient (undetectable HCV RNA during treatment but detectable in the follow-up period) HCV treatment experienced fewer clinical events post-HCV treatment in contrast to individuals who did not respond to HCV treatment or who did not undergo an HCV treatment. Thus, HCV treatment is required despite the many barriers, including decompensated liver disease, substance abuse, socioeconomic status and compliance issues.

Chronic HCV infection treatments

Guidelines recommend HCV therapy initiation prior to ART if CD4 T lymphocytes are > 500/μL based on the evidence that HCV therapy is associated with lower responses in individuals with CD4 T lymphocytes < 500/μL[120,121]. In individuals with CD4 T lymphocytes <

Table 1 Interferon-free clinical trials conducted in human immunodeficiency virus - hepatitis C virus coinfected individuals

Direct acting antiviral			Ribavirin	Study name/ identifier[1]	Patient population	Phase	Primary endpoint	Presented results
Ns3/4a protease inhibitor	Ns5b polymerase inhibitors	Ns5a inhibitors						
No	Sofosbuvir	No	Yes	Photon-I (Ncto1667731)	GT 1: TN and IFN ineligible GT 2 + 3: TE	3	SVR 12	GT 1: 76%[2] GT 2: 88% GT 3: 67%
No	Sofosbuvir	No	Yes	Ncto1783678	GT 1 + 2 + 3 + 4: TN and IFN ineligible GT 2 + 3: TE	3	SVR 12	No
ABT-450(r)	ABT-333	ABT-267	Yes	Turquoise I (Ncto1939197)	GT 1 TN + TE	3	SVR 12	No
MK-5172	No	MK-8742	Yes	c-WORHTy (Ncto01717326)	GT 1	2	SVR 12	No

[1]ClinicalTrials.gov; [2]Preliminary data presented at the Conference on Retroviruses And Opportunistic Infections, 2014. GT: Hepatitis C virus genotype; TN: Treatment naive; IFN: Interferon; TE: Treatment experienced; SVR: Sustained virological response; r: Ritonavir boosted.

Table 2 Treatment strategies including direct-acting antivirals in combination with ribavirin with or without pegylated interferon conducted in hepatitis C virus infected individuals with human immunodeficiency virus infection

Direct acting antiviral			Ribavirin/Peg Inf	Study name/ identifier[1]	Treatment duration	Phase	Primary endpoint	Presented results
Ns3/4a protease inhibitor	Ns5b polymerase inhibitors	Ns5a inhibitors						
Boceprevir	No	No	Yes	NCT00959699	48 wk	APPROVED	SVR24	GT 1: 63%[123]
Telaprevir	No	No	Yes	NCT00983853	48 wk	APPROVED	SVR12	GT 1: 74%[124]
Simeprevir	No	No	Yes	C212 NCT01479868	24/48 wk[2]	III[3]	SVR12	GT 1: 79%-87%
Faldaprevir	No	No	Yes	Startverso4 NCT01399619	24/48 wk[2]	III	SVR12	GT 1: 71%-72%

[1]ClinicalTrials.gov; [2]Simeprevir/faldaprevir+pegIFN/RBV for 12-24 wk, then pegIFN/RBV for 12-24 wk; [3]Approved in HCV monoinfected with HCV genotype 1. RBV: Ribavirin; GT: Hepatitis C virus genotype; TN: Treatment naive; IFN: Interferon; TE: Treatment experienced; SVR: Sustained virological response; r: Ritonavir boosted.

$500/\mu L$, ART is initiated prior to HCV treatment.

HCV therapies change faster than the international guidelines are updated, and in the following section, we will attempt to provide an overview of the current and future possible treatment strategies for HIV-HCV coinfected individuals. Pegylated (peg) IFN will remain the backbone of some HCV therapy combinations in 2014 and 2015, but it is then expected to disappear from HCV therapy regimens. We provide an overview of interferon free clinical trials that include HIV infected individuals in Table 1. Ribavirin (RBV) can be used to increase sustained virological response (SVR) rates or to shorten the treatment durations with pegIFN or IFN-free regimens and will most likely remain in some HCV therapy strategies. Direct-acting antiviral (DAA) agents in HCV therapies target different steps of the viral lifecycle. DAAs are comprised of NS3/4A protease inhibitors, NS5B polymerase inhibitors, nucleoside/nucleotide analogues, non-nucleoside analogues inhibitors of the HCV RNA dependent RNA polymerase, cyclophilin inhibitors and miRNA-122 antagonists (as reviewed in[122]). Few DAAs, however, are approved for HCV therapy (Table 2) and the most of them are in phase II or III development. The antiviral effect of a DAA therapy can be optimized by combining several DAAs with or without RBV (Table 3) and this combination strategy has shown that it is possible to achieve SVR with interferon-free regimens.

The first DAAs to be approved for HCV treatment were the NS3/4A protease inhibitor, telaprevir or boceprevir in combination with peg IFN and ribavirin. These compounds are on their way out of HCV therapy and are being replaced with the nucleotide analogue, sofosbuvir, in combination with RBV with or without peg IFN as the best treatment option in HCV genotype 1 and 4 infections. The addition of sofosbuvir to pegIFN/RBV (triple therapy) for 24 wk increases the 12-wk post-treatment termination SVR rate (SVR12) to 76%. For genotype 2 infections, the current best treatment option is an IFN-free regimen with sofosbuvir and RBV for 12 wk. This results in an 88% SVR12 rate. In genotype 3 infections, the same regimen is approved; however, the treatment duration is extended to 24 wk, which results in a 67% SVR12 rate. Data regarding HCV genotype 5 and 6 is limited, however, sofosbuvir + pegIFN + RBV appears to be the best treatment option for these HCV types.

The next DAAs to be approved will most likely be simeprevir, faldaprevir and daclatasvir (the available data from these DAA studies regarding HIV-HCV coinfected patients are summarized in Table 2). However, treatment with DAAs is costly and the high costs will most likely

Table 3 Current and future treatment strategies for chronic hepatitis C virus infected patients							
Treatment strategy	Compounds	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
Interferon Based	Sofosbuvir	×	×	×	×	×	×
	Simeprevir	×			×		
	Daclatasavir	×		×	×	×	×
Interferon free	Sofosbuvir + ribavirin		×	×			
	Sofosbuvir + simeprevir	×			×		
	Sofosbuvir + daclatasavir	×		×	×	×	×

influence the treatment strategy choice and result in first-, second- and third-line HCV treatment strategies.

With the potent therapeutic strategies combining different DAAs with or without RBV, the SVR rates are not fundamentally different between HCV mono-infected and HCV-HIV coinfected patients. However, drug-drug interactions (DDI) with ART are of concern as most HIV infected individuals are also treated for their HIV infection. Briefly, no clinically significant DDIs have been reported to occur between sofosbuvir and antiretrovirals. With respect to simeprevir, co-administration with antiretroviral CYP34A inducers is not recommended; however, with respect to daclatasvir dose reduction, it is recommended when administered with specific antiretroviral drugs. Still, data are limited and more studies are warranted to assess DDIs with ART. When initiating HCV therapy, the antiretroviral agents should be carefully assessed and if bidirectional interactions are present, then the HIV regimen should be switched to an acceptable combination. After an ART switch, the HCV therapy is suspended until the patient is virally stable and tolerating the new ART regimen.

Treatment indications for HCV in HIV-HCV coinfected individuals are based on liver disease progression. The decision to initiate or defer treatments to wait for more potent treatment regimens - which are expected to be available within the next 2-3 years - depends on the liver fibrosis stage, rapidity of fibrosis development and the former treatment responses. In individuals without fibrosis or with mild fibrosis (Metavir F0/F1), treatment deferral that is independent of any former treatment response may be reasonable[76]. In individuals with significant fibrosis (Metavir F2/F3), treatment can also be deferred; however, annual liver fibrosis progression assessments are required because the progression may be rapid[125]. Others suggest that individuals with significant fibrosis who are treatment naïve or relapsed with former anti-HCV treatments should be treated according to current guidelines (see below)[125,126]. The reason for not deferring therapy is the risk of liver decompensation among the coinfected individuals with bridging fibrosis within a short time period[125]. In individuals with cirrhosis (Metavir F4), HCV treatment is recommended independent of former treatment responses. Initiation of HCV therapy should be taken with a cautious approach because new DAAs with higher efficacy, lower pill burden, less pronounced interaction profiles and, hopefully, fewer side effects as well as new drug classes (also for non-genotype 1 patients)

are under way. Further, the potential risk of resistance development, especially in this group of co-infected individuals who have a higher viral load than mono-infected individuals, should be taken into consideration.

Acute HCV infection treatment

The standard of care treatment for acute HCV infection is pegIFN/RBV, and the therapy duration is based on rapid virological response regardless of genotypes. Treatment in the acute HCV phase leads to SVR rates of 50%-91%[127]. In persons with acute HCV, HCV RNA should be measured at initial presentation and 4 wk later. Treatment should be offered to patients without a 2 log10 HCV RNA decrease at 4 wk compared with the initial HCV RNA level and to persons with persistent detectable serum HCV RNA levels 12 wk after acute HCV diagnoses. Persons who do not achieve more than a 2 log10 decrease in HCV RNA level at week 12 should discontinue therapy[128]. Currently, DAAs are not recommended as a first-line treatment for acute HCV infections.

INFLUENCE OF HCV ON HIV PROGRESSION AND ANTI-RETROVIRAL THERAPY

The effect of ART is modified by HCV resulting in an earlier time to virological failure, lower CD4 T lymphocytes and a smaller and slower CD4 T lymphocyte increase than observed in HIV-treated infected individuals without HCV[129,130]. This is clinically relevant as HCV/HIV coinfection is associated with a higher risk of developing a new AIDS-related diagnosis or death. Thus, early ART initiation in HIV-HCV coinfected individuals is justified not only to delay liver fibrosis development but also to gain the protective effects of HIV therapy on HIV disease progression.

The total number of circulating CD4 T lymphocytes has well-validated predictive value for assessing progression to clinical AIDS and AIDS-related death, determining ART eligibility and monitoring responses to therapy. The number of CD4 T lymphocytes expressed as a percentage of lymphocytes (CD4%) has been suggested as a more appropriate HIV disease marker and predictor of HIV progression in individuals with HCV and CD4 T lymphocytes > 350 cells/mm^{3}[131]. CD4 discordance describes the phenomenon where the absolute and relative CD4 cell relationship differs from what would be

expected. CD4 discordance has been reported with high frequency in individuals with fibrosis, cirrhosis and ESLD[132,133] and thus, the consideration of CD4% measurements in individuals with HCV may be appropriate.

CONCLUSION

Due to shared routes of transmission, HIV and HCV coinfection is frequent and, in the western world, the majority of infected individuals are PWID. A minor subset of infected individuals has the ability to spontaneously resolve HCV infections, but the majority develop chronic HCV infection with the risk of cirrhosis, end-stage-liver-disease and hepatocellular carcinoma. With the decline in AIDS-related deaths, non-AIDS causes of morbidity and mortality have become prevalent and for HIV-HCV coinfected individuals, the burden of disease is largely related to their HCV disease. A consensus of the influence of HIV on the natural course of HCV exists; however, how HCV influences the natural course of HIV is still debated and no final conclusions have been drawn.

Treatment options for HCV are rapidly evolving towards an interferon-free all-oral treatment regimen. Currently, treatment responses to HCV therapy are lower than what is seen in individuals without HIV. With interferon- and even ribavirin-free combination treatment regimens, the response rates do not differ significantly from the ones seen in chronic HCV infected patients without HIV, and any coinfected individual should be evaluated for HCV therapy on an individual basis.

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