Chapter 5

Current Therapeutic Options for HCV-HIV Coinfection

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Additional information is available at the end of the chapter

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Abstract

Due to shared risk factors for transmission, coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is a very common event. The prevalence of HCV infection among HIV-positive patients averages about 35%. In HIV/HCV co-infected patients, liver-related morbidity and mortality is a prominent non-AIDS-defining complication: up to 90% of liver-related deaths in HIV-infected patients are attributable to HCV. The progression of liver fibrosis is accelerated in HIV/HCV-coinfected patients, particularly in individuals with low CD4 counts (≤350 cells/mm^3). Antiretroviral therapy may slow liver disease progression in HIV/HCV-coinfected patients and should, therefore, be considered for all coinfected patients regardless of CD4 cell count. Most patients with HIV/HCV coinfection are taking multi-drug antiretroviral therapy, which may pose a problem with drug–drug interactions when initiating therapy with HCV medications. Rapid advances in HCV drug development led to the discovery of new classes of direct-acting antiviral (DAA) agents that target the HCV replication cycle. Several studies demonstrated comparable rates of sustained virological response (SVR) in coinfected and monoinfected patients with new DAA-based therapy.

Keywords: HCV/HIV-coinfection, liver cirrhosis, CD4 T lymphocytes, antiretroviral therapy (ART), direct-acting antiviral (DAA) agents, drug–drug interaction

1. Introduction

By the Global AIDS Update: 2016, around 36.7 million people are living with human immunodeficiency virus (HIV) in the world today [1]. Five million of them are also infected with hepatitis C virus (HCV) [1]. HIV accelerate the progression of hepatitis C, inducing increased morbidity and mortality [2]. HIV-infected people are on average six times more likely than HIV-uninfected people to have HCV infection [3].

HIV and HCV share modes of transmission: often occurring by exposure to blood, sexual intercourse or by mother-to-child transmission.

2. Epidemiology

The prevalence of HCV antibodies varies widely among HIV transmission groups, ranging from 7–8% in men who have sex with men to 60–70% in hemophiliacs and 80–90% in intravenous drug users (IDUs), the most important group (**Figure 1**) [4].

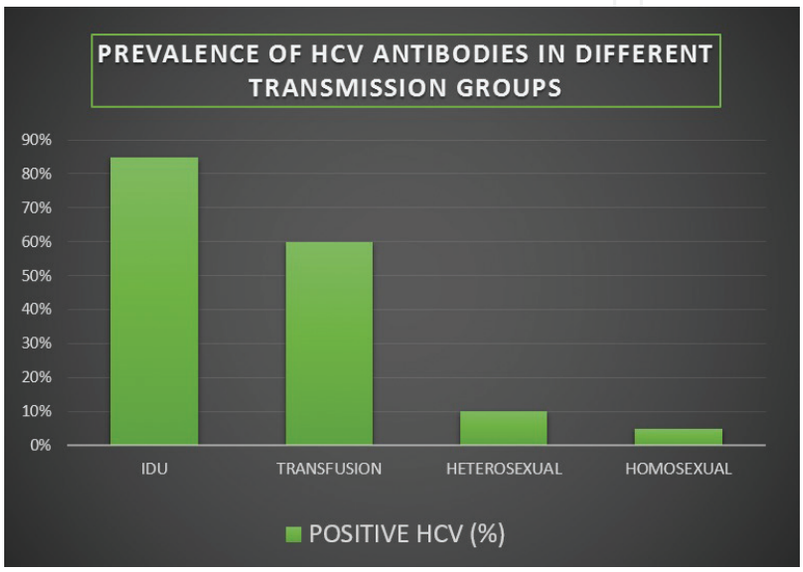

Figure 1. Prevalence of HCV antibodies in different transmission groups. IDU, intravenous drug users; HCV, hepatitis C virus. Inspired by Management of Hepatitis C and HIV coinfection, Clinical Protocol for the WHO European Region. Available at: http://www.euro.who.int/data/assets/pdf_file/0008/78146/E90840Chapter6.pdf, Version September 1th, 2015.

For HIV-infected patients with HCV coinfection, liver-related morbidity and mortality is a prominent non-AIDS-defining complication [5]. Up to 90% of liver-related deaths in HIV-infected patients are attributable to HCV [5].

Among patients with chronic HCV infection, approximately one-third progress to cirrhosis, at a median time of 20 years [6–8]. The risk of progression is even greater in HCV/HIV-coinfected patients with low CD4 T lymphocyte (CD4) cell counts (≤350 cells/mm^3) [6, 9, 10]. Cirrhosis has been observed to occur 12–16 years earlier in HIV/HCV-coinfected patients compared with those who have HCV monoinfection [11].

3. Antiretroviral therapy (ART) in HIV/HCV-coinfected patients

Antiretroviral therapy (ART) may slow liver disease progression in HIV/HCV-coinfected patients and should, therefore, be considered for all coinfected patients regardless of CD4

NRTIs	NNRTIs	Protease inhibitors	Entry inhibitors	Integrase inhibitors
Abacavir	Efavirenz	Atazanavir, atazanavir/ritonavir	Enfuvirtide	Dolutegravir
Didanosine	Etravirine	Darunavir/ritonavir Darunavir/cobicistat	Maraviroc	Raltegravir
Emtricitabine	Nevirapine	Fosamprenavir		
Lamivudine	Rilpivirine	Lopinavir		
Stavudine		Saquinavir		
Tenofovir				
Zidovudine				

Table 1. Standard recommended treatments for naive patients with HIV-1 infection.

cell count [12]. This recommendation is supported by observational studies that suggest that antiretroviral therapy may reduce the risk of liver-related morbidity. The key issues in the clinical management of HIV/HCV-coinfected patients are which treatment for each condition and when to initiate it [12].

Classes of antiretroviral agents are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs), entry/fusion inhibitors (FIs) and chemokine receptor antagonists (CCR5 antagonists).

Standard recommended treatments for naive patients with HIV-1 infection (**Table 1**) generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (booster) (cobicistat or ritonavir) [12].

Antiretroviral therapy (ART) associated with liver injury is more common in HIV/HCV-coinfected patients than in those with HIV monoinfection [6, 13]. Some older ART have been associated with higher rates of liver injury in patients with chronic HCV infection, but newer ART drugs currently in use appear to be less hepatotoxic [6, 13]. Patients with significant alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis) [6, 14]. Short-term interruption of the ART regimen or of the specific drug suspected of causing the liver injury may be required [6, 14].

4. Concurrent treatment of HIV and HCV by the Office of AIDS Research advisory council (OARAC 2016)

If the decision is made to treat HCV, the antiretroviral regimen may need to be modified before HCV treatment is initiated to reduce the potential drug–drug interactions and/or toxicities that may develop during the period of concurrent HIV and HCV treatment [6].

In patients with suppressed plasma HIV RNA and modified antiretroviral therapy, HIV RNA should be measured within 4–8 weeks after changing antiretroviral therapy to confirm the effectiveness of the new regimen [6]. After completion of HCV treatment, the modified ART regimen should be continued for at least 2 weeks before reinitiating the original regimen [6]. This is necessary because of the prolonged half-life of some HCV drugs and the potential risk of drug–drug interactions if a prior HIV regimen is resumed soon after HCV treatment is completed [6].

5. HCV therapy in HIV/HCV-coinfected patients by EASL recommendations on treatment of hepatitis C, 2016

With direct-acting antivirals (DAAs), HCV cure rates of both HCV mono and HIV/HCV-coinfected persons are greater than 95% [15]. Current treatment guidelines no longer separate these two groups. Indications for HCV treatment and choice of direct-acting antiviral (DAA) agents combination are now the same for all HCV patients. In HIV/HCV co-infection, drug interactions between HIV and HCV agents need be checked prior to starting HCV therapy [15]. The higher risk of hepatic decompensation in HIV/HCV-coinfected patients, including those receiving successful antiretroviral therapy, continues to make these patients a high priority group for receiving access to direct-acting antiviral (DAA) agents as combination therapy [15].

6. Key studies for treatment of HCV with HIV coinfection

Using DAA therapy, several studies demonstrated comparable rates of sustained virological response (SVR) in coinfected and monoinfected patients.

These trials, however, have primarily included individuals with CD4 counts >200 cells/mm^3, and most patients in these trials did not have cirrhosis.

6.1. Sofosbuvir for genotype 1–4 in HIV coinfection by Rodriguez-Torres et al.

In an open-label trial, 23 HCV/HIV-coinfected treatment-naive patients with genotype 1–4 received the 12-week triple therapy of peginterferon alfa-2a, ribavirin (weight-based) and sofosbuvir [16]. Mean CD4 count was 562 cells/mm^3, and all were on antiretroviral therapy (tenofovir-emtricitabine plus one of the following: efavirenz, atazanavir plus ritonavir, darunavir plus ritonavir, rilpivirine or raltegravir) [16]. The overall SVR12 rate was 91%; of the 19 patients with genotype 1, 89% achieved an SVR12 (**Figure 2**) [16].

6.2. TURQUOISE-I by Wyles et al.

This open-label study randomized treatment-naive and experienced patients with chronic HCV genotype 1 and HIV coinfection to receive a 12- or 24-week course of ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin [17]. Patients were required to have

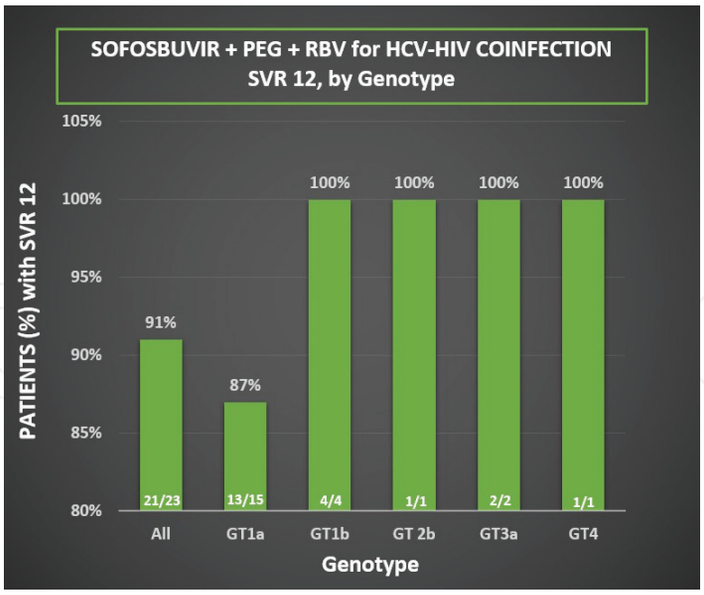

Figure 2. Sofosbuvir for genotype 1-4 in HIV coinfection. PEG, peginterferon alfa-2a; RBV, ribavirin; SVR12, sustained viral response 12 weeks after the end of treatment; GT, genotype. Inspired by http://slides.hcvonline.org/uploads/151/sofosbuvir_for_genotype_14_in_hiv_coinfection.pdf

a CD4 > 200 cells/mm^3 and an HIV RNA level < 40 copies while receiving an atazanavir- or raltegravir-based regimen [17]. The sustained virological response (SVR) 12 rates were 93.5% (29 of 31) in the 12-week group and 90.6% (29 of 32) in the 24-week group (**Figure 3**) [17].

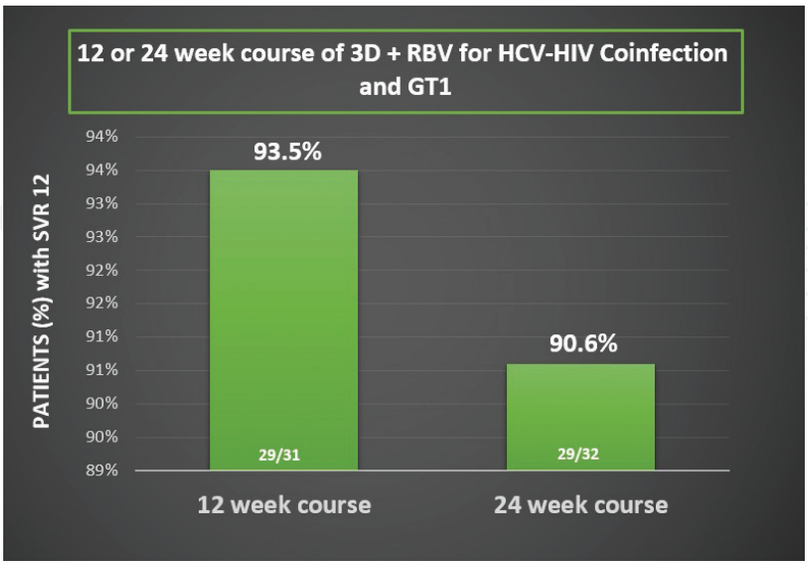

Figure 3. TURQUOISE-I. 3 D, Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; RBV, ribavirin; GT, genotype; SVR, sustained viral response. Inspired by https://depts.washington.edu/hepstudy/presentations/uploads/137/turquoise13d.pdf

6.3. ALLY-2 study (daclatasvir + sofosbuvir in HCV GT 1–4 and HIV coinfection) by Wyles et al.

Among HIV/HCV-coinfected patients who received 12 weeks of daclatasvir plus sofosbuvir, sustained virologic response across all genotypes was 97.0% (including black patients and those with cirrhosis) and 76.0% after 8 weeks [18].

6.4. ION-4 study (ledipasvir and sofosbuvir for HCV genotype 1 or 4 in patients coinfected with HIV-1) by Naggie et al.

In this multicenter, open-label, single-group study, 12 weeks of treatment with the once-daily, single-tablet regimen of ledipasvir-sofosbuvir resulted in a sustained virologic response in 96% of patients [19]. In exploratory subgroup analyses, rates of sustained virologic response 12 weeks after the end of therapy (the primary efficacy end point) were similar across all subgroups except that black patients, who made up 34% of the study population, had lower rates of sustained virologic response (**Figure 4**) [19].

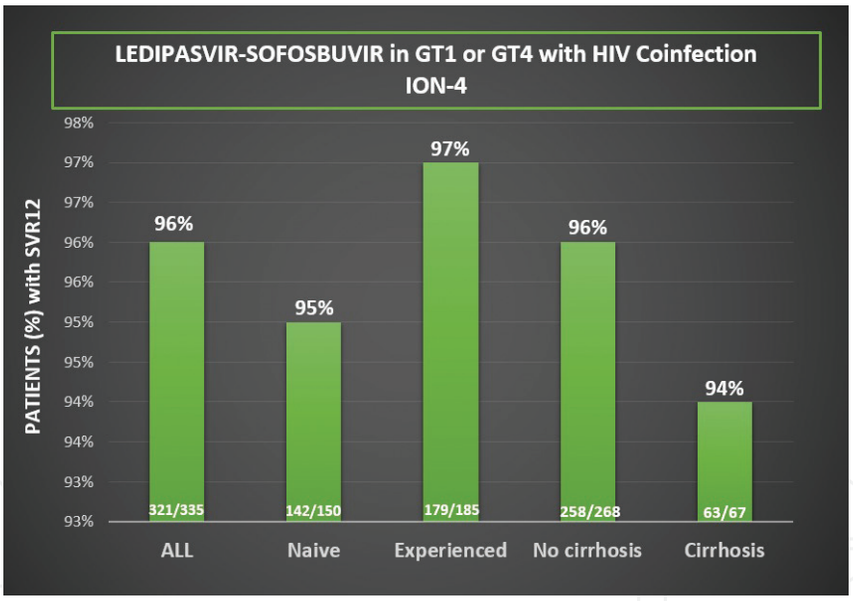

Figure 4. Ledipasvir and sofosbuvir for HCV genotype 1 or 4 in patients coinfected with HIV-1. GT 1 or 4, genotype 1 or 4; SVR 12, sustained viral response 12 weeks after the end of treatment. Inspired by http://slides.hcvonline.org/uploads/149/ion4_ls.pdf

7. Conclusions

Due to shared risk factors for transmission, HIV/HCV coinfection is a very common event, the prevalence averages about 35% in the United States and Europe [20, 21].

The progression of liver fibrosis is accelerated in HIV/HCV-coinfected patients. HCV guidance recommends using the same HCV treatment approach for patients coinfected with HIV as those with HCV monoinfection.

DAAs and interferon-free combination therapy has changed the landscape of therapy for HIV/HCV-coinfected patients.

Multiple studies demonstrating comparable rates of SVR in coinfected and monoinfected patients.

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