HIV/HCV Coinfection: Current Challenges

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Dominique Salmon-Ceron, J. E. Arends, C. Leoni, C. Solas, and G. Peytavin

7.1 Introduction

Both human immunodeficiency virus (HIV) infections and hepatitis C virus (HCV) infections rank high among global causes of death [1]. Due to shared routes of transmission, prevalence of coinfection with both viruses is high and therefore an area of concern as progression of liver disease was known to be accelerated by HIV. However, due to a number of important changes in the management of HIV and HCV, our beliefs have radically changed. In this chapter the changing dynamics in the field of HIV/HCV coinfection is discussed.

7.2 Changes in Epidemiology of Hepatitis C in HIV Infection

At a global level, there are 37 million people infected with HIV and 115 million people with antibodies to hepatitis C virus (HCV) [2]. Worldwide, there are approximately 2,278,400 HIV/HCV coinfections (IQR 1,271,300–4,417,000), of which

On Behalf of the ESCMID Study Group on Viral Hepatitis (ESGVH)

D. Salmon-Ceron (✉)
Infectious Diseases Department, Hôtel Dieu Hospital, University of Paris, Paris, France
e-mail: dominique.salmon@aphp.fr

J. E. Arends · C. Leoni
Department of Internal Medicine, Infectious Diseases Section, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, The Netherlands

C. Solas
APHM, Aix-Marseille Univ U105, Laboratoire de Pharmacocinétique et Toxicologie, SMARTc CRCM Inserm UMR1068 CNRS UMR7258, Hôpital La Timone, Marseille, France

G. Peytavin
APHP, Hôpital Bichat-Claude Bernard, Laboratoire de Pharmaco-Toxicologie and IAME, UMR 1137, Université Paris Diderot, Sorbonne Paris Cité and INSERM, Paris, France

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1,362,700 (847,700–1,381,800) are in people who inject drugs (PWID), equaling an overall coinfection prevalence in HIV-infected individuals of 6.2% (3.4–11.9) [3]. This estimation comes from a recent systematic review and meta-analysis of 783 epidemiological studies published between January 1st 2002 and January 28th 2015 [2]. In this study, odds ratios of HCV infection were six times higher in people living with HIV (5.8, 95% CI: 4.5–7.4) than their HIV-negative counterparts. The study also showed a wide variation in the mode of transmission: from a low seroprevalence within pregnant or heterosexually exposed individual (4.0%, 95% CI: 1.2–8.4) to 6.4% (3.2–10.0) in men who have sex with men (MSM), up to even 82.4% (55.2–88.5) in people who inject drugs (PWID).

Since injecting drug use was popular in most European countries in the late twentieth century, the number of PWID that were coinfected with both HIV and HCV in Europe was relatively high between 15 and 30% [4]. In those countries that reacted upon this IV drug epidemic with adequate harm reduction strategies, prevalence rates remained low like in the Netherlands with about 10% coinfection rate. However, seroprevalence rates have also declined in countries that have introduced preventive strategies for PWID more recently, as was shown for Spain, where prevalence of HIV/HCV coinfection has decreased from 25.3% (95% CI: 23.1–27.5) in 2004–2005 to 8.2% (95% CI: 6.9–9.5) in 2010–2011 [5].

7.3 Pathophysiology of Liver Fibrosis Progression in Patients with HIV and Recent Changes in Natural History

7.3.1 The Pre-highly Active Antiretroviral Therapies (HAART) Era

It was widely observed that HIV/HCV-coinfected patients suffered from faster progression of liver fibrosis (LF) compared to HCV-mono-infected patients, resulting in increased rates of cirrhosis and decompensation of liver disease [6, 7]. This was well established from several large observational studies and further meta-analyses [8, 9]. In 2001, Graham et al. performed a meta-analysis of eight studies to assess the risk of cirrhosis and end-stage liver disease (ESLD) in HIV/HCV-coinfected patients compared to HCV-mono-infected patients, and found that the risk of progression to cirrhosis and ESLD was twofold and sixfold higher, respectively, in coinfected patients than those with HCV mono-infection [8]. This was confirmed in a meta-analysis by Deng et al. that involved 16,750 patients from 29 trials, to quantify the effect of HIV coinfection on progression in liver disease in patients with HCV infection [9]. In this study, the overall OR for histological cirrhosis or decompensated liver disease or liver cancer or death was 3.40 (95% CI: 2.45–4.73) for HIV/HCV-coinfected as compared to HCV-infected patients. In subgroup analysis, the authors found that there was a substantial increased risk for decompensated liver disease and death, 5.45 (95% CI:

2.54–11.71), and 3.60 (95% CI: 3.12–4.15), respectively, but smaller difference regarding the development of cirrhosis or liver cancer, 1.47 (95% CI: 1.27–1.70) and 0.76 (95% CI: 0.50–1.14), respectively [9].

The pathophysiology of liver fibrosis progression in patients with HIV results from a multifactorial process (Fig. 7.1). The viral replication of HCV is generally higher in HIV/HCV-coinfected than in mono-infected subjects [10]. Besides this high viral replication, chronic immune activation, and inflammation due both to HIV and bacterial translocation [11], mitochondrial toxicity and steatosis triggered by some older nucleos(t)ide reverse transcriptase inhibitors (NRTI) such as stavudine and didanosine [12, 13] have contributed in the past to more severe intrahepatic damage in HIV/HCV-coinfected compared to mono-infected subjects [13].

7.3.2 Recent Changes in Natural History

The natural history of chronic HCV infection has dramatically changed over the past decade. Three steps have markedly changed the landscape:

First, from the early twenty-first century onwards, with the introduction of safe and effective antiretroviral drugs, the cutoff at which initiation of cART was recommended has increased gradually, from 200 to 350 cells/mm^3 until since 2015 to systematic initiation of cART in all HIV-positive persons, irrespectively of their CD4 count [14]. This major shift in HIV treatment guidelines has resulted in a

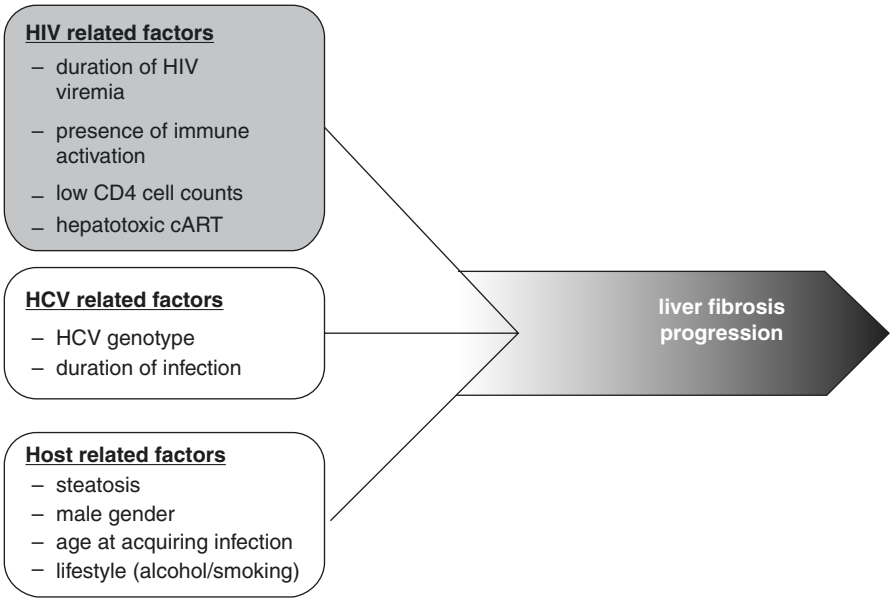

Fig. 7.1 Pathophysiology of liver fibrosis progression in patients with HIV (from Arends et al. [17])

corrected immune deficit in most patients. It is well known that higher CD4+ T-cell recovery protects HIV-coinfected individuals from HCV-related clinical events, and that undetectable plasma HIV-RNA and high CD4+ T cell appeared to protect from progression of liver fibrosis as was shown by FIB-4 transitions to worse stage [15]. The second major change was withdrawal of NRTI with mitochondrial toxicity such as didanosine and stavudine from the cART armamentarium [16] and introduction of safer antiretroviral drugs without liver toxicity. The third and last important change was the development of all-oral direct-acting antiviral (DAA) regimens, leading to HCV cure in more than 95% of the patients.

With all these changes, it is generally accepted that HIV-infected patients, especially those who newly acquire HCV, have the same liver fibrosis progression rate as HCV-mono-infected individuals [17, 18]. A recent French study performed in cirrhotic patients confirmed this fact showing that HIV/HCV-coinfected patients have now a similar risk of liver decompensation and of hepatocellular carcinoma compared to HCV-mono-infected patients with cirrhosis [18]. HIV/HCV-coinfected patients however keep an increased risk of overall mortality than HCV-mono-infected patients, mainly due to death from extrahepatic causes such as infections, cancers, and cardiovascular events [18].

7.4 Specificities of HCV Treatments in HIV Infection and Drug–Drug Interactions (DDIs)

In the pre-HAART era, sustained virological response (SVR) rates to interferon-based therapy were lower in HIV/HCV-coinfected people than in those who were not and did not exceed 50% overall and 15% in patients with cirrhosis [19, 20]. This has been well described in the literature [21].

With the development of all-oral direct-acting antiviral (DAA) drug regimens, the treatment of chronic hepatitis C has dramatically improved [22]. Up to 93–98% of patients obtain an SVR at 12 weeks (SVR12) in clinical trials, whatever the combinations and the fibrosis stage [23–28]. And the response rate in HIV/HCV-coinfected individuals has become similar to that of HCV-mono-infected ones [29–34] (Fig. 7.2). Furthermore, in real-life settings, several cohorts in France, Italy, and Spain have shown that this high efficacy and safety of DAA were similar as in clinical trials [35–37]. It is now firmly established that coinfected patients treated with all oral DAAs have comparable, if not equivalent, SVR rates to mono-infected patients treated with the same regimen and thus appear to be no longer a "hard-to-treat population."

Potential explanations for the improved, and now equivalent, SVR rates in coinfected and mono-infected patients are likely to rest with the differing mechanism of action of the different anti-HCV therapies. With the introduction of DAAs, the pharmacological mechanism of action of HCV therapies has shifted from immune regulation by peg-IFN-alfa/RBV to (predominately) direct viral inhibition. It is conceivable that with peg-IFN-alfa/RBV therapy even minor defects in the host cellular responsiveness might impact efficacy, while such minor deficits have little

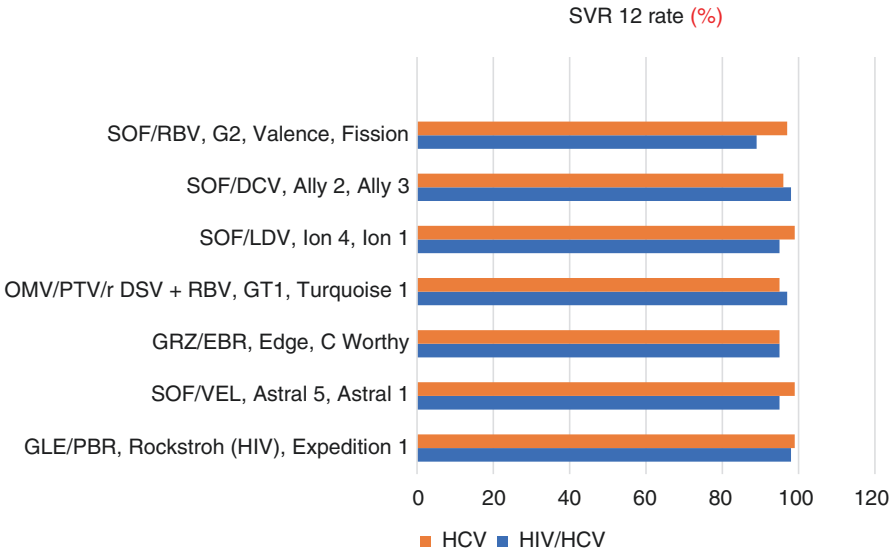

Fig. 7.2 Comparison of SVR rate after DAA treatment in clinical trials performed in HCV-mono-infected and HIV/HCV-coinfected populations

or negligible influence when the main activity is direct viral targeting. This view however may prove too simplistic [17].

The main particularity of the treatment of HCV in HIV infection remains in the fact that DAAs can cause drug–drug interactions (DDIs) with antiretrovirals and non-cART co-medication [38]. The ability of HCV protease inhibitors to inhibit cytochrome 450-3A4 (CYP3A4) and transporters (hepatic and/or intestinal and/or renal) can have significant clinical consequences [38].

Mainly throughout an induction or an inhibition of CYP3A4, most of the antiretroviral drugs can affect the metabolism of DAA and lead to abnormal drug exposures. But HCV DAA may also inhibit CYP3A4 and/or transporters leading to an increased exposure of several antiretrovirals (Table 7.1).

7.4.1 Effect of HIV Drugs on the Metabolism of HCV DAAs

HIV boosted protease inhibitors, and most HIV non-nucleoside reverse transcriptase inhibitors (NNRTI), interact via this mechanism of induction or inhibition of CYP3A4. In contrast, HIV integrase inhibitors (e.g., dolutegravir) do not or only marginally affect CYP3A4, and therefore are relatively free of DDI. Exposure to some HIV and HCV nucleos(t)ide analogues (e.g., tenofovir and sofosbuvir, respectively) is subject to competition on drug transporters (e.g., P-glycoprotein) and requires special attention in patients with renal insufficiency.

Table 7.1 Main interactions between antiretrovirals (ARV) and direct-acting antivirals (DAA)

Effect on antiretroviral drugs		Effect on anti-HCV drugs									
		Ribavirin (RBV)	Simeprévir (SMV)	Daclatasvir (DCV)	Sofosbuvir (SOF)	Sofosbuvir (SOF)/ ledipasvir (LDV)	Sofosbuvir (SOF)/ velpatasvir (VEL)	Sofosbuvir (SOF)/ velpatasvir (VEL)/ voxilaprevir (VOX)	Grazoprevir (GZR)/elbasvir (EBR)	Glecaprévir (GLE)/ pibrentasvir (PIB)	Paripatrevir/ ritonavir (PTV/r)/ ombitasvir (OBV) ± dasabuvir (DSV)
Nucleos(t)ide reverse transcriptase inhibitors (NRTI)	Zidovudine (ZDV)	Not recommended	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated
	Tenofovir disoproxil fumarate (TDF)	Possible	Possible	Possible	Possible	Possible TDM + renal monitoring Avoid if eGFR <60 mL/mm	Possible TDM + renal monitoring	Possible TDM + renal monitoring	Possible	Possible	Possible
	Tenofovir alafénamide (TAF)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Emtricitabine (FTC)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Lamivudine (3TC)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Abacavir (ABC)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible

Nonnucleoside reverse transcriptase inhibitors (NNRTI)	Efavirenz (EFV)	Possible	Not recommended	Possible DCV 90 mg qd + TDM	Possible	Possible	Not recommended	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Nevirapine (NVP)	Possible	Not recommended	Possible DCV 90 mg qd + TDM	Possible	Possible	Not recommended	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Etravirine (ETR)	Possible	Not recommended	Possible DCV 90 mg qd + TDM	Possible	Possible	Not recommended	Contraindicated	Contraindicated	Contraindicated	Not recommended
	Doravirine (DOR)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible TDM DOR
	Rilpivirine (RPV)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible TDM RPV + ECG monitoring	Possible TDM RPV + ECG monitoring
Protease inhibitors (PI)	Atazanavir/r (ATV/r)	Possible	Not recommended	Possible DCV 30 mg qd + TDM	Possible	Possible TDM ATV + bilirubin monitoring	Possible TDM ATV + bilirubin monitoring	Contraindicated	Contraindicated	Contraindicated	Possible ATV 300 mg *without RTV* administered at the same time + TDM
	Darunavir/r (DRV/r)	Possible	Not recommended	Possible DVC 60 mg qd + TDM	Possible	Possible	Possible	Contraindicated	Contraindicated	Contraindicated	Possible DRV 800 mg qd *without RTV* administered at the same time + TDM Absence of extensive PI resistance
	Lopinavir/r (LPV/r)	Possible	Not recommended	Possible DVC 60 mg qd + TDM	Possible	Possible	Possible	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Fosamprenavir/r (FPV/r)	Possible	Not recommended	Not recommended	Possible	Possible	Not recommended	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Tipranavir/r (TPV/r)	Possible	Not recommended	Possible DVC 60 mg qd + TDM	Possible +TDM SOF	Possible +TDM SOF/ LDV	Not recommended	Contraindicated	Contraindicated	Contraindicated	Contraindicated

(continued)

Table 2.1 (continued)

Effect on antiretroviral drugs		Effect on anti-HCV drugs									
		Ribavirin (RBV)	Simeprévir (SMV)	Daclatasvir (DCV)	Sofosbuvir (SOF)	Sofosbuvir (SOF)/ ledipasvir (LDV)	Sofosbuvir (SOF)/ velpatasvir (VEL)	Sofosbuvir (SOF)/ velpatasvir (VEL)/ voxilaprevir (VOX)	Grazoprevir (GZR)/elbasvir (EBR)	Glecaprévir (GLE)/ pibrentasvir (PIB)	Paripatrevir/ ritonavir (PTV/r)/ ombitasvir (OBV) ± dasabuvir (DSV)
Integrase inhibitors (INI)	Raltegravir (RAL)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Dolutegravir (DTG)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Elvitegravir/ cobicistat (EVG/c)	Possible	Not recommended	Possible DVC 30 mg qd + TDM	Possible	Possible	Possible	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Entry/fusion inhibitors	Maraviroc (MVC)	Possible	Possible MVC 150 mg bid + TDM	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible MVC 150 mg bid + TDM
	Enfuvirtide (T20)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible

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References:

http://www.ema.europa.eu/ema
http://www.hep-druginteractions.org
German P. AASLD: The Liver Meeting®, November 13–17, 2015, San Francisco, CA, USA. Abstract 1133
Mogalian E et al. AASLD: The Liver Meeting®, November 13–17, 2015, San Francisco, CA, USA. Abstract 2265
Mogalian E, et al. 15th IWCPHT May 2014, Washington, DC, USA. Abstract oral O_07
Mogalian E, et al. CROI, 2016, Boston, MA, USA. Abstract oral 100
Wyles D, et al. EASL 2016, Barcelone, Espagne. Sofosbuvir/Velpatasvir for 12 Weeks in Patients Coinfected With HCV and HIV-1: The ASTRAL-5 Study

7.4.2 Effect of HCV DAAs on the Metabolism of HIV Drugs

HCV protease inhibitors have the ability to inhibit cytochrome 450-3A4 (CYP3A4) and transporters (hepatic and/or intestinal and/or renal) and consequently can increase the drug concentrations of HIV proteases [38]. In contrast, HCV polymerase inhibitors, most HCV NS5A inhibitors, do not or only marginally affect CYP3A4, and therefore are relatively free of DDI.

7.4.3 Other Interactions Between DAA et Co-medications

Several other interactions are possible between DAA and co-medications often prescribed in HIV-infected patients such as statins or drug substrates of the CYP450 and/or transporters (e.g., P-glycoprotein, OATP1B1/1B3, BCRP) mainly with the HCV protease inhibitors and to a lesser extent with some HCV NS5A inhibitors.

These drug–drug interactions between DAA and cART should be known by physicians to prevent either toxicity due to drug overexposure or treatment failures due to suboptimal drug concentrations. These interactions can be easily found on the free-access checkers web site www.hcv-druginteractions.org or www.hiv-druginteractions.org. Interactions with cART are described in Table 7.1. Switching cART before DAA treatment can be an option and this was exemplified in a study from the Netherlands, in which category 2 and 3 DDIs were prevented by switching cART in 78 of 147 (53%) and 47 of 49 (98%) patients [39].

7.5 Beneficial Consequences of HCV Cure in HIV-Infected Patients

There have been many advances and changes in the management of both HIV and HCV over the past decade resulting in a decrease in liver fibrosis progression already demonstrated in the pre-DAA era. In addition to the increased SVR rates in coinfected patients treated with DAAs which are now similar to HCV-mono-infected patients, factors responsible for this favorable outcome are improved control of HIV with safer, less hepatotoxic cART and with commencement of HIV therapy at an earlier stage and higher CD4 count—all of which directly influence the degree of immune activation and dysregulation which impacts fibrosis (Fig. 7.3) [40]; the question is how this affects future development of liver-related complications.

7.5.1 Liver Events

Although more evidence has surfaced in mono-infected patients treated with DAAs, already several studies have now evaluated liver-related complications in HIV/HCV-coinfected patients cured of HCV [41–43]. Indeed, a similar reduction in liver decompensation and increased survival were demonstrated [41].

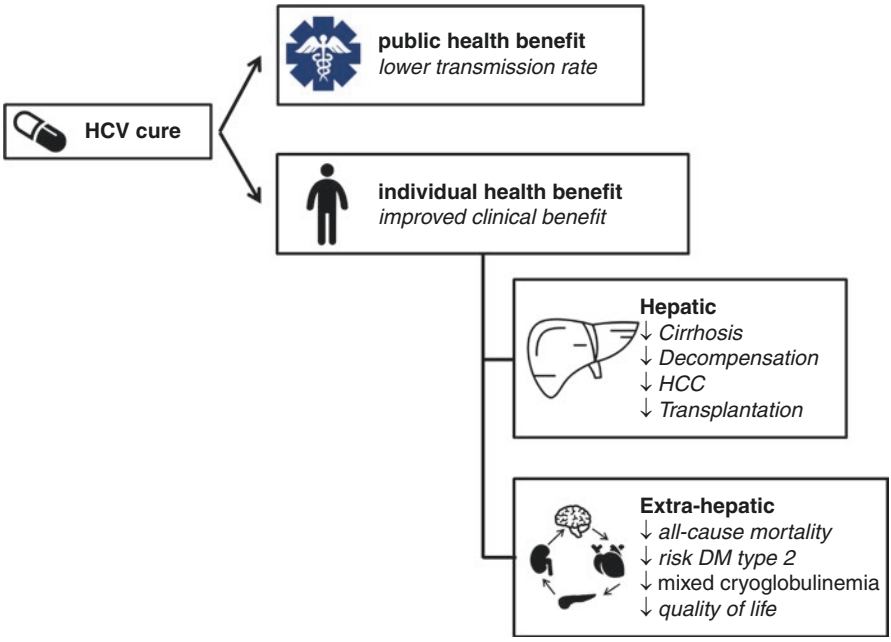

Fig. 7.3 Overview of benefits and challenges after HCV cure (Ref. [40])

It was also recently found that the incidence rates of diabetes mellitus, renal events, and non-AIDS-related infections were significantly lower in responders than in no responders to anti-HCV treatment [43].

7.5.2 Quality of Life

SVR is associated with improved long-term clinical outcomes, economic benefits, and improved health-related quality of life. DAA treatment has demonstrated to have less impairment on patient's quality of life, in terms of physical and mental functioning and social activities. This was mostly observed in pegIFN/RBV-experienced patients who were retreated with a new DAA regimen [44]. A study conducted in Germany suggested that cure of HCV with direct-acting antivirals is associated with positive metabolic effects with weight gain during long-term follow-up of 1 year [45]. Similar conditions were observed in HIV-coinfected patient. During treatment with ledipasvir/sofosbuvir and sofosbuvir/velpatasvir, patients showed an improvement in patient-reported outcome measures (PROMs: activity/energy, physical component, and fatigue score) compared to those treated with sofosbuvir/ribavirin. Those improvements remained present also after treatment cessation [46].

7.6 Residual Risk After Cure?

Despite the numerous demonstrated clinical benefits of HCV cure, the risk of HCC is not abolished in patients with severe fibrosis or cirrhosis before HCV cure. Cirrhosis is the main factor influencing the propensity to develop HCC after SVR, with a risk ranging from 1.0 to 2.2% per year in cirrhotic patients, whereas the risk is very low in patients without cirrhosis [47].

In those patients with cirrhosis or severe fibrosis, specific added risk factors have been identified that increase the risk for HCC occurrence after cure:

- Age is the most important risk factor, patients being older than 55, and especially 65+ being more likely than younger patients to develop HCC after SVR [47, 48]. This role of age among patients with cirrhosis was well demonstrated in a European study, in which the 8-year HCC incidence was 2.6% (95% CI: 0.0–5.5) among patients <45 years, 9.7% (95% CI: 5.8–13.6) among patients 45–60 years, and 12.2% (95% CI: 5.3–19.1) among patients >60 years at the start of therapy (aHR for those >60 years: 8.91; 95% CI: 1.12–70.79) [48].
- Furthermore, the severity of cirrhosis, as assessed by a low albumin blood level and a low platelet count [48], or a high elastometry score (over 20 kPa) [49] increases the risk of events as compared with patients with less severe, compensated cirrhosis.
- Finally, the metabolic syndrome and diabetes [defined by BMI $\geq$25 kg/m^2 and/or diabetes and/or dyslipidemia] carry a much higher risk of HCC occurrence after cure [48, 50]. In one study from France, the HCC incidence among cirrhotic patients cured of HCV but with the metabolic syndrome was around 6% at 6 years, while it was nearly zero in those without the metabolic syndrome [50].

7.7 HCV Reinfections

Modelling studies predict that universal HCV treatment will lead to a decrease in the incidence of new infections [51]. However, HCV is not an infection that confers protective immunity after cure. Reinfection is defined as having detectable plasma HCV-RNA following an undetectable level more than 12 weeks after the end of the treatment (SVR12) with demonstration of different genotype or clade compared with the primary infection.

Risk of reinfection varies according to populations and risk factors. A recent meta-analysis suggested that the rate of HCV reinfection was higher among HIV-coinfected than mono-infected patients, even if there is a great variability among different groups, such as PWID, MSM, and prisoners [52, 53].

7.7.1 Risk of Hepatitis C Reinfection Among MSM

Epidemics of acute hepatitis C have been observed since more than a decade, mostly among MSM with previous HIV infection and with sexual high-risk behaviors in

European countries, Australia, the USA, and Asia [53–55]. In the Swiss cohort, there was between 2014 and 2015 a 67.1% increase of the number of acute cases attributed to transmission among men who have sex with men, while it declined in PWID and remained stable <1 per 100 in heterosexuals [56]. In these populations, the transmission of HCV is linked to blood contacts via these extremely hard sexual behaviors. Several other factors have increased the incidence like increased cheap air travel, rising popularity of Internet, and use of drugs and stimulants for sexual pleasure ("chemsex") (see Chap. 11).

In MSM, the risk of HCV reinfection after a first episode of hepatitis is also very high [57, 58]. Prevention strategies are needed for this high-risk group to reduce morbidity and accelerate diagnosis and treatment to avoid transmission. HIV-positive MSM with a prior HCV infection should then be tested frequently for reinfection (every 3–6 months).

7.7.2 Risk of Hepatitis C Reinfection Among PWID

There is uncertainty about reinfection rates among PWID due to lack of available data for good-quality studies (retrospective designs, exclusion of recent PWID from trials, inability to distinguish reinfection from relapse). A study conducted in Australia estimated an incidence of reinfection of 7.4 per 100 patient-years [59]. Among people who injected drugs, the risk of reinfection was found to be low after successful treatment. Risk of reinfection may vary depending on the local background epidemic among the PWID population of HCV. Therefore, in communities with a higher local background HCV epidemic, treated PWID are likely to have a higher risk of reinfection [60]. In addition, injecting behavior after treatment, as well as implementation of a needle exchange program, influences the risk of reinfection among PWID [61].

This ongoing risk underlines that regular monitoring for reinfection is important following SVR, particularly in persons who continue to engage in IDU and for high-risk MSM. In order to increase the success of HCV treatment, it will be essential to establish a posttreatment surveillance [62].

References

1. Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, Abu-Raddad LJ, Assadi R, Bhala N, Cowie B, Forouzanfour MH, Groeger J, Hanafiah KM, Jacobsen KH, James SL, MacLachlan J, Malekzadeh R, Martin NK, Mokdad AA, Mokdad AH, Murray CJL, Plass D, Rana S, Rein DB, Richardus JH, Sanabria J, Saylan M, Shahraz S, So S, Vlassov VV, Weiderpass E, Wiersma ST, Younis M, Yu C, El Sayed Zaki M, Cooke GS. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet. 2016;388(10049):1081–8.
2. Mohd Hanaah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57:1333–42.

3. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, Yanny I, Razavi H, Vickerman P. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis. 2016;16(7):797–808.
4. Rockstroh JK, Peters L, Grint D, Soriano V, Reiss P, Monforte AD, Beniowski M, Losso MH, Kirk O, Kupfer B, Mocroft A, EuroSIDA in EuroCoord. Does hepatitis C viremia or genotype predict the risk of mortality in individuals co-infected with HIV? J Hepatol. 2013;59(2):213–20.
5. Serrano-Villar S, Sobrino-Vegas P, Monge S, Dronda F, Hernando A, Montero M, Viciana P, Clotet B, Pineda JA, Del Amo J, Moreno S, CoRIS. Decreasing prevalence of HCV coinfection in all risk groups for HIV infection between 2004 and 2011 in Spain. J Viral Hepat. 2015;22(5):496–503.
6. Macias J, Berenguer J, Japon MA, Giron JA, Rivero A, Lopez-Cortes LF, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. Hepatology. 2009;50:1056–63.
7. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology. 1999;30:1054–8.
8. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33:562–9.
9. Deng LP, Gui XE, Zhang YX, Gao SC, Yang RR. Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. World J Gastroenterol. 2009;15:996–1003.
10. Thomas DL, Rich JD, Schuman P, Smith DK, Astemborski JA, Nolt KR, Klein RS. Multicenter evaluation of hepatitis C RNA levels among female injection drug users. J Infect Dis. 2001;183(6):973–6.
11. Balagopal A, Philp FH, Astemborski J, Block TM, Mehta A, Long R, et al. Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. Gastroenterology. 2008;135:226–33.
12. Bani-Sadr F. Progression of fibrosis in HIV and hepatitis C virus-coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors. Clin Infect Dis. 2005;41(12):1806–9.
13. Debes JD, Bohjanen PR, Boonstra A. Mechanisms of accelerated liver fibrosis progression during HIV infection. J Clin Transl Hepatol. 2016;4(4):328–35.
14. Ryom L, Boesecke C, Gisler V, Manzardo C, Rockstroh JK, Puoti M, Furrer H, Miro JM, Gatell JM, Pozniak A, Behrens G, Battegay M, Lundgren JD, EACS Governing Board. Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons. HIV Med. 2016;17(2):83–8.
15. Focà E, Fabbiani M, Prosperi M, Quiros Roldan E, Castelli F, Maggiolo F, Di Filippo E, Di Giambenedetto S, Gagliardini R, Saracino A, Di Pietro M, Gori A, Sighinolfi L, Pan A, Postorino MC, Torti C, Italian MASTER Cohort. Liver fibrosis progression and clinical outcomes are intertwined: role of CD4+ T-cell count and NRTI exposure from a large cohort of HIV/HCV-coinfected patients with detectable HCV-RNA: a MASTER cohort study. Medicine (Baltimore). 2016;95(29):e4091.
16. Loko MA, Bani-Sadr F, Valantin MA, Lascoux-Combe C, Fontaine H, Bonnard P, Gervais A, Bouchaud O, Garipuy D, Quertainmont Y, Vittecoq D, Tehrani MS, Winnock M, Dabis F, Salmon D. Antiretroviral therapy and sustained virological response to HCV therapy are associated with slower liver fibrosis progression in HIV-HCV-coinfected patients: study from the ANRS CO 13 HEPAVIH cohort. Antivir Ther. 2012;17(7):1335–43.
17. Arends JE, Lieveld FI, Boeijen LL, de Kanter CT, van Erpecum KJ, Salmon D, Hoepelman AI, Asselah T, Ustianowski A. Natural history and treatment of HCV/HIV coinfection: is it time to change paradigms? J Hepatol. 2015;63(5):1254–62.

18. Salmon-Ceron D, Nahon P, Layese R, Bourcier V, Sogni P, Bani-Sadr F, Audureau E, Merchadou L, Dabis F, Wittkop L, Roudot-Thoraval F, ANRS CO12 CirVir and ANRS CO13 HEPAVIH Study Groups. HIV/HCV co-infected cirrhotic patients are no longer at higher risk for HCC or end-stage liver disease as compared to HCV mono-infected patients. Hepatology. 2018; https://doi.org/10.1002/hep.30400.
19. Carrat F, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA. 2004;292(23):2839–48.
20. Mira JA, et al. Response to pegylated interferon plus ribavirin among HIV/hepatitis C virus-coinfected patients with compensated liver cirrhosis. Clin Infect Dis. 2012;55(12):1719–26.
21. Martel-Laferrière V, Dieterich DT. Treating HCV in HIV 2013: on the cusp of change. Liver Int. 2014;34(Suppl 1):53–9. https://doi.org/10.1111/liv.12396.
22. Arends JE, Kracht PA, Hoepelman AI, European Study Group for Viral Hepatitis (ESGVH). Performance of hepatitis C virus (HCV) direct-acting antivirals in clinical trials and daily practice. Clin Microbiol Infect. 2016;22(10):846–52.
23. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, et al. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373:705–13.
24. Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV coinfection (C-EDGE COINFECTION): a non-randomised, open-label trial. Lancet HIV. 2015;2:e319–27.
25. Sulkowski MS, Eron JJ, Wyles D, Trinh R, Lalezari J, Wang C, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. JAMA. 2015;313:1223–31.
26. Wyles D, Bräu N, Kottilil S, Daar ES, Ruane P, Workowski K, Luetkemeyer A, Adeyemi O, Kim AY, Doehle B, Huang KC, Mogalian E, Osinusi A, McNally J, Brainard DM, McHutchison JG, Naggie S, Sulkowski M, ASTRAL-5 Investigators. Sofosbuvir and velpatasvir for the treatment of hepatitis C virus in patients coinfected with human immunodeficiency virus type 1: an open-label, phase 3 study. Clin Infect Dis. 2017;65(1):6–12.
27. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373:714–25.
28. Rockstroh JK, Lacombe K, Viani RM, Orkin C, Wyles D, Luetkemeyer AF, Soto-Malave R, Flisiak R, Bhagani S, Sherman KE, Shimonova T, Ruane P, Sasadeusz J, Slim J, Zhang Z, Samanta S, Ng TI, Gulati A, Kosloski MP, Shulman NS, Trinh R, Sulkowski M. Efficacy and safety of Glecaprevir/Pibrentasvir in patients coinfected with hepatitis C virus and human immunodeficiency virus Type 1: The EXPEDITION-2 Study. Clin Infect Dis. 2018;67(7):1010–7. https://doi.org/10.1093/cid/ciy220.
29. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P, ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889–98.
30. Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C, Towner WJ, Conway B, Ruane P, Bourlière M, Asselah T, Berg T, Zeuzem S, Rosenberg W, Agarwal K, Stedman CA, Mo H, Dvory-Sobol H, Han L, Wang J, McNally J, Osinusi A, Brainard DM, McHutchison JG, Mazzotta F, Tran TT, Gordon SC, Patel K, Reau N, Mangia A, Sulkowski M, ASTRAL-2 Investigators, ASTRAL-3 Investigators. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. 2015;373(27):2608–17.
31. Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, Abergel A, Mangia A, Lai CL, Chan HL, Mazzotta F, Moreno C, Yoshida E, Shafran SD, Towner WJ, Tran TT, McNally J, Osinusi A, Svarovskaia E, Zhu Y, Brainard DM, McHutchison JG, Agarwal K, Zeuzem S,

ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 2015;373(27):2599–607.
32. Forns X, Lee SS, Valdes J, Lens S, Ghalib R, Aguilar H, Felizarta F, Hassanein T, Hinrichsen H, Rincon D, Morillas R, Zeuzem S, Horsmans Y, Nelson DR, Yu Y, Krishnan P, Lin CW, Kort JJ, Mensa FJ. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. Lancet Infect Dis. 2017;17(10):1062–8.
33. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, Freilich BF, Younes ZH, Harlan W, Ghalib R, Oguchi G, Thuluvath PJ, Ortiz-Lasanta G, Rabinovitz M, Bernstein D, Bennett M, Hawkins T, Ravendhran N, Sheikh AM, Varunok P, Kowdley KV, Hennicken D, McPhee F, Rana K, Hughes EA, ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61(4):1127–35.
34. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, Alric L, Bronowicki JP, Lester L, Sievert W, Ghalib R, Balart L, Sund F, Lagging M, Dutko F, Shaughnessy M, Hwang P, Howe AY, Wahl J, Robertson M, Barr E, Haber B. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1075–86.
35. Piroth L, Wittkop L, Lacombe K, Rosenthal E, Gilbert C, Miailhes P, Carrieri P, Chas J, Poizot-Martin I, Gervais A, Dominguez S, Neau D, Zucman D, Billaud E, Morlat P, Aumaitre H, Lascoux-Combe C, Simon A, Bouchaud O, Teicher E, Bani-Sadr F, Alric L, Vittecoq D, Boué F, Duvivier C, Valantin MA, Esterle L, Dabis F, Sogni P, Salmon D, ANRS CO13 HEPAVIH Study Group. Efficacy and safety of direct-acting antiviral regimens in HIV/HCV-co-infected patients—French ANRS CO13 HEPAVIH cohort. J Hepatol. 2017;67(1):23–31.
36. d'Arminio Monforte A, Cozzi-Lepri A, Ceccherini-Silberstein F, De Luca A, Lo Caputo S, Castagna A, Mussini C, Cingolani A, Tavelli A, Shanyinde M, Gori A, Girardi E, Andreoni M, Antinori A, Puoti M, Icona Foundation and HepaIcona Study Group. Access and response to direct antiviral agents (DAA) in HIV-HCV co-infected patients in Italy: data from the Icona cohort. PLoS One. 2017;12(5):e0177402.
37. Mínguez C, García-Deltoro M, Flores J, Galindo MJ, Montero M, Reus S, Carmena J, Masiá M, Amador C, Ortega E, On the Behalf of the COINFECOVA-2 Study Group. Interferon-free therapy for treating HCV in difficult-to-treat HIV-coinfected patients as implemented in routine medical practice. AIDS. 2018;32(3):337–46.
38. Soriano V, Labarga P, Fernandez-Montero JV, Mendoza C, Benítez-Gutiérrez L, Peña JM, Barreiro P. Drug interactions in HIV-infected patients treated for hepatitis C. Expert Opin Drug Metab Toxicol. 2017;13(8):807–16.
39. Smolders EJ, Smit C, de Kanter C, Dofferhoff A, Arends JE, Brinkman K, Rijnders B, van der Valk M, Reiss P, Burger DM, ATHENA National HIV Observational Cohort. Management of drug interactions with direct-acting antivirals in Dutch HIV/hepatitis C virus-coinfected patients: adequate but not perfect. HIV Med. 2018;19(3):216–26.
40. Salmon D, Mondelli MU, Maticic M, Arends JE, The ESCMID Study. The benefits of hepatitis C virus cure: every rose has thorns. J Viral Hepat. 2018;25:320–8.
41. Van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308:2584–93.
42. Berenguer J, Alvarez-Pellicer J, Martin PM, Lopez-Aldeguer J, Von-Wichmann MA, Quereda C, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology. 2009;50:407–13.
43. Berenguer J, Rodríguez-Castellano E, Carrero A, Von Wichmann MA, Montero M, Galindo MJ, Mallolas J, Crespo M, Téllez MJ, Quereda C, Sanz J, Barros C, Tural C, Santos I, Pulido F, Guardiola JM, Rubio R, Ortega E, Montes ML, Jusdado JJ, Gaspar G, Esteban

H, Bellón JM, González-García J, GESIDA HIV/HCV Cohort Study Group. Eradication of hepatitis C virus and non-liver-related non-acquired immune deficiency syndrome-related events in human immunodeficiency virus/hepatitis C virus coinfection. Hepatology. 2017;66(2):344–56.
44. Younossi ZM, Stepanova M, Esteban R, Jacobson I, Zeuzem S, Sulkowski M, Henry L, Nader F, Cable R, Afendy M, Hunt S. Superiority of interferon-free regimens for chronic hepatitis C: the effect on health-related quality of life and work productivity. Medicine (Baltimore). 2017;96(7):e5914.
45. Schlevogt Z, Deterding K, Port K, Siederdissen CHZ, Sollik L, Kirschner J, Mix C, Manns MP, Cornberg M, Wedemeyer H. Interferon-free cure of chronic hepatitis C is associated with weight gain during long-term follow-up. Gastroenterology. 2017;55(9):848–56.
46. Younossi ZM, Stepanova M, Sulkowski M, Naggie S, Henry L, Hunt S. Sofosbuvir and ledipasvir improve patient-reported outcomes in patients co-infected with hepatitis C and human immunodeficiency virus. J Viral Hepat. 2016;23(11):857–65.
47. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct acting antiviral agents. Gastroenterology. 2017;17:10.
48. van der Meer AJ, Feld JJ, Hofer H, Almasio PL, Calvaruso V, Fernandez-Rodriguez CM, et al. Risk of cirrhosis-related complications in patients with advanced fibrosis following hepatitis C virus eradication. J Hepatol. 2017;66(3):485–93.
49. Salmon D, Gilbert C, Sogni P, Esterle L, Dabis F, Miailhes P, Piroth L, Bani-Sadr F, Wittkop L. Residual risk of disease progression after hepatitis C cure in HIV-HCV co-infected patients. In: CROI, 2016.
50. Nahon P, Bourcier V, Layese R, Audureau E, Cagnot C, Marcellin P, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterology. 2017;152(1):142–56.
51. Saab S, Le L, Saggi S, Sundaram V, Tong M. Towards the elimination of hepatitis C in the United States. Hepatology. 2018;67(6):2449–59.
52. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. Clin Infect Dis. 2016;62(6):683–94.
53. Lambers FA, Brinkman K, Schinkel J, Spijkerman IJ, Molenkamp R, Coutinho RA, Prins M, van der Meer JT, MOSAIC (MSM Observational Study of Acute Infection with Hepatitis C) Study Group. Treatment of acute hepatitis C virus infection in HIV-infected MSM: the effect of treatment duration. AIDS. 2011;25(10):1333–6.
54. Ghosn J, Pierre-François S, Thibault V, Duvivier C, Tubiana R, Simon A, Valantin MA, Dominguez S, Caumes E, Katlama C. Acute hepatitis C in HIV-infected men who have sex with men. HIV Med. 2004;5(4):303–6.
55. Browne R, Asboe D, Gilleece Y, Atkins M, Mandalia S, Gazzard B, Nelson M. Increased numbers of acute hepatitis C infections in HIV positive homosexual men; is sexual transmission feeding the increase? Sex Transm Infect. 2004;80(4):326–7.
56. Wandeler G, Schlauri M, Jaquier ME, Rohrbach J, Metzner KJ, Fehr J, Ambrosioni J, Cavassini M, Stöckle M, Schmid P, Bernasconi E, Keiser O, Salazar-Vizcaya L, Furrer H, Rauch A, Swiss HIV Cohort Study, Aubert V, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Gorgievski M, Günthard H, Haerry D, Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A, Regenass S, Rickenbach M, Rudin C, Schöni-Affolter F, Schmid P, Schüpbach J, Speck R, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S. Incident hepatitis C virus infections in the Swiss HIV Cohort Study: changes in treatment uptake and outcomes between 1991 and 2013. Open Forum Infect Dis. 2015;2(1):ofv026.
57. Ingiliz P, Martin TC, Rodger A, Stellbrink HJ, Mauss S, Boesecke C, Mandorfer M, Bottero J, Baumgarten A, Bhagani S, Lacombe K, Nelson M, Rockstroh JK, NEAT Study Group. HCV

reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. J Hepatol. 2017;66(2):282–7.
58. Garriga C, Manzanares-Laya S, García de Olalla P, Gorrindo P, Lens S, Solà R, Martínez-Rebollar M, Laguno M, Navarro J, Torras X, Gurguí M, Barberá MJ, Quer J, Masdeu E, Simón P, Ros M, de Andrés A, Caylà JA. Evolution of acute hepatitis C virus infection in a large European city: trends and new patterns. PLoS One. 2017;12(11):e0187893.
59. Martinello M, Hajarizadeh B, Grebely J, Dore GJ, Matthews GV. HCV cure and reinfection among people with HIV/HCV coinfection and people who inject drugs. Curr HIV/AIDS Rep. 2017;14(3):110–21.
60. Islam N, Krajden M, Shoveller J, Gustafson P, Gilbert M, Buxton JA, Wong J, Tyndall MW, Janjua NZ, British Columbia Hepatitis Testers Cohort (BC-HTC) Team. Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study. Lancet Gastroenterol Hepatol. 2017;2(3):200–10.
61. Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. Clin Infect Dis. 2013;57(Suppl 2):S105–10.
62. Young J, Rossi C, Gill J, Walmsley S, Cooper C, Cox J, Martel-Laferriere V, Conway B, Pick N, Vachon ML, Klein MB, Canadian Co-infection Cohort Investigators. Risk factors for hepatitis C virus reinfection after sustained virologic response in patients coinfected with HIV. Clin Infect Dis. 2017;64(9):1154–62. Young CID 2017.