Title: Trends in HCV treatment uptake, efficacy and impact on liver fibrosis in the Swiss HIV Cohort Study.

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Journal: Liver international : official journal of the International Association for the Study of the Liver

Year: 2018 Mar

Issue: 38

Volume: 3

Pages: 424-431

DOI: 10.1111/liv.13528

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Article type : Original Articles

Handling Editor: Jürgen Rockstroh

Trends in HCV treatment uptake, efficacy and impact on liver fibrosis in the Swiss HIV Cohort Study

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/liv.13528

http://www.shcs.ch/184-for-shcs-publications

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List of abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; SHCS, Swiss HIV Cohort Study; SVR, sustained virological response; peg-IFN, pegylated interferon; RBV, ribavirin; DAAs, direct-acting antiviral agents; PIs, protease inhibitors; WHO, World Health Organsization; SOF, sofosbuvir; IQR, interquartile range; ART, antiretroviral therapy; PWID, people who inject drugs; MSM, men who have sex with men; ACTG, AIDS Clinical Trials Group; LDV, ledipasvir; OMV, ombitasvir; PTV, paritaprevir; RTV, ritonavir; DSV, dasabuvir; HET, heterosexual; CDC, Centers for Disease Contorl; eGFR, estimated glomerular filtration rate; ALT, alanin-Aminotransferase; AST, aspartate-aminotransferase; GT; genotype; DCV, daclatasvir; SIM, simeprevir

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. They declared further conflicts of interest outside the submitted work using the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Financial support

This work was performed within the framework of the SHCS, supported by the Swiss National Science Foundation (SNF grant number 33CSC0-108787, SHCS project number 751), by the SHCS research foundation and the SHCS association. Further support was received through an investigator initiated trial (IST) supported by Gilead Sciences Switzerland Sàrl. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background & Aims:

Hepatitis C virus (HCV) therapies with interferon-free second-generation direct-acting antiviral agents (DAAs) are highly effective and well tolerated. They have the potential to increase treatment eligibility and efficacy in HIV-infected patients. We assessed the impact of DAAs on treatment uptake, efficacy as well as its impact on the burden of liver disease in the Swiss HIV Cohort Study (SHCS).

Methods:

We describe clinical and virological characteristics of patients treated with second generation DAAs. We compared treatment incidence, sustained virological response (SVR)12 and liver fibrosis stages between three time periods: period 1, 01/2009-08/2011 (prior to the availability of DAAs); period 2, 09/2011-03/2014 (first generation DAAs); period 3, 04/2014-12/2015 (second generation DAAs).

Results:

At the beginning of the third period, 876 SHCS participants had a chronic HCV infection of whom 180 (20%) started treatment with a second generation DAA. Three-quarters of them had advanced liver fibrosis (Metavir≥3) of whom 80% were cirrhotics. SVR12 was achieved in 173/180 (96%) patients, 3 patients died and 4

experienced a virological failure. Over the three time periods, treatment uptake (4.5/100py, 5.7/100py, 22.4/100py) and efficacy (54%, 70%, 96% SVR12) continuously increased. The number of cirrhotic patients with replicating HCV infection in the SHCS declined from 25% at the beginning to 12% at the end of the last period.

Conclusions:
After the introduction of second generation DAAs we observed an increase in treatment uptake and efficacy which resulted in a significant reduction in the number of cirrhotic patients with replicating HCV infection in the SHCS.

Key words: HCV treatment, uptake and efficacy, long-term trends, DAA, fibrosis

Key points:

- We observed a substantial increase in treatment uptake and efficacy after the introduction of interferon-free second generation DAA treatments.
- DAAs are well tolerated and highly efficacious, even among HIV/HCV-coinfected patients with advanced liver fibrosis or cirrhosis.
- The treatment of this population with advanced liver disease was driven by treatment priorities but also by limitations in reimbursement, and resulted in a significant reduction in the number of cirrhotic patients with replicating HCV.
- The burden of replicating HCV infection can only be reduced if reimbursement is not restricted to those with advanced liver fibrosis.

Introduction

Hepatitis C virus (HCV) infection is a common and an important comorbidity in HIV-infected patients[1,2]. Compared to HIV-monoinfected patients, HCV-coinfected patients have a higher risk for mortality[3,4]. In the Canadian coinfection cohort, EuroSIDA, as well as the Swiss HIV Cohort Study (SHCS), hepatic decompensation and hepatocellular carcinoma were among the most common causes of death in recent years[5-7]. Achieving a sustained virological response (SVR) substantially reduces HCV related mortality and morbidity and prevents further HCV transmission[3,6,8].

For years, contraindications to interferon-based therapy, long treatment durations, fear of side-effects and reluctance of patients and physicians to start HCV treatment were frequent barriers to treatment[9]. In the SHCS only 12.5% of HIV/HCV-coinfected individuals started treatment with pegylated interferon (peg-IFN) and ribavirin (RBV) during a period of 4 years[10]. Fortunately, there have been major breakthroughs in the treatment of HCV infection with the approval of numerous direct-acting antiviral agents (DAAs). The addition of the first generation protease inhibitors (PIs) to peg-IFN and RBV significantly increased rates of sustained virological response (SVR) in HCV genotype 1 infected patients[11,12]. As these drugs still had to be combined to peg-IFN and RBV, only 13% of HCV genotype 1 infected patients started treatment after the approval of first generation PIs in Switzerland[13]. Thus these treatments only had a very modest impact on the burden of HCV disease at the population level. The new era of interferon-free second generation DAA improved safety and tolerability compared to previous interferon-based therapies. Accordingly, previously reported treatment barriers for peg-IFN/RBV therapy do not apply anymore in more than 60% of patients[9]. Cure rates above 90% are now achieved in all HCV genotypes and treatment efficacy is similar in HIV/HCV-coinfected patient compared to HCV-monoinfected ones[14].

The World Health Organsization (WHO) defined ambitious targets with regard to viral hepatitis including a 65% reduction in mortality by 2030. To achieve this target, it is essential to understand the trends in HCV treatment uptake, and efficacy in real world settings. The SHCS provides an optimal framework to address the impact of DAAs in routine clinical practice in a nationwide representative HIV/HCV-coinfected population. The aims of this study were to assess the impact of new DAAs on treatment uptake and efficacy as well as its repercussion on liver disease burden in the SHCS.

Patients and methods

Study population:

The SHCS (www.shcs.ch) prospectively enrolls HIV-infected adults in Switzerland since 1988. It includes 73% of all diagnosed HIV-infections in Switzerland[15]. Representativity has remained stable over the years. Detailed clinical and laboratory

data are recorded at study entry and every 6 months thereafter and include information on HCV serology, HCV RNA, transaminases, HCV treatment and liver related events (decompensation, variceal bleeding or hepatic encephalopathy, hepatocellular carcinoma, and liver-related death), as well as data on liver histology and transient elastography. Local ethical committees (KEK-BE: Kantonale Ethikkommission Bern, KEK-ZH Kantonale Ethikkommission Zürich, EKBB: Ethikkommission beider Basel, EKSG: Ethikkommission St. Gallen, CER-GE: Commission cantonale d'éthique de la recherche, CER-VD: Commission cantonale d'éthique de la recherché sur l'être humain, Comitato etico cantonale-TI) of all participating study sites have approved the study and written consent is obtained from all participants. All HCV-seropositive participants with positive HCV RNA and at least two visits were considered for this analysis, however, patients treated during acute HCV infection were excluded.

Study periods:

We defined 3 distinctive analysis periods, based on the availability of HCV treatments in Switzerland:

-Period 1, termed "peg-IFN/RBV era", lasted from 01/2009-08/2011 and represents the period when DAAs were not yet available in Switzerland and patients were still treated with peg-IFN /RBV.

-Period 2, termed "1st-generation DAA era" lasted from 09/2011-03/2014 and represents the period after the approval of first generation DAAs in Switzerland for HCV genotype 1 infections (boceprevir and telaprevir).

-Period 3, termed "2nd-generation DAA era" lasted from 04/2014-12/2015 and represents the period after the approval of the first second generation DAA in Switzerland (sofosbuvir (SOF) in April 2014).

Assessment of HCV treatment:

Details on treatment safety, uptake and efficacy were assessed in all patients treated during period 3 (2nd-gen. DAA era). To analyze potential changes in the treated population over time we compared patients infected with HCV genotype 1 treated during period 2 (1st-gen. DAA era) and period 3 (2nd-gen. DAA era). Data on treatment uptake and efficacy form period 1 (peg-IFN/RBV era) and period 2 (1st-gen.

DAA era) were retrieved from our previous studies as well as from the SHCS database[3,13].

To capture the key events during HCV treatment, a case-report form was implemented from 2011 onwards, specifically designed to retrieve information that could have been missed with the 6-monthly follow-up visits. HCV viral loads were recorded at baseline, at treatment stop or treatment failure as well as 12 weeks after treatment stop. Treatment responses were defined according to the European Guidelines for the Study of the Liver (www.easl.eu). Sustained virological response was assessed at 12 weeks (SVR12) after treatment discontinuation and considered even after closure of the recruitment in December 2015. This avoided a systematic bias towards poorer outcomes, as those who failed or discontinued therapy prematurely were more likely to experience an endpoint within the study period. The treatment was at the discretion of the physician, however at the time SOF was approved in Switzerland, the treatment of chronic HCV with second generation DAAs was only reimbursed by Swiss health insurances for patients with advanced fibrosis (≥Metavir F3) or defined extrahepatic manifestations of chronic HCV infection. In August 2015, the reimbursement threshold was reduced to Metavir F2.

Study measurements:

Quantitative HCV RNA measurements were performed for all patients with the COBAS® TaqMan® HCV Test v2.0 on the COBAS AmpliPrep/TaqMan48 system (Roche Diagnostics International AG, Rotkreuz, Switzerland) according to the manufacturer's protocol, with a lower limit of detection of 15 IU/mL. Genotypes were determined using TaqMan® Genotyping Master Mix (Life Technologies, Carlsbad, CA, USA). Where available, liver fibrosis stage was derived from liver biopsy and expressed as a Metavir score. Alternatively, liver fibrosis was determined using transient elastography (Fibroscan®; Echosens S.A.S.U., Paris, France). According to previous studies in HIV/HCV-coinfected patients, we used the following cut-off values: 7.1kPa for Metavir F2, 9.5 kPa for Metavir F3, and 12.4 kPa for Metavir F4 (cirrhosis)[16].

Statistical analysis:

Demographic and clinical characteristics at HCV treatment start were described using absolute numbers and proportions, or medians and interquartile ranges (IQR) for

patients treated during period 3. Their main characteristics were compared to those of patients treated during period 2 using Chi-square, Fisher's exact or Mann-Whitney test, where appropriate. All testing was two-tailed and *P*-values < 0.05 were considered to indicate statistical significance. Treatment uptake was described as incidence of treatment initiations by period. Treatment uptake and efficacy, as well as liver fibrosis stages were compared between different time periods using the Chi-square test. Statistical analyses were performed using Stata Version 13.1.

Results

Characteristics of patients treated with 2nd generation DAAs

At the beginning of the third period, 876 participants had a chronic HCV infection and of those 180 (20%) started treatment with a second generation DAA. At baseline, patients were predominantly middle-aged (median: 52 years [IQR 48-56]), Caucasian (166/180 [92%]) and males (124/180 [70%]) (**Table 1**). Most individuals were on ART (170/180 [70%]) and 99% of them had a suppressed HIV viral load. Three-quarters had a CD4 count > 350 cells/µl. One hundred and twelve of 180 (62%) were people who injected drugs (PWID) previously and 18% of them reported active consumption of illicit drugs. There was only a small proportion (9%) of men who have sex with men (MSM). Depression was diagnosed in one third of all patients. Transaminases were elevated [ACTG (AIDS Clinical Trials Group) grade 1-4] in 94/168 (56%) of the patients. Most patients were infected with HCV genotype 1 (55%), followed by genotype 3 (21%), genotype 4 (18%) and finally genotype 2 (2%). Among the treated patients, 76% had advanced fibrosis (≥Metavir F3). Cirrhosis was present in 62% of patients, of whom 85% had compensated cirrhosis (Child A). One hundred and sixty-four of 180 (91%) patients were treated with a sofosbuvir (SOF) based regimen (**Table 1**), of whom 55% received the fixed combination of SOF/ ledipasvir (LDV). The combination of ombitasvir/ paritaprevir/ritonavir (OMV/PTV/RTV) and dasabuvir (DSV) was prescribed in 17/180 (9%). Additional ribavirin (RBV) was prescribed in one half of cases. Sixty-one percent (109/180) of the patients were treatment-experienced, 97 with peg-IFN/RBV, 11 with a PI and 1 with SOF. In 88% of patients the indication to start treatment was liver fibrosis. From the 11 patients that started treatment because of extrahepatic manifestations, 3 had a vasculitis, 3 had a glomerulonephritis, 2 had a porphyria cutanea tarda, 2 had fatigue and 1 had a cryoglobulinemia.

Efficacy and safety of patients treated with 2nd generation DAAs

Overall, 96% (95% confidence interval [CI], 93%-99%) of patients achieved an SVR12 (173/180) (**Figure 1**). Three patients treated with SOF and RBV had a virological relapse, 2 with a genotype 4 and one with a genotype 1A infection. One patient with genotype 3A experienced a virological breakthrough under a treatment with SOF and RBV. Detailed clinical, laboratory and treatment characteristics of these patients are summarized in **Supplementary Table 1**. Three patients died during treatment, 2 from liver decompensation and 1 from sepsis, all had cirrhosis and two of them had decompensated cirrhosis. Only one of 180 patients discontinued treatment. This patient developed a clinically and laboratory significant rhabdomyolysis (maximal creatinkinase level of 3'052 U/L) without relevant renal complications five weeks after the initiation of SOF/LDV for a HCV genotype 1A infection with advanced fibrosis. The physician in charge judged this event as being potentially related to HCV therapy. The symptoms resolved after treatment withdrawal, and despite this only very short treatment duration he achieved SVR12.

Characteristics of patients treated for HCV genotype 1 infection in period 3 (2nd-gen. DAA era) compared to period 2 (1st-gen. DAA era)

There were 99 patients with genotype 1 treated during period 3 and 57 during period 2. Compared to patients treated during period 2, patients treated during period 3 were slightly older (52 [IQR 47-56] *vs*. 48 [IQR 43-52]) (**Table 2**). No differences in laboratory values or HIV-related characteristics were noted between individuals treated in either one or the other period. Patients treated during period 3 were more likely to have advanced liver fibrosis [77/99 (77%) vs. 33/57 (58%) p<0.01], or cirrhosis [63/99 (64%) vs. 20/57 (35%) p<0.01], compared to those treated during period 2.

Changes in treatment uptake and efficacy over the three periods

Overall treatment uptake continuously increased through the 3 periods (from 4.5 to 5.7 to 22.4 per 100 patient-years), with a 4-fold increase after the introduction of second generation DAAs during period 3 (**Figure 1**). During period 2, treatment uptake increased only in HCV genotype 1 infected patients, whereas it diminished in all other genotypes. Treatment efficacy increased through the 3 periods (SVR 12:

from 55% [95% CI, 44%-64%] to 70% [95% CI, 63%-79%] and 96% [95% CI, 93%-99%]) and was observed among all genotypes.

Changes in liver fibrosis stages over time

At the end of the second period in April 2014 data on liver fibrosis stages was available for 623 patients with a chronic HCV infection in the SHCS (**Figure 2**). Of those, 33% (204/623) had advanced fibrosis (≥Metavir F3) of which158 (77%) had a cirrhosis. At the end of period 3, the proportion of patients with advanced fibrosis still to be treated declined to 15% (67/438) and only 12% (51/438) had a cirrhosis ($p<0.01$).

Discussion

After the approval of interferon-free second generation DAAs, we observed a 4-fold increase in treatment uptake and a 2-fold increase in treatment efficacy leading to SVRs above 90% across all HCV genotypes in the SHCS. Even traditionally difficult-to-treat, pre-treated patients with advanced liver fibrosis achieved high SVR rates with DAA treatments in a clinical routine setting. Because of treatment priorities and reimbursement limitations, three-quarters of patients treated with second generation DAAs had advanced fibrosis. The successful treatment of these patients led to a 2-fold reduction of patients with cirrhosis and a replicating HCV infection in the SHCS.

As in the French ANRS CO13-HEPAVIH cohort and the German hepatitis C cohort (GECCO), patients treated with second generation DAAs in the SHCS were predominantly middle aged, males, who previously injected drugs[17,18]. In our study three-quarters of them had advanced fibrosis and 60% were previously treated, traditionally representing the difficult-to-treat population **(Table 1)**. Similar findings were described in the French cohort, with 73% cirrhotic patients and 70% who had failed previous treatment. Ninety percent of patients were treated with a SOF based regimen and of those 55% received the fixed combination of SOF/LDV in the SHCS, which contrasts with the French cohort where a regimen containing SOF/DCV was predominantly used (68%). In the SHCS second generation DAA treatments were highly effective, leading to an overall SVR12 rate of 96%. Similar overall SVR12 rates were found in the French (92%) and the German (96%) cohorts. These data confirm that efficacy in real world settings is similar to those found in registered trials, with

response rates in HIV/HCV-coinfected patients similar to those in HCV-moninfected[19-22]. All 3 patients who died during treatment had cirrhosis, two already being in a decompensated state. This underscores that the benefits of treatment are not universal, particularly in patients with decompensated cirrhosis and high MELD scores[23]. Similarly to the French cohort where only 4% of patients prematurely stopped their therapy, all DAA combinations were generally well tolerated in the SHCS, with only one patient having to discontinue treatment. This underscores the dramatic improvement of tolerability of second generation DAAs compared to previous treatments[24,25]. The four virological failures in our study occurred among patients treated with only one DAA. Similarly, lowest cure rates were also described with the combination of SOF/RBV in the two other European cohorts, particularly among genotype 3 infected patients.

Compared to patients treated in the 1st-generation DAA era, patients treated during the 2nd-generation DAA era had significantly higher fibrosis stages and twice as much patients were cirrhotics **(Table 2)**. This reflects the improvements in treatment eligibility as contraindications to interferon-based therapy did not apply any more in the 2nd-generation DAA era. But it is also driven by treatment prioritization of those with advanced liver disease and by reimbursement restrictions according to the Metavir stage.

We observed an increase in treatment uptake over time, especially in the last study period, when 2nd generation DAA were available. Treatment uptake in the peg-IFN/RBV era was similarly low in the SHCS as in other European cohorts, ranging from 3.4 to 5.9 per 100 patient years [3,26,27]. Before 2011, less than one third of HIV/HCV-coinfected patients in the SHCS were eligible for treatment and only a minority started treatment [9,10,28]. Similar rates were found in a large registry of 99,166 US veterans with HCV viremia, were only 11.6% started treatment, and 57% of those not treated had contraindications to treatment[29]. After the approval of first generation DAAs (PIs, only against genotype 1) in Switzerland in September 2011, only 13% of HCV genotype 1 infected patients started treatment and treatment incidence increased only slightly in routine clinical care (from 3.8 to 6.1 per 100 patient-years), thereby only having a very modest impact on the burden of HCV disease at the population level[13]. In this period, we noticed a decrease in treatment uptake across

all other genotypes **(Figure 1)**, highlighting the fact that physicians postponed treatment awaiting for more efficient and more tolerable treatments for non-1 genotype infected individuals. In the 2nd generation DAA era, we observed an impressive fourfold increase in treatment uptake, reaching a treatment incidence of 22 per 100 patient-years, which is close to the 25 per 100 patient-years found in EuroSIDA[30].

As a consequence of the improvement in treatment tolerability and efficacy, and because of treatment priorities and reimbursement limitations, three-quarters of patients treated in the 2nd-generation DAA era had advanced fibrosis. This led to a twofold reduction of cirrhotics with a replicating HCV infection in the SHCS from April 2014 to December 2015**.** Close monitoring of patients treated at a stage of advanced liver disease is warranted, as these are at ongoing risk of experiencing liver-related events, particularly HCC. The combination of the increasing treatment uptake and efficacy, as well as the treatment of a large proportion of patients with advanced liver disease should contribute to the reduction of the HCV disease burden in the near future[31]. Moreover, we demonstrated previously, that this increase in treatment uptake combined with stabilization in risk behavior can efficiently reduce HCV transmission[32]. However because of reimbursement limitations only very few MSM with high risk behavior could be treated because they often had low fibrosis stages. As the remaining patients to be treated often have mild fibrosis, the burden of replicating HCV infection will only be further reduced if reimbursement is not restricted to those with advanced fibrosis. Unfortunately, universal access to HCV therapy is restricted to few countries worldwide due to the huge costs of these treatments[33]. The successful negotiations with pharmaceutical companies in Australia and Egypt to substantially lower DAA costs exemplify that this can be achieved.

We report on one of the largest prospective observational studies assessing long-term HCV treatment uptake and outcomes in HIV-infected individuals. The detailed and systematic clinical and biological monitoring within the SHCS provided detailed information on treatment safety, efficacy as well as on liver fibrosis stages and allowed us to compare these parameters over different time periods. But this study also has limitations. The continuous approval of new drugs as well as changes in

guidelines and reimbursement policies over time resulted in a heterogeneity of treatments used, precluding comparisons between different treatment regimens. Rather than comparing the safety and efficacy of different regimens, our study focused on the description of the overall uptake, efficacy and tolerability of HCV therapy in routine clinical practice. As treatment uptake is directly linked to reimbursement policies, our data might not be generalizable to settings with different regulations.

In conclusion, we observed a substantial increase in treatment uptake and efficacy after the approval of interferon-free second generation DAA treatments. DAAs were well tolerated and highly efficacious, even among HIV/HCV-coinfected patients with advanced liver fibrosis or cirrhosis in the SHCS. The treatment of this population with advanced liver disease was driven by treatment priorities but also by limitations in reimbursement, and resulted in a significant reduction in the number of cirrhotic patients with replicating HCV. However many with mild fibrosis are still untreated. Thus, we will only be able to further reduce the burden of replicating HCV infection if reimbursement is not restricted to those with advanced fibrosis.

Acknowledgments:
This study has been performed within the framework of the Swiss HIV Cohort Study. The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers). We thank the participating patients, physicians and study nurses for excellent patient care, the data- and the coordination center for continuous support.

The members of the SHCS are: Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the

Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

References:

1. Klein MB, Rockstroh JK, Wittkop L. Effect of coinfection with hepatitis C virus on survival of individuals with HIV-1 infection. *Curr Opin HIV AIDS.* 2016;11(5):521-526.
2. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med.* 2006;166(15):1632-1641.
3. Kovari H, Ledergerber B, Cavassini M, et al. High hepatic and extrahepatic mortality and low treatment uptake in HCV-coinfected persons in the Swiss HIV cohort study between 2001 and 2013. *J Hepatol.* 2015;63(3):573-580.
4. Chen M, Wong WW, Law MG, et al. Hepatitis B and C Co-Infection in HIV Patients from the TREAT Asia HIV Observational Database: Analysis of Risk Factors and Survival. *PLoS One.* 2016;11(3):e0150512.
5. Grint D, Peters L, Rockstroh JK, et al. Liver-related death among HIV/hepatitis C virus-co-infected individuals: implications for the era of directly acting antivirals. *Aids.* 2015;29(10):1205-1215.
6. Klein MB, Rollet-Kurhajec KC, Moodie EE, et al. Mortality in HIV-hepatitis C co-infected patients in Canada compared to the general Canadian population (2003-2013). *Aids.* 2014;28(13):1957-1965.
7. Weber R, Ruppik M, Rickenbach M, et al. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. *HIV Med.* 2013;14(4):195-207.
8. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;61(5):730-740.
9. Rauch A, Egger M, Reichen J, Furrer H, Swiss HIVCS. Chronic hepatitis C in HIV-infected patients: low eligibility and applicability of therapy with pegylated

interferon-alpha plus ribavirin. *Journal of acquired immune deficiency syndromes.* 2005;38(2):238-240.

10. Zinkernagel AS, von Wyl V, Ledergerber B, et al. Eligibility for and outcome of hepatitis C treatment of HIV-coinfected individuals in clinical practice: the Swiss HIV cohort study. *Antivir Ther.* 2006;11(2):131-142.
11. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med.* 2009;360(18):1827-1838.
12. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med.* 2011;364(13):1195-1206.
13. Schaerer V, Haubitz S, Kovari H, et al. Protease inhibitors to treat hepatitis C in the Swiss HIV Cohort Study: high efficacy but low treatment uptake. *HIV Med.* 2015;16(10):599-607.
14. Saeed S, Strumpf EC, Walmsley SL, et al. How Generalizable Are the Results From Trials of Direct Antiviral Agents to People Coinfected With HIV/HCV in the Real World? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2016;62(7):919-926.
15. Kohler P, Schmidt AJ, Cavassini M, et al. The HIV care cascade in Switzerland: reaching the UNAIDS/WHO targets for patients diagnosed with HIV. *Aids.* 2015;29(18):2509-2515.
16. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol.* 2008;48(5):835-847.
17. Sogni P, Gilbert C, Lacombe K, et al. All-oral Direct-acting Antiviral Regimens in HIV/Hepatitis C Virus-coinfected Patients With Cirrhosis Are Efficient and Safe: Real-life Results From the Prospective ANRS CO13-HEPAVIH Cohort. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2016;63(6):763-770.
18. Christensen S et al.: Directly Acting Agents Against HCV - Results From the German Hepatitis C Cohort (GECCO) 23rd Conference on Retroviruses and Opportunistic Infections, February 22-25, 2016, Boston; abstract 584.
19. Sulkowski MS, Eron JJ, Wyles D, 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(12):1223-1231.

20. Naggie S, Cooper C, Saag M, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med.* 2015;373(8):705-713.
21. Wyles DL, Ruane PJ, Sulkowski MS, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med.* 2015;373(8):714-725.
22. Molina JM, Orkin C, Iser DM, et al. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. *Lancet.* 2015;385(9973):1098-1106.
23. Cheung MC, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol.* 2016;65(4):741-747.
24. Hezode C, Fontaine H, Dorival C, et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology.* 2014;147(1):132-142 e134.
25. Miailhes P, Gilbert C, Lacombe K, et al. Triple therapy with boceprevir or telaprevir in a European cohort of cirrhotic HIV/HCV genotype 1-coinfected patients. *Liver international : official journal of the International Association for the Study of the Liver.* 2015;35(9):2090-2099.
26. Martin NK, Foster GR, Vilar J, et al. HCV treatment rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact. *J Viral Hepat.* 2015;22(4):399-408.
27. Grint D, Peters L, Schwarze-Zander C, et al. Temporal changes and regional differences in treatment uptake of hepatitis C therapy in EuroSIDA. *HIV Med.* 2013;14(10):614-623.
28. Martel-Laferriere V, Bichoupan K, Dieterich DT. Hepatitis C direct-acting antiviral agents: changing the paradigm of hepatitis C treatment in HIV-infected patients. *J Clin Gastroenterol.* 2014;48(2):106-112.
29. Kramer JR, Kanwal F, Richardson P, Mei M, El-Serag HB. Gaps in the achievement of effectiveness of HCV treatment in national VA practice. *J Hepatol.* 2012;56(2):320-325.
30. Peters L. et al. Uptake of HCV Therapy in HIV/HCV Coinfected Patients across Europe in the Era of Direct-Acting Antivirals, AASLD, Nov. 11-15, 2016, Abstract 1954.

31. Wedemeyer H, Duberg AS, Buti M, et al. Strategies to manage hepatitis C virus (HCV) disease burden. *J Viral Hepat.* 2014;21 Suppl 1:60-89.
32. Salazar-Vizcaya L, Kouyos RD, Zahnd C, et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. *Hepatology.* 2016.
33. Iyengar S, Tay-Teo K, Vogler S, et al. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. *PLoS Med.* 2016;13(5):e1002032.

Figure 1: Treatment uptake and efficacy over the 3 periods.
(period 1: peg-IFN/RBV era, 01/2009-08/2011 ; period 2: 1st-gen. DAA era, 09/2011-03/2014; period 3: 2nd-gen. DAA era, 04/2014-12/2015)
Abreviations: py, patient years; GT, genotype; SVR, sustained virological response

Figure 2: Distribution of liver fibrosis among patients with active HCV infection in the different periods
At the end of period 2 in April 2014, 876 patient had a chronic HCV infection. In December 2015 at the end of Period 3, 692 patients had a chronic HCV infection.

Table 1: Baseline characteristics of all patients of the SHCS treated during period 3 (2nd-generation DAA era)

	All treatment
N	180
Demographic characteristics	
Age, median (IQR)	52 (48-56)
Male (%)	124/180 (70)
Caucasian (%)	166/180 (92)
Illicit drug use (%)	20/180 (11)
Depression (%)	53/180 (29)
HIV characteristics	
Median HIV RNA in log cp/ml (IQR)	0 (0-0)
Controlled HIV RNA<20 copies/ml (%)	168/180 (93)
Patients on ART (%)	170/180 (94)
CDC Stage C (%)	64/180 (36)
Median CD4 in cells/ul (IQR)	508 (467-749)
CD4 cell category (cells/ul)	
1-200	16/180 (9)
200-350	26/180 (15)
>350	138/180 (76)
HIV Transmission group (%)	
MSM	17/180 (9)
IDU	112/180 (62)
HET	37/180 (21)
Other	14/180 (8)
Laboratory values	
Median eGFR in ml/min (IQR)*	94 (74-104)
Median Thrombocytes in G/L (IQR)	141 (95-182)
Liver Enzymes, median (IQR)	
ALT (U/L)	58 (36-101)
AST (U/L)	57 (39-91)
ALT elevation** (%)	94/168 (56)
Hepatitis C characteristics	
HCV viral load (log10 copies/ml), median (IQR)	6.1 (5.4-6.5)
HCV Genotype (%)	
GT 1	99/180 (55)
GT 2	4/180 (2)
GT 3	37/180 (21)
GT 4	32/180 (18)
Liver Fibrosis stage (%)	
F0-1	22/180 (12)
F2	21/180 (12)
F3	25/180 (14)
F4	112/180 (62)
Treatment	
SOF (%)	164/180 (91)
SOF LDV	90/180
SOF DCV	24/180
SOF SIM	6/180
SOF IFN	17/180
OMV/PTV/RTV + DSV(%)	16/180 (9)
Ribavirin (%)	88/180 (49)
Treatment history (%)	
Treatment naïve	71/180 (39)
Experienced	109/180 (61)
Treatment indication (%)	
Fibrosis	159/180 (88%)
Extrahepatic manifestations	11/180 (6%)
Other	10/180 (6%)

Abbreviations: SHCS, Swiss HIV Cohort Study; IQR, interquartile range; MSM, men who have sex with men; IDU, injection drug user; HET, heterosexual; HIV, human immunodeficiency virus; ART, antiretroviral therapy; CDC, Centers for Disease Contorl; eGFR, estimated glomerular filtration rate; ALT, alanin-Aminotransferase; AST, aspartate-aminotransferase; HCV, hepatitis C virus; GT; genotype; SOF, sofosbuvir; LDV, ledipasvir; DCV, daclatasvir; SIM, simeprevir; INF, interferon; OMV, ombitasvir; PTV, paritaprevir; RTV, ritonavir; DSV, dasabuvir

*eGFR: calculated with the CKD-EPI formula

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Table 2: Comparison of genotype 1 treated patients between period3 (2nd-generation DAA era) and period 2 (1st-generation DAA era)

	Period 2	**Period 3**
N	57	99
Demographic characteristics		
Age, median (IQR)	48 (43-52)	52 (47-56)
Male (%)	47/57 (82)	71/99 (73)
Caucasian (%)	51/57 (89)	91/99 (92)
Illicit drug use (%)	7/57 (12)	14/99 (14)
Depression (%)	13/57 (23)	31/99 (31)
HIV characteristics		
Median HIV RNA in log cp/ml (IQR)		
Controlled HIV RNA<20 copies/ml (%)	50/57 (88)	95/99 (96)
Patients on ART (%)	54/57 (95)	93/99 (94)
CDC Stage C (%)	20/57 (35)	36/99 (36)
Median CD4 in cells/ul (IQR)	496 (380-697)	521 (408-800)
CD4 cell category (cells/ul)		
1-200	4/57 (7)	4/99 (4)
200-350	8/57 (14)	16/99 (16)
>350	45/57 (79)	79/99 (80)
HIV Transmission group (%)		
MSM	11/57 (19)	10/99 (10)
IDU	33/57 (58)	60/99 (61)
HET	8/57 (14)	20/99 (20)
Other	5/57 (9)	9/99 (9)
Laboratory values		
Median eGFR in ml/min (IQR)*	100 (86-108)	93 (77-104)
Median Thrombocytes in G/L (IQR)	156 (104-226)	140 (105-174)
Liver Enzymes, median (IQR)		
ALT (U/L)	50 (33-76)	50 (36-94)
AST (U/L)	45 (36-59)	50 (34-87)
ALT elevation** (%)	27/57 (47)	45/99 (45)
Hepatitis C characteristics		
HCV viral load (log10 copies/ml), median (IQR)	6.1 (5.1-6.4)	6.1 (5.6-6.5)
Liver Fibrosis stage (%)		
F0-1	10/57 (17)	10/99 (10)
F2	14/57 (24)	12/99 (12)
F3	13/57 (23)	14/99 (14)
F4	20/57 (35)	63/99 (64)

Abbreviations: SHCS, Swiss HIV Cohort Study; IQR, interquartile range; MSM, men who have sex with men; IDU, injection drug user; HET, heterosexual; HIV, human immunodeficiency virus; ART, antiretroviral therapy; CDC, Centers for Disease Contorl; eGFR, estimated glomerular filtration rate; ALT, alanin-Aminotransferase; AST, aspartate-aminotransferase; HCV, hepatitis C virus;

*eGFR: calculated with the CKD-EPI formula

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