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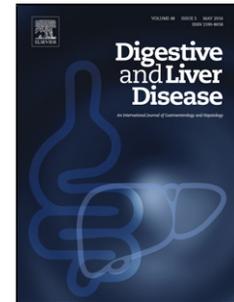
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Interferon-free direct-acting antiviral therapy for acute hepatitis C virus infection in HIV-infected individuals: a literature review**Running title:** DAA therapy for acute HCV infection in HIV-infected individuals**First author:**

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Abstract:

Dramatic rises in hepatitis C virus (HCV) coinfection rates in human immunodeficiency virus (HIV)-infected individuals have been observed recently, largely attributable to increasing recreational drug use combined with increased testing for HCV. In the era of direct-acting antiviral (DAA) therapy, treatment of acute HCV infection in HIV-infected individuals with short durations of these drugs may potentially reduce the disease and economic burden associated with HCV infection as well as reducing the likelihood of onward HCV transmission. We performed an extensive literature search of PubMed, Embase and Google Scholar up to 05 September 2017 for clinical trials of acute HCV infection in HIV-infected individuals. In the studies identified, rates of sustained virologic response at 12 weeks post-treatment (SVR12) ranged from 21% with 6 weeks of therapy up to 92% with 12 weeks of therapy with sofosbuvir/ribavirin. Ledispavir/sofosbuvir for 6 weeks achieved an SVR of 77%. No HIV-related events occurred regardless of whether patients were receiving antiretroviral therapy (ART) and DAAs were well tolerated. Data is currently limited with regards to optimal regimens and durations of therapy, which need to be tailored based on potential interactions with concurrent ART and consideration for the fact that patients with higher baseline HCV RNA levels may require extended duration of treatment.

Abbreviations:**HCV** hepatitis C virus**PLWH** people living with HIV**MSM** men-who-have-sex-with-men**ART** antiretroviral therapy**DAA** direct-acting antiviral**IFN** interferon**SVR** sustained virologic response**EASL** European Association for the Study of the Liver**AASLD** American Association for the Study of Liver Diseases**NRTI** Nucleoside reverse transcriptase inhibitor**NNRTI** Non-nucleoside reverse transcriptase inhibitor**PI** Protease inhibitor**INSTI** Integrase inhibitor**HBV** hepatitis B virus**Keywords:** DAA, interferon-sparing, acute HCV, HIV**Introduction**

Globally, hepatitis C virus (HCV) coinfection affects 5 to 10 million people living with HIV (PLWH)¹ and in certain populations, rates of HCV/HIV coinfection been found to exceed 90% amongst those who inject drugs.^{2,3,4} Recent epidemics of acute HCV infection have been witnessed amongst HIV positive men-who-have-sex-with-men (MSM).⁵ A recent study also reported an increased prevalence of HCV infection in HIV-negative MSMs who were about to embark on HIV pre-exposure prophylaxis.⁶ These surges in rates of HCV infection, which have been observed in several parts of the world, are becoming increasingly associated with sexualised recreational drug use known as 'chemsex'.⁷ The rising numbers of tattooing (in prisons for example) and non-surgical cosmetic percutaneous procedures being performed in various settings (many of which are unregulated) could also be contributing to the increased rates of HCV transmission in both HIV positive and HIV negative individuals.^{8,9} The first 6 months after acquisition of HCV has classically been recognised as the acute phase and only 15% to 20% of people PLWH with acute HCV infection will spontaneously clear their HCV infection.^{10,11} The European AIDS Treatment Network (NEAT) guidelines for acute hepatitis C in HIV-infected individuals suggest a viral kinetic model for HCV infection taking into

consideration the fact that less than a 2 log₁₀ IU/mL reduction in HCV RNA at 4 weeks after diagnosis and a positive HCV-RNA 12 weeks into acute hepatitis have both shown an association with progression to chronicity.¹² Individuals who exhibit these viral kinetics may therefore serve as primary targets for early therapeutic strategies. Once chronicity is established, as occurs in the majority of HCV-infected individuals, HIV/HCV coinfecting patients demonstrate faster rates liver fibrosis progression¹³, and are at an increased risk of developing cirrhosis and hepatocellular carcinoma compared to individuals not infected with HIV.¹⁴ Development of cirrhosis occurs 12 to 16 years earlier in HCV/HIV coinfecting individuals compared to HCV monoinfected individuals and once hepatic decompensation occurs, estimated median survival is only 13 months in coinfecting patients.¹⁵ Treatment of PLWH with acute HCV infection is important in preventing the development of chronic infection, preventing accelerated progression of liver disease and to minimise the risk of onward HCV transmission. Additionally, HIV/HCV coinfecting individuals demonstrate reduced immunological responses to antiretroviral therapy (ART) compared to HIV monoinfected individuals.¹⁶

Prior to the recent, wider availability of direct-acting antivirals (DAAs), treatment of acute HCV infection in PLWH with interferon (IFN)-based therapy for 24 week's duration achieved significantly higher overall sustained virologic response (SVR) rates (up to 80%) compared to those seen with 48 weeks of interferon-based treatment (up to 40%) for chronic HCV infection in PLWH.^{17,18,19} Currently used DAAs, available for the treatment of all 6 genotypes chronic HCV infection, offer improved SVR rates, shorter durations of therapy and lower incidences of adverse effects compared to previous IFN-based therapy.²⁰ Indications for the treatment of chronic HCV infection with DAAs are currently the same for monoinfected and HCV/HIV coinfecting individuals and treatment duration ranges from 8 weeks to 24 weeks.²¹ A recent large observational study found similar high rates of SVR with IFN-sparing DAA therapy for chronic HCV infection in HCV/HIV coinfecting (n = 482) and HCV monoinfected (n = 1152) individuals (94% vs 97%).²²

Based on findings that a minimum of 8 weeks therapy is needed to achieve optimal SVR rates in the treatment of chronic HCV infection, the most recent European Association for the Study of the Liver (EASL) guidelines recommend sofosbuvir (an HCV NS5B nucleotide polymerase inhibitor) combined with an NS5A inhibitor for a duration of 8 weeks in the treatment of acute HCV infection (with possible extension up to 12 weeks for PLWH and/or a baseline HCV RNA level >6.0 log₁₀ IU/mL). The American Association for the Study of Liver Diseases (AASLD) recommends the same type and duration of DAA therapy for acute HCV infection as used in treating chronic HCV infection.²³ Treatment of acute HCV infection in PLWH reduces patient morbidity and the financial burden associated with longer term follow-up,¹⁹ therefore potentially shorter durations of therapy with these high cost DAAs could provide even greater health and economic benefits, provided maximal SVR rates are still achieved. We review the current literature on the use of DAAs for the treatment of acute HCV infection in PLWH.

Search strategy and selection criteria

A comprehensive literature search was performed using the MEDLINE/PubMed, Embase and Google Scholar databases up to 05 September 2017. Various combinations of the following keywords were used to identify relevant studies: 'acute HCV', 'HIV and acute HCV', 'HCV/HIV coinfection', 'DAA', 'NS5B inhibitor', 'NS5A inhibitor', 'NS3/4A inhibitor', 'polymerase inhibitor' and 'protease inhibitor'. We searched the references of identified publications and utilised the PubMed 'similar articles' tool to identify any further relevant studies. Additionally, we searched for abstracts from recent conferences and clinicaltrials.gov for unpublished studies.

Types of therapy

The ability of HCV in an acute infection to escape host antiviral immune response mechanisms leads to viral persistence and chronic infection in the majority (80 to 85%) of HCV/HIV coinfecting individuals.²⁴ Impairment of CD4+ T cells directed against HCV²⁵²⁶ and suppression of the antiviral activity of host type 1 interferons (alpha and beta)²⁷²⁸ are proposed mechanisms by which the virus escapes immune control. Exogenously administered interferon (IFN), in the form of pegylated-IFN (pegIFN) achieves SVR rates of 60-70% even as monotherapy in the treatment of acute HCV in PLWH²⁹ thus highlighting the impact of immunomodulators on viral clearance. The addition of ribavirin can increase SVR rates to approximately 80%.³⁰ Twelve weeks of triple therapy for genotype 1 acute HCV coinfection with pegIFN/ribavirin taken in combination with the HCV protease inhibitor boceprevir showed comparable rates of SVR12 with historical controls that received 24 weeks of pegIFN/ribavirin only (SVR12 86% vs 84%).³¹ In the CHAT study, where patients with genotype 1 acute HCV coinfection received pegIFN/ribavirin and the HCV protease inhibitor telaprevir for 12 to 24 weeks, similar SVR12 rates were also seen when compared to those that received pegIFN/ribavirin for 24 to 48 weeks (SVR12 78.9% vs 80%).³² However, due to the additional toxicities and the finding of telaprevir-induced selection of protease inhibitor resistance mutations associated with treatment non-response seen in their study, the investigators concluded that 'first-generation' protease inhibitors should not be used in treating acute HCV coinfection.

In PLWH, cellular mediated immunity is affected by both numerical and functional depletion of CD4+ cells³³ thus potentially compromising their ability to clear HCV in the acute phase. The CD4/CD8 ratio, which serves as a marker of immune dysfunction improves with ART but infrequently normalises in chronic HIV-1 infection even with long-term suppressive ART (29.4% estimated probability of CD4/CD8 normalisation at 5 years after starting ART).³⁴ It has, however, been shown to have a

significantly higher likelihood of restoration to normal levels when ART is initiated in the early stages of HIV-1 infection.³⁵ IFN-based re-treatment in HCV/HIV coinfecting patients that had previously failed to achieve an SVR with IFN-based therapy for HCV, demonstrated significantly higher re-treatment SVR rates when patients were successfully HIV-1 RNA suppressed with ART³⁶. In the current era where ART is now recommended for all PLWH,³⁷ the significant numerical and functional restoration of CD4+ T cells that typically occurs with ART,³³ will be seen in many more PLWH as increasing numbers of individuals receive ART earlier in the course of their HIV infection. This immune restoration may render the likelihood of PLWH achieving SVR following treatment of acute HCV coinfection with IFN-sparing DAA regimens on par with that of HCV monoinfected patients therefore negating the need for immunomodulatory agents.

IFN-sparing sofosbuvir-based regimens are licensed for and are highly effective in the treatment of all genotypes of HCV mono-infection and coinfection in patients with chronic hepatitis C and are well tolerated over a 12 to 24-week period.²¹ There are no absolute contraindications to sofosbuvir itself (caution is advised in renal impairment) apart from in patients taking amiodarone. The four published studies to date using IFN-sparing DAA regimens in acute HCV coinfection have investigated the use of sofosbuvir-containing therapy (table 1).³⁸⁻⁴¹ There are three studies in progress for treatment of acute HCV coinfection with grazoprevir/elbasvir with an intended treatment duration of 8 weeks (table 2).

The purine nucleoside analogue ribavirin has been a major component in the success of HCV treatment in the era of pegIFN-based therapy^{42,43} but with the high SVR rates achieved for chronic HCV with novel IFN-sparing DAAs its future role is less well defined. Even with IFN-sparing DAA regimens, however, there is still evidence that ribavirin hastens rates of decline in blood HCV ribonucleic acid (RNA) levels and reduces the likelihood of viral relapses.⁴⁴ It does still therefore remain an important component of therapy for chronic HCV infection, particularly in decompensated cirrhotic patients and in certain patients who have previously failed treatment with pegIFN-based and/or DAA-containing regimens.^{21,45} Its role as part of IFN-sparing therapy for acute HCV infection in PLWH is not clear and needs further justification if it is to be an established component of future treatment regimens given that it is not free from side effects such as haemolytic anaemia⁴⁶ and adds further to their pill burden (albeit temporarily). A recent study of varying dual-DAA regimens for the treatment of chronic HCV infection in 323 PLWH reported that the use of ribavirin in addition to a dual-DAA regimen did not result in improved SVR rates (SVR12 of 92.7% with ribavirin vs 95.2% without ribavirin).⁴⁷ However, if SVR rates are consistently found to be suboptimal with DAA-only regimens for acute HCV infection, then ribavirin may serve as an important adjunct to DAAs in future therapeutic strategies.

Direct-acting antiviral interactions with antiretroviral drugs

There are several DAA-ART interactions for clinicians to be aware of in HCV/HIV coinfecting patients and a recent study of varying IFN-sparing DAA regimens for chronic HCV infection in PLWH reported that 37% of patients required modification of

their ART regimen prior to starting DAAs.⁴⁸ A study which evaluated potential drug interactions between sofosbuvir (currently recommended by EASL as a component of therapy for acute HCV infection) and commonly prescribed ART in PLWH treated for chronic HCV coinfection found no clinically significant drug interactions between sofosbuvir and any of the studied NRTIs (zidovudine, lamivudine, tenofovir and emtricitabine), NNRTIs (efavirenz), HIV PIs (atazanavir, darunavir and ritonavir) and INSTIs (raltegravir).⁴⁹ Sofosbuvir itself is therefore considered safe when used with all four major classes of ART.²¹ The University of Liverpool HIV drug interactions website⁵⁰ is an up-to-date resource for checking specific DAA-ART (and other drug) interactions and the EASL hepatitis C treatment guidelines²¹ also provides useful information (table 3 summarises the known potential DAA-ART interactions). Clinicians need to also consider and enquire about ongoing use of recreational drugs, some of which have potential interactions with certain DAAs.⁵¹

Timing of direct-acting antiviral therapy initiation

IFN-based therapy for acute HCV infection in monoinfected individuals has been shown to achieve higher SVR rates when initiated immediately compared to when delayed for 12 weeks from the time of diagnosis (SVR 67% vs 54%).⁵² In IFN-based studies of acute HCV infection in PLWH, treatment has typically been commenced 12 to 24 weeks after diagnosis.^{53,54} Data from the ATACH trial found that SVR rates with IFN-based therapy in PLWH were similar in those treated in the acute phase of HCV infection compared to those treated in the late acute/early chronic phase of infection (SVR 77% vs 86%).^{30,18}

In the SWIFT-C study, in which PLWH with acute HCV infection received 12 weeks of treatment with sofosbuvir and ribavirin, univariate analysis found no significant difference in time between diagnosis of acute HCV infection and point of study entry for treatment in those that had HCV RNA <15 IU/mL at least 12 weeks after completion of therapy (SVR12) compared to those that did not achieve SVR12 (median 115.5 days vs 98 days, $p = 0.459$).³⁸ Similarly, no association was found between the estimated duration of acute HCV infection and SVR12 in the DARE-C II study with 6 weeks of sofosbuvir and ribavirin in PLWH.³⁹ Of note is that in the DARE-C II study, the median estimated duration of infection at baseline was 37 weeks and therefore included patients that would be in the (albeit early) chronic phase of their infection on the basis of the classical definition of acute versus chronic HCV infection.³⁹ Additionally, in the study by El Sayed and colleagues, the time from diagnosis to treatment initiation varied from 1 to 9 months.⁴⁰

Recent studies of DAAs in chronic HCV monoinfected⁵⁵ and HCV/HIV coinfecting⁵⁶ patients (on ART) found that despite successful elimination of HCV, DAA therapy failed to restore normal immune regulatory parameters (CD4+ regulatory T cells and myeloid-derived suppressor cells; which can impair host antiviral immune responses), even up to one year after HCV clearance. This immune impairment could have significant implications in terms of re-exposure to HCV possibly resulting in a

reduced likelihood of spontaneous viral clearance in cases of HCV re-infection as well as a potentially higher risk of acquisition/reactivation of other viral infections. This is of particular significance in PLWH who will already have a degree of immune dysfunction. These findings also raise the question as to whether earlier initiation of DAA therapy would therefore minimise the degree of HCV-mediated immune dysregulation. It has already been demonstrated with IFN-based therapy that host adaptive immunity may be preserved when treatment is initiated early after diagnosis of acute HCV mono-infection whereas (potentially irreversible) impairment of antiviral immune responses can occur in those treated during chronic HCV mono-infection.⁵⁷

Data is limited on when to start DAA therapy in acute HCV infection, which is at least in part related to difficulties in determining the precise timing of HCV acquisition in patients. However, there is no current evidence to suggest that treatment of PLWH with DAAs in the earlier stages of acute HCV infection improves rates of SVR compared to treatment later on in the course of an acute HCV infection or in the early stages of chronicity. Earlier treatment may however improve the likelihood of immune preservation and also patient engagement, which is an important consideration given that recent data suggests approximately 40% of PLWH demonstrate evidence of significant liver fibrosis (METAVIR stage F2 or higher) at just 3 years after their first diagnosis of an acute HCV infection.⁵⁸

Unlike with HIV-1 infection where there is strong evidence indicating that there are particularly high rates of transmission during the acute/early phase of infection,^{59,60} there is a paucity of data to suggest that similar patterns of transmission occur with HCV infection. Recent mathematical modelling data based on the HCV epidemic amongst MSMs in the UK does however suggest that upscaling of DAA therapy for example by treating 60%, 80% or 100% of recently diagnosed (<1 year) HCV infections in HIV-infected MSMs in the year of diagnosis (compared with a baseline rate of 46%) could result in 15%, 25% or 36% relative declines in HCV incidence in 2025, respectively.⁶¹ Recent data from Holland has already demonstrated a 52% reduction in the incidence of acute HCV infection amongst HIV-infected MSMs 1 year after access to DAA therapy became unrestricted for treating acute and chronic HCV infections.⁶² Theoretically at least, it is possible that earlier initiation of DAA therapy could therefore serve as a preventative measure thereby potentially reducing rates of HCV transmission.

Duration of direct-acting antiviral therapy

Lengthy courses of IFN and ribavirin therapy typically lasting 24 to 48 weeks (and even longer in certain instances) for both acute and chronic HCV infection were able to be shortened with the introduction of 'first-generation' DAAs.^{24,29,63,64} Fierer et al reported that the addition of telaprevir to pegIFN and ribavirin for the treatment of acute HCV infection in PLWH halved the overall treatment duration, with all patients in the telaprevir group (SVR12 84%) receiving 12 weeks (or less) of therapy compared to 24 weeks of treatment in the pegIFN and ribavirin-only group (SVR12 63%).⁶⁴

Two studies have investigated the treatment of acute HCV infection in PLWH with 12 weeks of IFN-sparing DAA therapy using sofosbuvir and ribavirin.^{38,40} In a study by El Sayed et al in which 12 patients with genotype 1 acute HCV coinfection (11 patients with genotype 1a and 1 patient with genotype 1b) received 12 weeks of therapy with sofosbuvir and ribavirin, ninety-two percent (11/12) achieved an SVR12.⁴⁰ This is similar to the SVR12 rate of 90% seen in a study of chronic genotype 1 HCV monoinfected patients that received 16 to 24 weeks of sofosbuvir and ribavirin.⁶⁵ In the SWIFT-C study however, a high relapse rate of 41% (59% achieved SVR12) was seen in the seventeen PLWH with acute HCV infection (11 genotype 1a, 2 genotype 1b, 2 genotype 1 with unknown subtype, 1 genotype 2 and 1 genotype unspecified) treated with 12 weeks of sofosbuvir and ribavirin.³⁸ When comparing the two studies, patients in the study by El Sayed et al had a lower baseline median baseline HCV viral load compared to the SWIFT-C study (4.5 vs 6.4 log₁₀ IU/mL) and higher median baseline CD4 counts (545 vs 498 cells/ μ L).^{40,38} Spontaneous HCV clearance in PLWH has been shown to be significantly associated with higher CD4 counts (particularly >500 cells/ μ L) and lower baseline HCV RNA levels⁶⁶ therefore it is a possibility that patients in the study by El Sayed et al were more likely to achieve spontaneous HCV clearance regardless of the receiving antiviral treatment.

A high relapse rate was observed by Martinello and colleagues with a shortened treatment duration of 6 weeks sofosbuvir and ribavirin for acute HCV infection in PLWH.³⁹ Only 3/14 (21%) achieved the primary outcome of SVR12 in their study. Six weeks of therapy with ledipasvir/sofosbuvir in another recent study for genotypes 1a & 4 acute HCV infection in PLWH achieved an SVR 12 of 77%.⁴¹ Although these findings are encouraging, ledipasvir/sofosbuvir for 6 weeks in the treatment of genotype 1 acute HCV mono-infection achieved an even higher SVR12 of 100% in the HepNet study.⁶⁷ Additionally, in the SLAM C pilot study, just 4 weeks of ledipasvir/sofosbuvir in 14 patients with acute HCV mono-infection achieved an SVR12 rate of 100%.⁶⁸ Six weeks of sofosbuvir with ribavirin, however, only achieved an SVR rate of 60% in HCV monoinfected patients.³⁹ Therefore the type of regimen (and other baseline characteristics including pre-treatment HCV RNA levels and possibly the presence of resistance-associated variants) may be more important for treatment response rather than HIV status. Three of the studies included in table 1 used a drug regimen (sofosbuvir with ribavirin) which is no longer recommended as treatment for HCV infection.^{21,38-40} The majority (>65%) of patients in the studies of DAAs for acute HCV coinfection had genotype 1 infections;³⁸⁻⁴¹ a genotype which has demonstrated unfavourable responses to therapy with sofosbuvir and ribavirin compared to the SVR rates achieved with currently recommended newer regimens.²¹

From the data currently available, SVR rates with shortened 6-week DAA regimens in PLWH treated for acute HCV infection are far from the SVR rates that have been achieved with longer courses of DAA therapy (>90%)⁶⁹ in PLWH treated for chronic HCV infection. The incomplete HCV-driven dampening of host immune responses in the early phase of HCV infection provides a possible explanation as to why shorter courses of (antiviral response-enhancing) IFN-based therapy may be permitted in acute HCV infection compared to in chronic HCV infection. However, it is not yet clear whether a similar rationale for shortened therapy applies to IFN-free DAA regimens in view of differing mechanisms and potential drivers for viral clearance. Further studies are needed to determine the feasibility of shortened courses of DAA therapy for acute HCV infection and should also aim to identify factors that may influence the duration and/or type of therapy required by specific individuals.

Treatment responses, baseline and on-treatment predictors of achieving a sustained virologic response

Although a single nucleotide polymorphism upstream of the *IL28B* gene has shown association with spontaneous clearance of acute HCV,⁷⁰ a challenge faced by studies investigating and clinicians deciding on the treatment of acute HCV in PLWH is the identification and exclusion of individuals from receiving treatment that are likely to achieve spontaneous clearance. One approach adopted by investigators has been to exclude patients that have $\geq 1 \log_{10}$ IU/mL fluctuations in HCV viral loads and/or a level $< 4 \log_{10}$ IU/mL prior to initiating therapy.⁴⁰³⁹ Ragonnet et. al prospectively studied HCV/HIV coinfecting individuals and found that spontaneous HCV clearance frequently occurred late at a median time of 184 days after infection.⁷¹ Therefore, it remains uncertain what proportions of patients, if any, that achieved an SVR in the studies of acute HCV coinfection discussed may have spontaneously cleared their infections and whether a watch and wait policy should be adopted given that there is no current data to suggest that earlier treatment improves likelihood of achieving SVR12. Adopting a delayed approach does however risk patients not returning for treatment at a later stage with subsequent potential development of liver fibrosis and also onward HCV transmission.

In the SWIFT-C study, all 17 patients achieved undetectable HCV RNA whilst on-treatment and in the 7 (41%) that eventually relapsed, HCV RNA was only detectable after completion of therapy and occurred by week 4 post-treatment in all 7 cases.³⁸ When comparing those who achieved SVR12 to those that relapsed, there were no differences in baseline HCV RNA levels or differences in changes of HCV RNA levels between the time of diagnosis and the time of study entry. Additionally, the time to achieving undetectable HCV RNA was not predictive of SVR12. In the study by El Sayed et al where PLWH also received 12 weeks of sofosbuvir and ribavirin for acute HCV coinfection, all 12 patients had undetectable HCV RNA at the end of treatment and at 4 weeks post-completion of therapy.⁴⁰ Eleven patients (92%) achieved SVR12 and the 1 patient who did not achieve

SVR12 had detectable HCV RNA at post-treatment week 8. This patient had a genotype 1a HCV infection (baseline HCV RNA of $6.1 \log_{10}$ IU/mL) and had had a previous null response to treatment with pegIFN and ribavirin for a previous HCV infection.

Another study by Martinello and colleagues, in which PLWH received 6 weeks of sofosbuvir and ribavirin for HCV coinfection, reported that virological failure was associated with a baseline HCV RNA $>6 \log_{10}$ IU/mL ($p = 0.009$).³⁹ Their study found that undetectable HCV RNA at week 1 was associated with achieving SVR12 whereas no association was found between achieving SVR12 and HCV RNA levels at 2 or 4 weeks into treatment. Eighty six percent (12/14) had undetectable HCV RNA at the end of treatment but only 36% (5/14) and 21% (3/14) achieved SVR4 and SVR12 respectively. This study was the only one of the identified published trials of IFN-sparing DAA therapy for acute HCV infection in PLWH that included patients with genotype 3 HCV infection. Sofosbuvir with ribavirin has been shown to be suboptimal in comparison to sofosbuvir/velpatasvir and sofosbuvir/daclatasvir regimens for the treatment of genotype 3 chronic HCV infection.^{21,727374} In a study of 382 patients treated with varying DAA regimens for chronic HCV infection, 62 of whom were HIV infected, genotype 3 HCV was a negative predictor of SVR in both univariate (odds ratio 5.49, 95% confidence interval 1.9-15.7, $p = 0.002$) and multivariate analysis (odds ratio 21.6, 95% confidence interval 3.81-123, $p = 0.001$).⁴⁸ An SVR12 rate of 77% (20/26) was observed in the study by Rockstroh et al. in which PLWH received 6 weeks of ledipasvir/sofosbuvir for acute HCV infection.⁴¹ Of the 6 patients that did not achieve SVR12; three relapsed after completing treatment with detectable HCV RNA by week 4; one was re-infected with a different genotype of HCV; two were lost to follow up after completing treatment (both had undetectable HCV RNA at the end of treatment). Rockstroh and colleagues also found that baseline HCV RNA levels were associated with SVR12. Eighty-six percent (12/14) with a baseline HCV RNA $< 5.9 \log_{10}$ IU/mL achieved SVR12 compared to 67% (8/12) of those with a baseline HCV RNA of $\geq 5.9 \log_{10}$ IU/mL. The 3 patients in their study that relapsed had baseline HCV RNA levels $> 6.96 \log_{10}$ IU/mL.

These findings indicate that null response to interferon-sparing DAA regimens is uncommon however relapses tend to occur at week 4 or 8 post-treatment in those not achieving SVR12. Moreover, individuals with baseline HCV RNA levels $> 6 \log_{10}$ IU/mL may respond less well to shorter duration therapy and therefore need to be considered for longer courses of treatment (up to 12 weeks). HCV RNA levels whilst on treatment do not appear to accurately predict outcome although rapid treatment responses with undetectable HCV RNA levels within the first week of treatment may be a positive indicator for achieving SVR12. Undetectable HCV RNA at the end of treatment was not found to be predictive of SVR12. Table 4 describes the SVR rates achieved in identified clinical trials of the treatment of acute HCV infection in patients coinfecting with HIV and in HCV mono-infected patients (including combined SVR rates from various studies).

Adverse effects of direct-acting therapy

DAA, although known to have their own unique adverse effects, are generally well and far better tolerated than earlier IFN-based therapy, even in those with cirrhosis and other patient groups such as transplant recipients.⁷⁵⁷⁶ In PLWH, careful selection of DAA regimens (and modification of ART regimens where necessary) to avoid drug-drug interactions is important but it is also crucial that DAA therapy exerts no direct adverse effects on HIV disease. In a recent study of IFN-sparing DAA therapy for the treatment of chronic HCV infection there were no observed differences with regards to adverse effects or treatment discontinuations between HCV monoinfected and HCV/HIV coinfecting patients.⁴⁸ DAA therapy was found to be safe (4.5% serious adverse events; 2.61% treatment discontinuations) and effective (SVR12 95.5%) overall in both study groups, even with 67% (256/382) of their study patients being cirrhotic.

Rockstroh and colleagues found that with 6 weeks of ledipasvir/sofosbuvir for acute HCV infection in PLWH, 22/26 (85%) experienced at least one adverse event with fatigue, nasopharyngitis and headache being most commonly reported symptoms.⁴¹ No patients had their treatment temporarily or permanently discontinued due to adverse events. No patients experienced HIV rebound.

In the study by El Sayed et al with 12 weeks of sofosbuvir and ribavirin for acute HCV infection, fatigue and irritability were frequently experienced symptoms,⁴⁰ which has previously been described in PLWH receiving sofosbuvir and ribavirin for chronic HCV coinfection⁷⁷. No patients developed significant anaemia (Hb < 10g/dL) and no-one required dose reductions of ribavirin or discontinuation of treatment. No HIV-related events occurred. Martinello and colleagues also reported that with 6 weeks of sofosbuvir and ribavirin, no treatment discontinuations due to adverse events occurred and no dose reductions of ribavirin were required.³⁹ They reported no loss of HIV virological control and no decline in the median CD4 count at the end of treatment. In the SWIFT-C study for the treatment of acute HCV infection, no serious adverse events were reported in any of the HIV-1 infected patients that received sofosbuvir and ribavirin and there were no treatment discontinuations due to adverse events.³⁸ Absolute CD4 count decreased by a mean of 50 cells/ μ L from baseline by week 12 of treatment but by 24 weeks post-treatment mean CD4 counts were 62 cells/ μ L above baseline. All 17 patients maintained an HIV-1 RNA load <50 copies/ml whilst receiving DAA therapy.

Based on the currently available data, sofosbuvir-containing DAA regimens are relatively well tolerated in PLWH. Mild to moderate adverse effects are not infrequent but do not appear to impact upon adherence or completion of therapy. Serious adverse events were rare in the studies conducted and in most, if not all cases, these were deemed unlikely to have been related to the study drug administration. Importantly, there is no evidence to suggest that treatment with DAAs has any sustained effects on CD4 counts or HIV dynamics within the host.

For the 7 patients that relapsed in the SWIFT-C study, the NS5B region of the HCV genomes were amplified and sequenced on pre- and post-treatment samples. None of the relapsers were found to possess the S282T mutation at any time point, which is the primary mutation associated with resistance to HCV NS5B polymerase inhibitors such as sofosbuvir.⁷⁸ In contrast, deep sequencing of post-treatment HCV genomes from PLWH unsuccessfully treated for acute HCV infection with the ‘first-generation’ NS3 protease inhibitor boceprevir in combination with IFN and ribavirin found that NS3 mutations (T54A and R155K) emerged.⁷⁹ The NS3/4A protease inhibitors boceprevir and telaprevir, however, are known to have a low genetic barrier to resistance and have been shown to select for HCV resistance-associated variants.⁸⁰

In the study by Rockstroh et al in which patients received 6 weeks of sofosbuvir in combination with the NS5A inhibitor ledipasvir for acute HCV (genotype 1 or 4) infection, two of the 3 patients who experienced virological relapse were found to possess HCV NS5A resistance-associated mutations at baseline that persisted and therefore were also detected at relapse.⁴¹ A study of ledipasvir/sofosbuvir for patients with genotype 1 chronic HCV infection demonstrated that a significant reduction in SVR rate was seen amongst treatment-naïve patients with baseline NS5A resistance-associated variants that received 8 weeks of therapy, and that the effects of these mutations could be overcome by extending the duration of therapy to 12 or 24 weeks or with the addition of ribavirin.⁸¹ Additionally, Wyles et al found that the majority of HCV NS5A resistance-associated variants persisted for long periods of time (>96 weeks) in subjects that had failed treatment with regimens containing an NS5A inhibitor without sofosbuvir, suggesting that even in the absence of drug selection pressure these variants can maintain high levels of fitness.⁸²

The presence of baseline resistance-associated variants could therefore impact upon outcome following treatment for acute HCV infection depending on both the type and the duration of the regimen selected, and may also affect responses to subsequent retreatment in cases of virological relapse. Further work is also needed to elucidate whether short courses of interferon-sparing ‘second-generation’ DAA therapy in PLWH can exert significant mutational effects on HCV in those that fail treatment and the longer term clinical impact of such mutations if they do arise.

Other considerations with direct-acting antiviral therapy: coinfection with hepatitis B

Despite the availability of the hepatitis B virus (HBV) vaccination, approximately 10% of the of PLWH also have a chronic HBV coinfection⁸³ with risk factors for HCV acquisition being shared with those for HBV. In a study of DAAs in the treatment of chronic HCV infection, virological reactivation of HBV (re-appearance of detectable HBV DNA in blood at low levels) was observed in 57.1% of HIV-uninfected patients who had a concurrent chronic HBV infection.⁸⁴ Clinical reactivation of HBV in their study responded to the administration of entecavir. There were no instances of HBV reactivation in their HBsAg

negative/HBcAb positive study patients. A recent large study of 263 HBsAg negative/HBcAb positive patients (including 2 HIV-infected patients receiving tenofovir-containing ART and 8 post-liver transplant patients on immunosuppressants) treated for HCV infection with DAAs found that HBV reactivation occurred in none of the 263 patients.⁸⁵ The investigators did however find in their small number of HBsAg positive patients that 56% (5/9) experienced HBV reactivation during or after DAA therapy.

HBV reactivation in HBV/HCV coinfecting patients following HCV treatment initiation has not been limited only to recent DAA therapy, however, a recent meta-analysis found that HBV reactivation occurred earlier and was of greater severity in patients treated with DAAs compared to those that received IFN-based therapy for chronic HCV infection.⁸⁶ Some, but not all, studies suggest that the HCV core and NS5A proteins inhibit HBV replication⁸⁷⁻⁸⁹ and thus whether the rapid suppression of HCV that occurs with DAAs⁹⁰ then permits heightened replication of HBV in HBV/HCV coinfecting patients requires further investigation. We also require a more in-depth understanding of the immunological mechanisms underlying the occurrence of HBV reactivation during and after successful DAA therapy for HCV infection as this may help to determine which groups of patients are at particular risk of HBV reactivation and that therefore require closer and/or longer periods of monitoring.

HBV reactivation with DAA therapy may be less of a concern in PLWH receiving tenofovir-containing ART, and the EASL hepatitis B guidelines⁹¹ recommend that HBV/HIV coinfecting individuals are treated with tenofovir as part of their ART regimen unless there are contraindications.

Conclusions

Increasing rates of recreational drug use amongst MSM, more widespread and more frequent testing for HCV in PLWH along with widening access to DAAs will identify more patients who could potentially be treated with DAAs in the acute phase of their HCV infection. This will also provide further information regarding the effectiveness, tolerability and long-term outcomes of using DAAs in this setting. Furthermore, with newer, shorter duration IFN-sparing DAA regimens there is a higher degree of willingness amongst HCV/HIV coinfecting people who use drugs to receive treatment for their HCV infection (>70% willingness in a recent population survey).⁹² The data currently available demonstrates that these drugs can be effective in treatment of acute HCV infection but the optimal duration of therapy is yet to be determined and may need to be individualised based on factors such as baseline HCV RNA level. It is important to check for specific DAA-ART interactions prior to starting therapy. DAA regimens are generally well tolerated with no significant HIV-related complications observed.

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References:

1. Birger RB, Le T, Kouyos RD, Grenfell B, Hallett TB, Khudyakov YE. The impact of HCV therapy in a high HIV-HCV prevalence population: A modeling study on people who inject drugs in Ho Chi Minh City, Vietnam. *PLoS One*. 2017;12:e0177195.
2. Taylor LE, Swan T, Mayer KH. HIV coinfection with hepatitis C virus: evolving epidemiology and treatment paradigms. *Clin Infect Dis*. 2012;55 Suppl 1. doi:10.1093/cid/cis367.
3. Quan VM, Go VF, Nam L Van, et al. Risks for HIV, HBV, and HCV infections among male injection drug users in northern Vietnam: a case-control study. *AIDS Care*. 2009;21(1):7-16. doi:10.1080/09540120802017610.
4. Garten RJ, Lai S, Zhang J, et al. Rapid transmission of hepatitis C virus among young injecting heroin users in Southern China. *Int J Epidemiol*. 2004;33(1):182-188. doi:10.1093/ije/dyh019.
5. M. D, D. B, S. B, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS*. 2007;21(8):983-991.
<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2007218397>.
6. Hoornenborg E, Achterbergh RCA, Schim van der Loeff MF, et al. MSM starting preexposure prophylaxis are at risk of hepatitis C virus infection. *AIDS*. 2017;31(11):1603-1610. doi:10.1097/QAD.0000000000001522.
7. Elliot ER, Singh S, Tyebally S, Gedela K, Nelson M. Recreational drug use and chemsex among HIV-infected in-patients: A unique screening opportunity. *HIV Medicine*. 2017.
8. Tohme RA, Holmberg SD. Transmission of Hepatitis C Virus Infection Through Tattooing and Piercing: A Critical Review. *Clin Infect Dis*. 2012;54(8):1167-1178. doi:10.1093/cid/cir991.
9. Amodio E, Di Benedetto MA, Gennaro L, Maida CM, Romano N. Knowledge, attitudes and risk of HIV, HBV and HCV infections in hairdressers of Palermo city (South Italy). *Eur J Public Health*. 2010;20(4):433-437. doi:10.1093/eurpub/ckp178.
10. Shores NJ, Maida I, Soriano V, N????ez M. Sexual transmission is associated with spontaneous HCV clearance in HIV-infected patients. *J Hepatol*. 2008;49(3):323-328. doi:10.1016/j.jhep.2008.04.010.
11. Thomson EC, Fleming VM, Main J, et al. Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. *Gut*. 2011;60(6):837-845. doi:10.1136/gut.2010.217166.
12. Panel IC. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. *AIDS*. 2011;25(4):399-409. doi:10.1097/QAD.0b013e328343443b.
13. Glässner A, Eisenhardt M, Kokordelis P, et al. Impaired CD4+ T cell stimulation of NK cell anti-fibrotic activity may contribute to accelerated liver fibrosis progression in HIV/HCV patients. *J Hepatol*. 2013;59(3):427-433. doi:10.1016/j.jhep.2013.04.029.
14. Soriano V, Vispo E, Fernandez-Montero JV, Labarga P, Barreiro P. Update on HIV/HCV coinfection. *Curr HIV/AIDS Rep*. 2013;10(3):226-234. doi:10.1007/s11904-013-0169-5.
15. Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. *Lancet*. 2011;377(9772):1198-1209. doi:10.1016/S0140-6736(10)62001-6.
16. Miller MF, Haley C, Koziel MJ, Rowley CF. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. *Clin Infect Dis*. 2005;41(5):713-720. doi:10.1086/432618.
17. Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med*. 2004;351(5):451-459. doi:10.1056/NEJMoa032653.

18. Dore GJ, Hellard M, Matthews G V., et al. Effective Treatment of Injecting Drug Users With Recently Acquired Hepatitis C Virus Infection. *Gastroenterology*. 2010;138(1). doi:10.1053/j.gastro.2009.09.019.
19. Taylor LE, DeLong AK, Maynard MA, et al. Acute hepatitis C virus in an HIV clinic: a screening strategy, risk factors, and perception of risk. *AIDS Patient Care STDS*. 2011;25(10):571-577. doi:10.1089/apc.2011.0106.
20. D'Ambrosio R, Degasperis E, Colombo M, Aghemo A. Direct-acting antivirals: the endgame for hepatitis C? *Curr Opin Virol*. 2017;24:31-37. doi:10.1016/j.coviro.2017.03.017.
21. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol*. 2016;in press.
22. Montes ML, Oliveira A, Ahumada A, et al. Similar effectiveness of direct-acting antiviral against hepatitis C virus in patients with and without HIV infection. *AIDS*. 2017;1. doi:10.1097/QAD.0000000000001465.
23. Chung RT, Davis GL, Jensen DM, et al. Hepatitis C guidance: AASLD-IDS recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62(3):932-954. doi:10.1002/hep.27950.
24. Diepolder HM. Interferon- α for hepatitis C: antiviral or immunotherapy? *J Hepatol*. 2004;40:1030-1031.
25. Ulsenheimer A, Gerlach JT, Gruener NH, et al. Detection of functionally altered hepatitis C virus-specific CD4 T cells in acute and chronic hepatitis C. *Hepatology*. 2003;37(5):1189-1198. doi:10.1053/jhep.2003.50194.
26. Holz L, Rehermann B. T cell responses in hepatitis C virus infection: Historical overview and goals for future research. *Antiviral Res*. 2015;114:96-105. doi:10.1016/j.antiviral.2014.11.009.
27. Duong FHT, Filipowicz M, Tripodi M, La Monica N, Heim MH. Hepatitis C virus inhibits interferon signaling through up-regulation of protein phosphatase 2A. *Gastroenterology*. 2004;126(1):263-277. doi:10.1053/j.gastro.2003.10.076.
28. Gale Michael J J, Korth MJ, Tang NM, et al. Evidence That Hepatitis C Virus Resistance to Interferon Is Mediated through Repression of the PKR Protein Kinase by the Nonstructural 5A Protein. *Virology*. 1997;230(2):217-227. doi:10.1006/viro.1997.8493.
29. Boesecke C, Ingiliz P, Reiberger T, et al. Dual treatment of acute HCV infection in HIV co-infection: influence of HCV genotype upon treatment outcome. *Infection*. 2015. doi:10.1007/s15010-015-0856-9.
30. Matthews G V, Hellard M, Haber P, et al. Characteristics and treatment outcomes among HIV-infected individuals in the Australian Trial in Acute Hepatitis C. *Clin Infect Dis*. 2009;48(5):650-658. doi:10.1086/596770 [pii].
31. Hulleger SJ, Claassen MAA, Van Den Berk GEL, et al. Boceprevir, peginterferon and ribavirin for acute hepatitis C in HIV infected patients. *J Hepatol*. 2016;64(4):807-812. doi:10.1016/j.jhep.2015.12.004.
32. Boesecke C, Jagjit Singh GK, Scholten SH-A, et al. Telaprevir-containing triple therapy in acute HCV coinfection: The CHAT Study. *Antivir Ther*. 2017. doi:10.3851/IMP3143.
33. Okoye AA, Picker LJ. CD4+ T-Cell Depletion In Hiv Infection: Mechanisms Of Immunological Failure. *Immunol Rev*. 2013;254(1):54-64. doi:10.1111/imr.12066.
34. Mussini C, Lorenzini P, Cozzi-Lepri A, et al. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: An observational cohort study. *Lancet HIV*. 2015;2(3):98-106. doi:10.1016/S2352-3018(15)00006-5.
35. Thornhill J, Inshaw J, Kaleebu P, et al. Brief Report: Enhanced Normalization of CD4/CD8 Ratio With Earlier Antiretroviral Therapy at Primary HIV Infection. *J Acquir Immune Defic Syndr*. 2016;73(1):69-73. doi:10.1097/QAI.0000000000001013.
36. Basso M, Parisi SG, Mengoli C, et al. Sustained Virological Response and Baseline Predictors in HIV-HCV Coinfected Patients Retreated with Pegylated Interferon and Ribavirin after Failing a Previous Interferon-Based Therapy: Systematic Review and Meta-Analysis. *HIV Clin Trials*. 2013;14(4):127-139. doi:10.1310/hct1404-127.

37. Churchill D, Waters L, Ahmed N, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. *HIV Med.* 2016;17(S4):s2-s104.
38. Naggie S, Marks KM, Hughes M, et al. Sofosbuvir Plus Ribavirin Without Interferon for Treatment of Acute Hepatitis C Virus Infection in HIV-1–Infected Individuals: SWIFT-C. *Clin Infect Dis.* 2017;64:1035-1042.
39. Martinello M, Gane E, Hellard M, et al. Sofosbuvir and ribavirin for 6 weeks is not effective among people with recent hepatitis C virus infection: The DARE-C II study. *Hepatology.* 2016;64(6):1911-1921. doi:10.1002/hep.28844.
40. El Sayed A, Barbati ZR, Turner SS, et al. Sofosbuvir in the treatment of early HCV infection in HIV-infected men. *HIV Clin Trials.* 2017;18:60-66.
41. Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir–sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. *Lancet Gastroenterol Hepatol.* 2017;2:347-353. doi:10.1016/S2468-1253(17)30003-1.
42. Feld JJ, Hoofnagle JH. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature.* 2005;436(7053):967-972. doi:10.1038/nature04082.
43. Feld JJ, Jacobson IM, Sulkowski MS, Poordad F, Tatch F, Pawlotsky JM. Ribavirin revisited in the era of direct-acting antiviral therapy for hepatitis C virus infection. *Liver Int.* 2017;37(1):5-18. doi:10.1111/liv.13212.
44. Clark V, Nelson DR. The role of ribavirin in direct acting antiviral drug regimens for chronic hepatitis C. *Liver Int.* 2012;32 Suppl 1:103-107. doi:10.1111/j.1478-3231.2011.02711.x.
45. Hézode C, Bronowicki JP. Ideal oral combinations to eradicate HCV: The role of ribavirin. *J Hepatol.* 2016;64(1):215-225. doi:10.1016/j.jhep.2015.09.009.
46. Webster DP, Klenerman P, Dusheiko GM. Lancet Seminar – Hepatitis C. *Lancet (London, England).* 2015;385(9973):1124-1135. doi:10.1016/S0140-6736(14)62401-6.
47. Piroth L, Wittkop L, Lacombe K, et al. 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. doi:10.1016/j.jhep.2017.02.012.
48. Bruno G, Saracino A, Scudeller L, et al. HCV-infected and HIV/HCV co-infected individuals treated with direct-acting antivirals: to what extent do they differ? *Int J Infect Dis.* 2017. <http://dx.doi.org/10.1016/j.ijid.2017.07.001>.
49. Rodriguez-Torres M, Gaggar A, Shen G, et al. Sofosbuvir for Chronic Hepatitis C Virus Infection Genotype 1-4 in Patients Coinfected With HIV. *J Acquir Immune Defic Syndr.* 2015;68(5):543-549. doi:10.1097/QAI.0000000000000516.
50. Liverpool HIV interactions. www.hiv-druginteractions.org. Accessed June 14, 2017.
51. Saeed S, Strumpf EC, Walmsley SL, et al. How generalizable are the results from trials of direct antiviral agents to people coinfecting with HIV/HCV in the real world? *Clin Infect Dis.* 2016;62(7):919-926. doi:10.1093/cid/civ1222.
52. Deterding K, Grüner N, Buggisch P, et al. Delayed versus immediate treatment for patients with acute hepatitis C: A randomised controlled non-inferiority trial. *Lancet Infect Dis.* 2013;13(6):497-506. doi:10.1016/S1473-3099(13)70059-8.
53. Boesecke C, Vogel M. HIV and hepatitis C co-infection: acute HCV therapy. *Curr Opin HIV AIDS.* 2011;6(6):459-464. doi:10.1097/COH.0b013e32834b87de.
54. Boesecke C, van Assen S, Stellbrink HJ, et al. Peginterferon-alfa mono-therapy in the treatment of acute hepatitis C in HIV-infection. *J Viral Hepat.* 2014;21(11):780-785. doi:10.1111/jvh.12272.
55. Langhans B, Nischalke HD, Kr??mer B, et al. Increased peripheral CD4+ regulatory T cells persist after successful direct-acting antiviral treatment of chronic hepatitis C. *J Hepatol.* 2017;66(5):888-896. doi:10.1016/j.jhep.2016.12.019.

56. Tumino N, Casetti R, Fabbri G, et al. In HIV/HCV co-infected patients T regulatory and myeloid-derived suppressor cells persist after successful treatment with directly acting antivirals. *J Hepatol.* 2017;67(2):422-424. doi:10.1016/j.jhep.2017.03.036.
57. Abdel-Hakeem MS, Bédard N, Badr G, et al. Comparison of immune restoration in early versus late alpha interferon therapy against hepatitis C virus. *J Virol.* 2010;84(19):10429-10435. doi:10.1128/JVI.01094-10.
58. Steining K, Boyd A, Dupke S, et al. HIV-positive men who have sex with men are at high risk of development of significant liver fibrosis after an episode of acute hepatitis C. *J Viral Hepat.* 2017;Apr 25. [Epub ahead of print].
59. Miller WC, Rosenberg NE, Rutstein SE, Powers K a. Role of acute and early HIV infection in the sexual transmission of HIV. *Curr Opin HIV AIDS.* 2010;5:277-282. doi:10.1097/COH.0b013e32833a0d3a.
60. Brenner BG, Roger M, Routy J, et al. High Rates of Forward Transmission Events after Acute/Early HIV-1 Infection. *J Infect Dis.* 2007;195(7):951-959. doi:10.1086/512088.
61. Martin NK, Thornton A, Hickman M, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic among Men Who Have Sex with Men in the United Kingdom? Epidemiological and Modeling Insights. *Clin Infect Dis.* 2016;62(9):1072-1080. doi:10.1093/cid/ciw075.
62. Boerekamps A, van den Berk G, Lauw F, Leyten EMS, Arends JE. SUBSTANTIAL DECLINE IN ACUTE HCV INFECTIONS AMONG DUTCH HIV+MSM AFTER DAA ROLL OUT. In: *CROI 2017.* ; 2017.
63. Wiegand J, Buggisch P, Boecher W, et al. Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: The HEP-NET acute-HCV-II study. *Hepatology.* 2006;43(2):250-256. doi:10.1002/hep.21043.
64. Fierer DS, Dieterich DT, Mullen MP, et al. Telaprevir in the Treatment of Acute Hepatitis C Virus Infection in HIV-Infected Men. *Clin Infect Dis.* 2013;7. doi:10.1093/cid/cit799.
65. Shah S, Chowdhury A, Mehta R, et al. Sofosbuvir plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 or 3 infection in India. *J Viral Hepat.* 2017;24:371-379.
66. Gilleece YC, Browne RE, Asboe D, et al. Transmission of hepatitis C virus among HIV-positive homosexual men and response to a 24-week course of pegylated interferon and ribavirin. *J Acquir Immune Defic Syndr.* 2005;40(1):41-46. doi:10.1097/01.qai.0000174930.64145.a9.
67. Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 mono-infection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. *Lancet Infect Dis.* 2017;17(2):215-222. doi:10.1016/S1473-3099(16)30408-X.
68. Basu PP, Shah NJ, Aloysius MM, Brown Jr. RS. Sofosbuvir and ledipasvir versus sofosbuvir and simeprevir for acute hepatitis C: A RCT:SLAM C study. *Hepatol Int.* 2016;10(1):S14-S15. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L72199935%5Cnhttp://dx.doi.org/10.1007/s12072-016-9707-8>.
69. 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. doi:10.1056/NEJMoa1501315.
70. Tillmann HL, Thompson AJ, Patel K, et al. A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. *Gastroenterology.* 2010;139(5). doi:10.1053/j.gastro.2010.07.005.
71. Ragonnet R, Deuffic-Burban S, Boesecke C, et al. Estimating the Time to Diagnosis and the Chance of Spontaneous Clearance During Acute Hepatitis C in Human Immunodeficiency Virus-Infected Individuals. *Open Forum Infect Dis.* 2017;4:ofw235.
72. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. *N Engl J Med.* 2014;140504060027001. doi:10.1056/NEJMoa1316145.

73. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *N Engl J Med*. 2015;373(27):2599-2607. doi:10.1056/NEJMoa1512610.
74. Luetkemeyer AF, McDonald C, Ramgopal M, Noviello S, Bhore R, Ackerman P. 12 Weeks of Daclatasvir in Combination with Sofosbuvir for HIV-HCV Coinfection (ALLY-2 Study): Efficacy and Safety by HIV Combination Antiretroviral Regimens. *Clin Infect Dis*. 2016;62(12):1489-1496. doi:10.1093/cid/ciw163.
75. Banerjee D, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. *Aliment Pharmacol Ther*. 2016:1-23. doi:10.1111/apt.13514.
76. Asselah T, Bourgeois S, Pianko S, et al. Sofosbuvir/Velpatasvir in Patients With Hepatitis C Virus Genotypes 1-6 and Compensated Cirrhosis or Advanced Fibrosis. *Liver Int*. July 2017. doi:10.1111/liv.13534.
77. Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV Coinfection. *JAMA*. 2014;312(4):353-361. doi:10.1001/jama.2014.7734.
78. Franco S, Casadellà M, Noguera-Julian M, et al. No detection of the NS5B S282T mutation in treatment-naïve genotype 1 HCV/HIV-1 coinfecting patients using deep sequencing. *J Clin Virol*. 2013;58(4):726-729. doi:10.1016/j.jcv.2013.09.022.
79. Christiansen MT, Hullegie SJ, Schutten M, et al. Use of whole genome sequencing in the Dutch Acute HCV in HIV study: focus on transmitted antiviral resistance. *Clin Microbiol Infect*. 2017;23(2):123.e1-123.e4. doi:10.1016/j.cmi.2016.09.018.
80. Pawlotsky JM. Treatment failure and resistance with direct-acting antiviral drugs against hepatitis C virus. *Hepatology*. 2011;53(5):1742-1751. doi:10.1002/hep.24262.
81. Sarrazin C, Dvory-Sobol H, Svarovskaia ES, et al. Prevalence of Resistance-Associated Substitutions in HCV NS5A, NS5B, or NS3 and Outcomes of Treatment With Ledipasvir and Sofosbuvir. *Gastroenterology*. 2016;151(3):501-512.e1. doi:10.1053/j.gastro.2016.06.002.
82. Wyles D, Mangia A, Cheng W, et al. Long-term persistence of HCV NS5A resistance-associated substitutions after treatment with the HCV NS5A inhibitor, ledipasvir, without sofosbuvir. *Antivir Ther*. 2017. doi:10.3851/IMP3181.
83. Kourtis AP, Bulterys M, Hu DJ, Jamieson DJ. HIV-HBV coinfection--a global challenge. *N Engl J Med*. 2012;366(19):1749-1752. doi:10.1056/NEJMp1201796.
84. Yeh M-L, Huang C-F, Hsieh M-H, et al. Reactivation of hepatitis B in patients of chronic hepatitis C with hepatitis B virus infection treated with direct acting antivirals. *J Gastroenterol Hepatol*. 2017. doi:10.1111/jgh.13771.
85. Mücke VT, Mücke MM, Peiffer K-H, et al. No evidence of hepatitis B virus reactivation in patients with resolved infection treated with direct-acting antivirals for hepatitis C in a large real-world cohort. *Aliment Pharmacol Ther*. 2017;46(4):432-439. doi:10.1111/apt.14177.
86. Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfecting patients treated with antiviral agents: A systematic review and meta-analysis. *Hepatology*. 2017;66(1):13-26. doi:10.1002/hep.29109.
87. Jamma S, Hussain G, Lau DTY. Current concepts of HBV/HCV coinfection: Coexistence, but not necessarily in harmony. *Curr Hepat Rep*. 2010;9(4):260-269. doi:10.1007/s11901-010-0060-4.
88. Schüttler CG, Fiedler N, Schmidt K, Repp R, Gerlich WH, Schaefer S. Suppression of hepatitis B virus enhancer 1 and 2 by hepatitis C virus core protein. *J Hepatol*. 2002;37(6):855-862. doi:10.1016/S0168-8278(02)00296-9.
89. Chen S-Y, Kao C-F, Chen C-M, et al. Mechanisms for inhibition of hepatitis B virus gene expression and replication by hepatitis C virus core protein. *J Biol Chem*. 2003;278(1):591-607. doi:10.1074/jbc.M204241200.
90. Götte M, Feld JJ. Direct-acting antiviral agents for hepatitis C: structural and mechanistic insights. *Nat Publ Gr*. 2016;13(6):338-351. doi:10.1038/nrgastro.2016.60.

91. EASL. EASL Clinical Practice Guidelines : Management of chronic hepatitis B virus infection. *J Hepatol.* 2012;57(1):167-185. doi:10.1016/j.jhep.2012.02.010.
92. Socías M, Ti L, Dong H, et al. High prevalence of willingness to use direct-acting antiviral-based regimens for hepatitis C virus (HCV) infection among HIV/HCV coinfecting people who use drugs. *HIV Med.* 2017. doi:10.1111/hiv.12501.

ACCEPTED MANUSCRIPT

Table 1. Published studies of directly acting antiviral therapy without interferon for the treatment of acute hepatitis C virus infection in HIV-infected individuals

Abbreviations: sustained virologic response (SVR), antiretroviral therapy (ART)

ACCEPTED MANUSCRIPT

Study location	Year of publication	Number treated	Genotypes treated	Estimated duration of acute HCV infection	Drugs used	Duration of treatment (weeks)	Baseline HCV RNA in log ₁₀ IU/mL	ART status, HIV-1 RNA level in copies/ml & CD4 count in cells/μL	ART which excluded patients from the study	SVR 12 or 24 [n (%)]	Treatment discontinuations, dose modifications and HIV-related events
Germ any& UK ⁴¹	2017	26	1a, 4a,4c & 4d	<24 weeks prior to study entry	ledipasvir/sofosbuvir 90/400 mg daily	6	Median 5.6	25/26 on ART 26/26 on ART had baseline HIV-1 RNA <200 Median CD4 count 675 (none had a CD4 count <200)	No ART exclusions specified	20/26 (77%) achieved SVR12	No premature treatment discontinuations No HIV-related events
USA ³⁸	2017	17	1a,1b & 2	<24 weeks prior to study entry Median 140 (range 91-172) days from first laboratory diagnosis of acute HCV infection to study entry	sofosbuvir 400mg/day + ribavirin (1200mg/day if body weight ≥75mg; 1000mg/day if <75mg)	12	Median 6.4	16/17 on ART; 15/16 on ART had baseline HIV-1 RNA <50, 1/16 on ART had missing baseline result Median CD4 count 498	didanosine , zidovudine , stavudine, ritonavir-boosted tipranavir	10/17 (59%) achieved SVR12	No dose reductions were required No premature treatment discontinuations No HIV-related events
USA ⁴⁰	2017	12	1a & 1b	Time from laboratory diagnosis to treatment ranged from 1 month to 9 months	sofosbuvir 400mg/day + ribavirin (1200mg/day if body weight ≥75mg; 1000mg/day if <75mg)	12	Median 4.5	10/12 on ART, 8/12 had baseline HIV-1 RNA <50 copies/ml Median CD4 count 545 (none had a CD4 count <200)	tipranavir	11/12 (92%) achieved SVR12	No dose reductions were required No premature treatment discontinuations No HIV-related events

Australia and New Zealand ³⁹	2016	19 in total in the study but 14 co-infected with HIV	1a, 2b, 3(untyped) & 3a	Median estimated duration of infection at baseline was 37 (range 12-55) weeks	sofosbuvir 400mg/day + ribavirin (1200mg/day if body weight ≥ 75 mg; 1000mg/day if < 75 mg)	6	Median 5.4	12/14 on ART 11/12 on ART had baseline HIV-1 RNA < 50 Median CD4 count 598 (none had a CD4 count < 200)	didanosine , zidovudine , ritonavir-boosted tipranavir	3/14 (21%) achieved SVR12	One patient failed to complete the treatment course No HIV-related events
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Table 2. Unpublished trials of directly acting antiviral therapy without interferon for the treatment of acute hepatitis C virus infection in HIV-infected individuals

Study location(s) (clinical trials.gov or study identifier)	Phase of study	Estimated number of patients to be treated	Genotypes included	Drugs to be/being used	Treatment duration (weeks)	ART status, HIV-1 RNA level in copies/ml & CD 4 count in cells/ μ L	ART which exclude patients from the study	Estimated study completion date
Australia, New Zealand, United Kingdom (NCT02634008)	3	90	1-6	Paritaprevir/ritonavir/ombitasvir + dasabuvir +/- ribavirin glecaprevir/pibrentasvir	4, 6 & 8	If on ART for then baseline HIV-1 RNA must below the limit of detection and CD4 count must be >200	Not specified	December 2022
Global (NCT02625909)	3	250	1-6	Sofosbuvir/velpatasvir	6 & 12	If on ART for then baseline HIV-1 RNA must below the limit of detection and CD4 count must be >200	Efavirenz, didanosine, zidovudine, tipranavir	August 2019
France (NCT02886624)	2	50	1 & 4	grazoprevir/elbasvir	8	Without HIV treatment or with an authorized stable HIV treatment for at least two weeks	Not specified	April 2019
Holland, Belgium (NCT02600325)	3	80	1 & 4	grazoprevir/elbasvir	8	If on ART for 6 months then baseline HIV-1 RNA must be <400, if not on ART CD4	PIs, NNRTIs	December 2017

						count must be >500		
USA, Puerto Rico(N CT0212 8217)	1	44	1 & 4	ledipasvir/sof osbuvir	8	If on ART then baseline HIV-1 RNA must be <50, if not on ART CD4 count must be >500	didanosine, stavudine, ritonavir-boosted tipranavir	May 2017

Abbreviations: sustained virologic response (SVR), antiretroviral therapy (ART), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI)

Table 3. Potential interactions between hepatitis C virus directly acting antivirals and HIV antiretroviral drugs

		Sofosbuvir	Velpatasvir/ Sofosbuvir	Ledipasvir/ Sofosbuvir	3D	Daclatasvir	Simeprevir	Grazoprevir/ Elbasvir	Glecaprevir/ Pibrentasavir	Sofosbuvir/ Velpatasvir/ Voxilaprevir
NRTIs	Tenofovir	✓	○	○	✓	✓	✓	✓	✓	○
	Lamivudine	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Emtricitabine	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Abacavir	✓	✓	✓	✓	✓	✓	✓	✓	✓
NNRTIs	Efavirenz	✓	✗	○	✗	○	✗	✗	✗	✗
	Nevirapine	✓	✗	✓	✗	○	✗	✗	✗	✗
	Etravirine	✓	✗	✓	✗	○	✗	✗	✗	✗
	Rilpivirine	✓	✓	✓	○	✓	✓	✓	✓	✓
	Rilpivirine/emtricitabine/tenofovir alafenamide	✓	✓	✓	○	✓	✓	✓	✓	✓
PIs	Atazanavir (including ritonavir- and cobicistat-boosted formulations)	✓	✓	✓	○ (✗ with cobicistat)	○	✗	✗	✓	✗
	Darunavir (including ritonavir- and cobicistat-boosted formulations)	✓	✓	✓	○ (✗ with cobicistat)	○	✗	✗	✓	○
	Ritonavir-boosted lopinavir	✓	✓	✓	✗	✓	✗	✗	✓	✗
INSTIs/ Entry Inhibitors	Dolutegravir	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	✓	○	○	✗	○	✗	✗	✓	○
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	✓	✓	✓	✗	○	✗	✗	✓	✓
	Raltegravir	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Maraviroc	✓	✓	✓	○	✓	✓	✓	✓	✓

Abbreviations: nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), integrase inhibitor (INSTI), ombitasvir/dasabuvir/paritaprevir + low-dose ritonavir (3D)

Key: ✓ no significant drug interactions expected; ○ caution in view of potential drug interactions; ✗ co-administration is not recommended

This table is adapted and updated from the EASL hepatitis C management 2016 guidelines and drug-drug interactions are primarily based on information from the University of Liverpool HIV drug interactions website <http://www.hiv-druginteractions.org/>, which should be checked prior to initiating directly acting antiviral therapy in all patients taking HIV antiretroviral therapy and/or other drugs including those for recreational use

Table 4. Sustained virologic response rates and rates of grade 3/4 adverse events in clinical trials of direct-acting antiviral therapy for acute hepatitis C virus infection (including HIV-infected individuals and HCV monoinfected individuals)

Duration of HCV antiviral therapy	HCV antiviral regimen [HCV genotypes this regimen is currently recommended for by EASL]	HCV/HIV-1 infected individuals			HCV monoinfected individuals		
		SVR rates for each particular genotype	Overall SVR rate for each study	Number of study participants experiencing grade 3 or 4 adverse events	SVR rates for each particular genotype (G)	Overall SVR rate for each study	Number of study participants experiencing grade 3 or 4 adverse events
4 weeks	ledipasvir/sofosbuvir [1, 4, 5 & 6]	-	-	-	G1: 93% (13/14) ⁶⁸	93% (13/14) ⁶⁸	0% (0/14) ⁶⁸
6 weeks	ledipasvir/sofosbuvir [1, 4, 5 & 6]	G1: 79% (15/19) ⁴¹ G4: 71% (5/7) ⁴¹	77% (20/26) ⁴¹	8% (2/26) ⁴¹	G1: 100% (20/20) ⁶⁷	100% (20/20) ⁶⁷	5% (1/20) ⁶⁷
	sofosbuvir + ribavirin [none]	G1-3*: 21% (3/14) ³⁹	21% (3/14) ³⁹	Not available	G1-3*: 60% (3/5) ³⁹	60% (3/5) ³⁹	Not available
8 weeks	sofosbuvir + simeprevir [4]	-	-	-	G1: 93% (14/15) ⁶⁸	93% (14/15) ⁶⁸	0% (0/15) ⁶⁸
12 weeks	Sofosbuvir + ribavirin [none]	G1: 53% (8/15) ³⁸ G2: 100% (1/1) ³⁸ Not typable: 100% (1/1) ³⁸	59% (10/17) ³⁸	0% (0/17) ³⁸	-	-	-
		G1: 92% (11/12) ⁴⁰	92% (11/12) ⁴⁰	0% (0/12) ⁴⁰	-	-	-
Combined rates from studies of all types and duration of regimen	-	G1: 74% (34/46) G2: 100% (1/1) G4: 71% (5/7) Indeterminate*: 27% (4/15)	64% (44/69)	3.6% (2/55)	G1: 96% (47/49) Indeterminate*: 60% (3/5)	93% (50/54)	2.0% (1/49)

Abbreviations: European Association for the Study of the Liver (EASL), sustained virologic response (SVR), hepatitis C virus (HCV), pegylated interferon (pegIFN), genotype (G)

*Genotype-specific data was not reported for this group of patients