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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

# HCV Cure and Reinfection Among People With HIV/HCV Coinfection and People Who Inject Drugs

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## Abstract

*Purpose of Review* Highly effective, well-tolerated interferon-free direct-acting antivirals (DAA) have revolutionised hepatitis C virus (HCV) therapeutics, with the opportunity for broad treatment scale-up among marginalised or "high-risk" populations, including people who inject drugs (PWID) and people with HIV/HCV coinfection.

*Recent Findings* Concern that HCV reinfection may compromise HCV treatment outcomes is sometimes cited as a reason for not offering treatment to current and former PWID. However, the incidence of reinfection following interferon-based treatment for chronic HCV is low among PWID. Reinfection rates in HIV-positive men-who-have-sex-with-men (MSM) are varied, with high incidence reported in some cohorts. Mathematical modelling suggests that substantial reductions in HCV incidence and prevalence could be achieved with targeted DAA therapy among those at the highest risk of ongoing transmission.

*Summary* This review will summarise the recent literature on DAA efficacy in PWID and people with HIV/HCV coinfection, discuss the individual- and population-level impact of DAA treatment scale-up and reinfection, and highlight ongoing and future research questions in expanding HCV care and treatment to those populations at high risk of ongoing HCV transmission.

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## Introduction

Highly effective, well-tolerated interferon-free direct-acting antivirals (DAA) have revolutionised hepatitis C virus (HCV) therapeutics [1], with daily fixed-dose combination DAA regimens providing cure in greater than 95% of individuals with chronic infection [2–4]. The availability of DAA therapy has given rise to significant therapeutic optimism, providing an opportunity for broad treatment scale-up with the potential for HCV elimination among marginalised or "high-risk" populations, including people who inject drugs (PWID) and people with HIV/HCV coinfection [5–8].

One challenge in achieving HCV elimination is reinfection. There is concern that HCV reinfection may compromise HCV treatment outcomes in populations with ongoing risk behaviour, with the risk of reinfection cited as a reason for not offering treatment to PWID [9, 10]. However, the incidence of reinfection following interferon-based treatment for chronic HCV is low among lifetime PWID [11••, 12]. Reinfection rates in HIV-positive men-who-have-sex-with-men (MSM) are varied, with high incidence reported in some cohorts [13–15]. Mathematical modelling suggests that substantial reductions in HCV incidence and prevalence could be achieved with targeted DAA therapy among those at the highest risk of ongoing transmission [6, 16].

This review will summarise the recent literature on interferon-free DAA efficacy in PWID and people with HIV/HCV coinfection, discuss the individual- and population-level impact of DAA treatment scale-up and reinfection among PWID and HIV-positive MSM, and highlight

ongoing and future research questions in expanding HCV care and treatment to those populations deemed at high risk of ongoing HCV transmission.

## Who Is "High-Risk"? Defining the Population of Interest

When assessing suitability for interferon-based HCV therapy, certain populations, including PWID, people who are incarcerated, people with HIV/HCV coinfection, and MSM, had been considered "high-risk", based on concerns regarding efficacy, toxicity, adherence, and particularly, the potential for reinfection [11••]. However, these populations are heterogeneous with different levels of reinfection risk attributable to specific subgroups.

Subpopulations of PWID include those who report injecting an illicit drug at least once (lifetime PWID), those who have ceased injecting drug use (former PWID), and those who continue to inject drugs (recent PWID, with definitions of "recent" varying between 1 and 12 months) [17]. Among lifetime PWID, there also exists a group of people receiving opioid substitution therapy (OST), some of whom may be recent PWID. Understanding the definitions for different PWID populations is crucial to accurately define outcomes and reinfection risk following DAA therapy.

Similarly, not all people with HIV/HCV coinfection demonstrate contemporary behaviours placing them at "high risk". The higher HCV reinfection incidence reported in some studies among people with HIV/HCV coinfection, as compared to HCV mono-infection, has been driven by cohorts of acute HCV infection in HIV-positive MSM [11••]. Caution should be taken not to extrapolate these reinfection rates to general HIV/HCV coinfected populations. While similar risk behaviours are observed in HIV-positive and HIV-negative MSM [18], HCV incidence is significantly higher among HIV-positive MSM [19]. As DAA treatment scale-up occurs, a better understanding of drug use and sexual behaviours which pose a risk of reinfection is required.

## DAA Efficacy Among People With HIV/HCV Coinfection and People Who Inject Drugs

### Evidence From Clinical Trials

Phase II and III interferon-free DAA clinical trials have been undertaken in various populations, previously deemed "high-risk", including PWID, people receiving OST, and people with HIV/HCV coinfection (Table 1). Overall efficacy and safety data have been similar to that seen in general populations.

### HIV/HCV Coinfection

In contrast to results achieved with interferon-based therapy, HIV coinfection does not appear to compromise DAA efficacy. Phase III trials have demonstrated high sustained virological response at 12 weeks post-treatment (SVR12), equivalent to that observed in HCV mono-infection [3, 23, 24, 26, 27]. Following 12 weeks of interferon-free, ribavirin-free DAA therapy, SVR12 was achieved in greater than 95% of HIV/HCV coinfected participants receiving sofosbuvir/ledipasvir [3], sofosbuvir plus daclatasvir [23], grazoprevir/elbasvir [26], and sofosbuvir/velpatasvir [27].

However, the generalisability of these clinical trial results has been questioned, in large part due to the exclusion criteria pertaining to antiretroviral therapy, active drug use, CD4 T cell count, and detectable HIV RNA. Saeed et al. [33] reviewed phase III DAA clinical trial eligibility and compared this with the demographic, behavioural, and clinical characteristics of patients within the Canadian coinfection cohort ($n = 874$). They demonstrated that a minority (6–10%) of HIV/HCV coinfected patients would have been eligible for enrolment in the majority of HIV/HCV phase III trials, largely related to prescription of specific antiretroviral agents (drug–drug interactions) and active drug use. ALLY-2 [23], which assessed the efficacy and safety of sofosbuvir and daclatasvir, was the exception, with 43% of HIV/HCV coinfected patients potentially eligible for inclusion. Drug and alcohol use per se was not an exclusion criteria, with "active substance abuse" only regarded as exclusionary if the investigator deemed it "inappropriate". The study by Saeed et al. [33] is important in highlighting the potential gap between clinical trial-based efficacy and "real-world" impact.

### People Who Inject Drugs

Evidence from clinical trials with interferon-containing regimens indicated that recent drug use did not compromise HCV treatment outcomes [12]. Phase II and III trials of DAA therapy have demonstrated similar high efficacy among people receiving OST as compared with people not receiving OST [28–31]. However, in large part, these individuals have been stable on OST and people reporting recent drug use have been excluded, either by time since the last reported drug use or by urine drug screen.

A post hoc analysis of treatment efficacy and safety was performed among people who use drugs (PWUD) while receiving treatment in the ION-1 studies, in which participants with chronic HCV genotype 1 received sofosbuvir/ledipasvir (with or without ribavirin) for 8–24 weeks. As a positive urine drug test at screening was exclusionary, in order to assess drug use on treatment, stored samples were retrieved and tested retrospectively. Drug use during therapy was seen in 23% ($n = 70$), with the majority of positive samples detecting

**Table 1**  Phase II and III trials of interferon-free DAA regimens in people with HIV/HCV coinfection and people who inject drugs

| Author, year | Trial phase Trial acronym | Study population and key inclusion/exclusion criteria | DAA regimen | HCV GT | Treatment duration (weeks) | SVR 12 |
|---|---|---|---|---|---|---|
| **HIV/HCV coinfection** | | | | | | |
| [20] Sulkowski 2014 | Phase III PHOTON-1 | HIV/HCV CD4 > 200, HIV RNA < 50[a] Exclusion: active drug use[b] | SOF + RBV | 1–3 | 12  24 | G2: 88% G3: 67% G1: 76% G2: 92% G3: 94% |
| [21] Molina 2015 | Phase III PHOTON-2 | HIV/HCV CD4 > 200, HIV RNA < 50[a] Exclusion: active drug use[b] | SOF + RBV | 1–4 | 12 24 | G2: 88% G1: 85% G3: 89% G4: 84% |
| [22] Osinusi 2015 | Phase II ERADICATE | HIV/HCV CD4 > 100, HIV RNA < 50[a] | SOF/LDV | 1 | 12 | 98% |
| [3] Naggie 2015 | Phase III ION-4 | HIV/HCV CD4 > 100, HIV RNA < 50[a] Exclusion: active drug use[b] | SOF/LDV | 1 | 12 | 96% |
| [23] Wyles 2015 | Phase III ALLY-2 | HIV/HCV CD4 > 200, HIV RNA < 50[1] | SOF + DCV | 1–4 | 8 12 | 76% 97% |
| [24] Sulkowski 2015 | Phase III TURQUOISE-I | HIV/HCV CD4 > 200, HIV RNA < 40[a] Exclusion: active drug use[b] | PrO + D +/−RBV | 1 | 12 24 | 94% 91% |
| [25] Sulkowski 2015 | Phase II C-WORTHY | HIV/HCV CD4 > 300, HIV RNA < 20[a] Exclusion: active drug use | GZR/EBR GZR/EBR + RBV | 1 | 12 | 87% 97% |
| [26] Rockstroh 2015 | Phase III C-EDGE COINFECTION | HIV/HCV CD4 > 200, HIV RNA < 20[a] Exclusion: drug use within 12 months of screening | GZR/EBR | 1, 4, 6 | 12 | 96% |
| [27] Wyles 2016 | Phase III ASTRAL 5 | HIV/HCV CD4 > 100, HIV RNA < 50[a] Exclusion: active drug use[b] | SOF/VEL | 1–4 | 12 | 95% |
| **PWID and/or OST** | | | | | | |
| [28] Puoti 2014 | Phase II: AVIATOR, M14-103 Phase III: PEARL II–IV, SAPPHIRE I-II, TURQUOISE-II | OST Exclusion: active drug use[b] | PrO + D +/−RBV | 1 | 12–24 | G1a: 96% G1b: 100% |
| [29] Lalezari 2015 | Phase II – | OST Exclusion: active drug use[b] | PrO + D +/−RBV | 1 | 12 | 97% |
| [30] Grebely 2016 | Phase III ION-1 | PWUD[c] OST Exclusion: active drug use[b] | SOF/LDV +/−RBV | 1 | 8–24 | PWUD: 97% OST: 94% |
| [31] Grebely 2016 | Phase III ASTRAL 1–3 | OST Exclusion: active drug use[b] | SOF/VEL | 1–4 | 12 | 96% |
| [32••] Dore 2016 | Phase III C-EDGE COSTAR | OST (current PWUD 58%) | GZR/EBR | 1, 4, 6 | 12 | 92% |

[a] CD4 T cell count >200 cells/mm$^3$ (>100 cells/mm$^3$ in ION-4, >300 cells/mm$^3$ in C-WORTHY) and HIV RNA <50 copies/mL (<40 copies/mL in TURQUOISE-1) if on combination antiretroviral therapy (>90% of study population) or CD4 T cell count >500 cells/mm$^3$ if not on combination antiretroviral therapy

[b] Active drug or alcohol use at enrolment: history of clinically relevant drug or alcohol use within 6–12 months of screening, confirmed by urine drug screen at screening

[c] PWUD on treatment: stored serum samples from participants enrolled in ION-1 collected on-treatment (weeks 8 and 12) tested retrospectively testing for the following illicit drugs: amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, oxycodone, phencyclidine, propoxyphene, and cannabinoids

Abbreviations: *DCV* daclatasvir, *D* dasabuvir, *FDC* fixed-dose combination, *GT* genotype, *GZR/EBR* grazoprevir/elbasvir, *OST* opiate substitution therapy, *PrO* paritaprevir/ritonavir/ombitasvir fixed-dose combination, *PWID* people who inject drugs, *RBV* ribavirin, *SOF* sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir fixed-dose combination, *SOF/VEL* sofosbuvir/velpatasvir, *SVR* sustained virological response

cannabinoids (19%). Use of opiates (1%), cocaine (1%), or amphetamine/methamphetamine (<1%) was demonstrated in a minority. High treatment efficacy and adherence were seen, regardless of on-treatment drug use (any drug use on-treatment: SVR12 97%, 68/70; no drug use on-treatment: SVR12 99%, 652/657).

In the C-EDGE COSTAR trial, the efficacy and safety of grazoprevir/elbasvir for 12 weeks in chronic HCV genotypes 1, 4, and 6 were assessed among people receiving OST ($n = 301$), the majority of whom had ongoing drug use during treatment and follow-up [32••]. Active drug use was assessed by regular urine drug screen; 58% had a positive urine drug

screen at treatment initiation with stable patterns of drug use throughout treatment. At treatment initiation in the immediate treatment group, active use of benzodiazepines, opiates, cocaine, or amphetamines/methamphetamines was seen in 25, 22, 10, and 5%, respectively. Overall SVR12 was 92%, with similar treatment adherence and efficacy to the other C-EDGE phase III studies that excluded people with recent drug use [26, 34].

## Evidence From "Real-World" Cohorts

Observational cohorts that have evaluated DAA regimens among broader populations in the "real world" have generally shown favourable treatment outcomes [35–42]. In the large US Veterans Affairs (VA) cohort [35], a high proportion of people with chronic HCV genotypes 1–4 achieved SVR (91%) following, predominately sofosbuvir-containing, DAA therapy initiated between January 2014 and June 2015. The VA cohort included individuals with a history of substance use disorder (37%), history of alcohol use disorder (44%), and HIV coinfection (4%). A history of "alcohol use disorder" did not impact SVR. HIV coinfection and history of substance use disorder were not included in the model.

The "real-world" efficacy of DAA therapy among people with HIV/HCV coinfection appears to be comparable to clinical trial efficacy [38–41, 43]. In a population traditionally designated difficult to treat, given poor outcomes with pegylated interferon and ribavirin (SVR ≤ 30%) [44, 45], high SVR12 (93%) was demonstrated among people with HIV/ HCV coinfection and cirrhosis enrolled in the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) CO13 HEPAVIH cohort [40]. Of 189 treated (75% male, 58% HCV genotype 1, 16% Child-Pugh class B or C), the vast majority received 24 weeks of sofosbuvir in combination with an NS5A inhibitor, daclatasvir (65%), or ledipasvir (12%), with or without ribavirin.

Similarly, high SVR has been reported in cohorts of PWUD. In a single-centre US cohort of PWUD (defined as people receiving OST, people reporting recent drug use, or people with a positive urine drug screen) treated with interferon-free DAA therapy, SVR12 was 96% (44/46), compared with 95% (41/43) in non-PWUD [46]. Most of the cohort reported recent drug use (65%) and receipt of OST (78%). In a small single-centre Austrian cohort of active PWID (n = 15), directly observed DAA therapy was initiated in concert with OST [47]. SVR12 was achieved in 100%, with excellent adherence (100%). While encouraging, further research is required to determine the feasibility and efficacy of DAA therapy in broader populations of recent PWID.

## Reinfection Following HCV Treatment

There is concern that HCV reinfection may compromise the individual- and population-level benefits of HCV treatment in some populations [10]. In a recent meta-analysis, Simmons et al. [11••] examined the risk of HCV recurrence following interferon-based treatment-induced SVR in three different populations, defined by their perceived risk of reinfection—HCV mono-infected "low risk" (no recognised risk factors for reinfection), HCV mono-infected "high risk" (recognised risk factors for reinfection: former or recent injecting drug use, incarceration, MSM), and HIV/HCV coinfection. Reinfection incidence was 0.0 per 100 py (95% 0.0, 0.0) in those deemed "low risk", 1.9 per 100 py (95% CI 1.1, 2.8) in those deemed "high risk", and 3.2 per 100 py (95% CI 0.0, 12.3) in those with HIV/HCV coinfection. Regardless of risk category, reinfection incidence was low. However, it was unclear what proportion of those included in the "high-risk" group continued to demonstrate behaviours following SVR which posed a risk for HCV reinfection. Despite being included in the definition, no studies of MSM were included in the "high-risk" analysis. Also noteworthy, the higher reinfection incidence in the group with HIV/HCV coinfection was primarily driven by a single study of acute HCV infection in HIV-positive MSM [14].

A summary of primary studies and meta-analyses assessing HCV reinfection incidence following treatment in PWID and people with HIV/HCV coinfection is presented in Table 2, with the primary studies divided by duration of HCV infection. In general, HCV reinfection incidence in cohorts of acute or recent HCV infection is higher than that in cohorts of chronic HCV infection, presumably given contemporary risk behaviours for HCV transmission in acute HCV cohorts.

### HCV Reinfection Among People Who Inject Drugs

The risk of reinfection is cited as a reason for not offering treatment to PWID [9]. However, the incidence of reinfection following interferon-based treatment for chronic HCV is generally low among people who have ever injected drugs (lifetime PWID, reinfection incidence 0–5 per 100 py) [11••, 12] (Table 2).

The risk of HCV reinfection is significantly higher in people treated for chronic HCV infection who report ongoing risk behaviour, with reinfection incidence in those reporting injecting drug use post-treatment ranging between 0.0 and 33.0 per 100 py [12, 49, 50, 56, 60, 62–64]. In a meta-analysis examining reinfection incidence among PWUD (recent and lifetime), overall reinfection incidence was 2.4 per 100 py (95% CI 0.9, 6.1), rising to 6.4 per 100 py (95% CI 2.5, 16.7) in those who reported injecting drug use post-SVR [12]. Several recent studies have demonstrated the impact of ongoing injecting drug use following treatment on reinfection

incidence. Midgard et al. [49] followed "former" PWID for up to 7 years after successful treatment with pegylated interferon and ribavirin in Norway (*n* = 94). One of the inclusion criteria for initial study entry and interferon-based treatment was abstinence from injecting for more than 6 months; 39% reported injecting drug use during follow-up. In this cohort, 12 cases of reinfection were identified for an overall reinfection incidence of 2.0 per 100 py (95% CI 1.0, 3.5). Reinfection incidence rose to 5.8 per 100 py (95% CI 3.0, 10.2) among participants reporting injecting drug use post-treatment. Similarly, Weir et al. [50] examined reinfection incidence among lifetime PWID following SVR in Scotland (*n* = 277), with seven cases of reinfection identified and an overall reinfection incidence of 1.7 per 100 py (95% CI 0.7, 3.5). Among PWID who had been hospitalised for an opiate- or injection-related cause post-SVR (11%, *n* = 29), the risk of HCV reinfection was significantly higher (adjusted hazard ratio 12.9, 95% CI 2.2, 76.0, *p* = 0.002) with an increase in reinfection incidence to 5.7 per 100 py (95% CI 1.8, 13.3).

Evidence is being to emerge regarding reinfection following treatment with DAA therapy. In the C-EDGE COSTAR trial among people receiving OST, six cases of reinfection were identified at or prior to post-treatment week 24, with five cases of reinfection detected at post-treatment week 8. Reinfection incidence was 4.6 per 100 py (95% CI 1.7, 10.0) [32••]. Urine drug screen was positive both during and following treatment in five of the six cases. Of noted, reinfection cleared spontaneously in three of the six cases. Reinfection occurring soon after completion of treatment highlights that, in the era of interferon-free therapy, reinfection incidence will need to be calculated from end of treatment and sequencing used to accurately determine the aetiology of post-treatment HCV RNA recurrence to avoid misclassification. No cases of reinfection were identified up to 24 weeks post-treatment in the ION-1 or ASTRAL 1–3 trials [30, 31].

### HCV Reinfection Among HIV-Positive MSM

An increase in HCV incidence and prevalence has been reported in HIV-positive MSM over the last decade [48•, 65], although the burden of disease remains significantly lower than among PWID. In the Swiss Cohort Study, HCV incidence increased 18-fold in MSM between 1998 and 2011, while it declined in PWID and remained <1 per 100 py in heterosexuals [66]. In a recent meta-analysis examining HCV incidence in HIV-positive MSM who denied ever injecting drugs, estimated annual HCV incidence rates rose from 0.4 per 100 py in 1991 (95% CI 0.2, 0.8) to 1.3 per 100 py in 2012 (95% CI 0.8, 2.4) [48•]. The increase in HCV incidence has been associated with a reported increase in sexual risk behaviour and recreational drug use [48•]. Risk factors for HCV acquisition in HIV-positive MSM include condomless traumatic anal intercourse, higher number of

sexual partners, group sex, ulcerative sexually transmitted diseases, and sexual acts that involve trauma and bleeding [48•, 66–71]. However, HIV-positive MSM who inject drugs remain at significantly higher risk of HCV acquisition than HIV-positive MSM who do not inject drugs [65, 72].

Reinfection rates in HIV-positive MSM following primary HCV infection are varied, with high incidence reported in acute HCV cohorts [13–15] (Table 2). A meta-analysis examining reinfection HCV incidence among HIV-positive MSM who denied injecting drug use reported a reinfection incidence of 11.4 per 100 py (95% CI 7.4, 17.7) [48•], though results were pooled from only two retrospective acute HCV cohorts in Europe [13, 14]. Ingiliz et al. [15] analysed reinfection incidence in a large cohort of HIV-positive MSM in western Europe (*n* = 552), with 143 reinfections demonstrated over 1952 py of follow-up. Overall reinfection incidence was 7.3 per 100 py (95% CI 6.2, 8.6) with 25% reinfected at 3 years. Multiple reinfections were noted in some individuals (second reinfection, *n* = 69; third reinfection, *n* = 13) for a secondary reinfection incidence of 18.8 per 100 py (95% CI 12.9, 27.5). Importantly, the results combined two different populations at risk for reinfection, those with treatment-induced clearance and those with spontaneous clearance. Individuals with acute HCV infection and spontaneous clearance appear to be at higher risk of reinfection [73–75] than those with chronic HCV infection and treatment-induced SVR, indicative of different rates of ongoing risk behaviour [11••].

Reinfection has been documented in phase II and III DAA trials among people with HIV/HCV coinfection, in some cases prior to the primary endpoint of the study (SVR12). In TURQUOISE-I [24], two cases of reinfection were detected after the participants achieved SVR12; high-risk sexual behaviour was reported. In C-EDGE COINFECTION [26], two cases of reinfection were documented prior to SVR12; risk factors for reinfection were not reported.

Populations at high risk of reinfection, such as PWID and HIV-positive MSM, are not mutually exclusive. While often discussed as separate cohorts, it is important to remember that there is significant overlap [76]. Among a cohort of HIV/HCV coinfected individuals (of whom 86% reported ever injecting drugs), overall reinfection incidence was 1.2 per 100 py (95% CI 0.3, 3.1) [51]. Reinfection incidence in those individuals who used heroin and/or cocaine during follow-up was 8.7 per 100 py (95% CI 4.8, 23.7). In an Australian and New Zealand cohort of individuals treated for recent HCV infection (duration of HCV infection <18 months), ten cases of reinfection were identified in the population at risk (*n* = 120) [61]. Of the ten participants (seven HIV-positive MSM) with reinfection, eight reported injecting drug use during follow-up. The remaining two cases occurred in HIV-positive MSM who denied ever injecting drugs. Overall reinfection incidence was 7.4 per

**Table 2** HCV reinfection incidence following treatment-induced viral clearance (2011–2016)

| Author, year | Population | Location and study design | Number of subjects | Number of reinfections | Reinfection incidence per 100 py (95% CI) |
|---|---|---|---|---|---|
| Meta-analysis studies: reinfection post-treatment for acute and chronic HCV infection | | | | | |
| [11••] Simmons 2016 | "Low risk"[a] | Meta-analysis (31 studies) | 7969 | 4 | 0.0 (0.0, 0.0) |
| [11••] Simmons 2016 | "High risk": PWID, incarcerated[a] | Meta-analysis (14 studies) | 771 | 36 | 1.9 (1.1, 2.8) |
| [11••] Simmons 2016 | HIV/HCV coinfection[a] | Meta-analysis (4 studies) | 309 | 31 | 3.2 (0.0, 12.3) |
| [48•] Hagan 2015 | HIV-positive MSM | Meta-analysis (2 studies) | 170 | 38 | 11.4 (7.4, 17.7) |
| [12] Aspinall 2013 | PWUD | Meta-analysis (5 studies) | 131 | 7 | 2.4 (0.9, 6.1) |
| Primary studies: reinfection post-treatment for chronic HCV infection | | | | | |
| [32••] Dore 2016 | OST (100%) Recent PWUD (58%) | International, multicentre Prospective | 301 | 6 | 4.6 (1.7, 10.0) |
| [49] Midgard 2016 | Lifetime PWID (100%) Recent PWID (39%) | Norway Prospective | 94 | 12 | 2.0 (1.0, 3.5) |
| [50] Weir 2016 | Lifetime PWID (100%) | Scotland Retrospective | 277 | 7 | 1.7 (0.7, 3.5) |
| [51] Pineda 2015 | HIV-positive (100%) Lifetime PWID (86%) | Spain Prospective | 84 | 4 | 1.2 (0.3, 3.1) |
| [52] Conway[b] 2013 | Recent PWID (100%) | Canada Prospective | 70 | 4 | 2.9 (1.1, 7.2) |
| [53] Deshaies[b] 2013 | Recent PWID (100%) | Canada Prospective | 20 | 2 | 6.3 (1.7, 20.3) |
| [54] Edlin[b] 2013 | Recent PWID (100%) | US Not reported | 15 | 1 | 2.2 (3.9, 11.5) |
| [55] Hilsden[b] 2013 | Recent PWUD (100%) | Canada Prospective | 23 | 1 | 2.8 (0.0, 14.5) |
| [56] Marco[b] 2013 | Incarcerated (100%) Recent PWID (10%) HIV-positive (15%) | Spain Retrospective | 119 | 9 | 5.3 |
| [57] Ruzic[b] 2013 | Former PWID (100%) | Serbia Retrospective-prospective | 20 | 0 | 0 (0.0, 3.7) |
| [58] Grady[b] 2012 | Recent PWUD (100%) | The Netherlands Prospective | 42 | 1 | 0.8 (0.0, 3.7) |
| [59] Manolakopoulos[b] 2012 | Lifetime PWID (100%) Recent PWID (57%) | Greece Retrospective | 61 | 5 | 4.1 (1.8, 9.2) |
| Primary studies: reinfection post-treatment for recent HCV infection | | | | | |
| [13] Lambers[c] 2011 | HIV-positive MSM (100%) | The Netherlands Retrospective | 56 | 11 | 15.2 (8.0, 26.5) |
| [60] Grebely 2012 | PWID HIV-positive MSM | Australia Prospective | 67 | 5 | 12.3 (5.1, 29.6) |
| [14] Martin[b,c] 2013 | HIV-positive MSM (100%) | England Retrospective | 114[d] | 27 | 9.6 (6.6, 14.1) |
| [61] Martinello 2016 | HIV-positive MSM (53%) Recent PWID (49%) | Australia Prospective | 120 | 10 | 7.4 (4.0, 13.8) |

[a] Simmons et al. [11••] examined the risk of HCV recurrence following SVR in three different populations, defined by their risk of reinfection—HCV mono-infected "low risk" (no recognised risk factors for reinfection), HCV mono-infected "high risk" (recognised risk factors for reinfection: former or recent injecting drug use [12 studies], incarceration [2 studies], MSM [0 studies]), and HIV/HCV coinfection

[b] Studies included in meta-analysis performed by Simmons et al. [11••]

[c] Studies included in meta-analysis performed by Hagan et al. [48•]

[d] Documented primary HCV infection only

Abbreviations: *MSM* men-who-have-sex-with-men, *OST* opiate substitution therapy, *PWID* people who inject drugs, *PWUD* people who use drug

100 py (95% CI 4.0, 13.8), rising to 15.5 per 100 py (95% CI 7.8, 31.1) in those who reported injecting drug use at end of or post-treatment. On adjusted analysis, reinfection was associated with injecting drug use during follow-up. Among PWID (including HIV-positive MSM), HCV reinfection was specifically associated with use of unsterile needles and syringes during follow-up. High reinfection incidence following treatment for HCV infection in individuals with ongoing

high-risk behaviour emphasises the need for post-treatment surveillance, harm reduction strategies, and education.

## Mathematical Modelling: Treatment-as-Prevention and the Impact of Reinfection

The burden of disease attributed to HCV is high among PWID and is increasing among HIV-infected MSM. Mathematical modelling suggests that substantial reductions in HCV incidence and prevalence could be achieved by targeted DAA treatment scale-up among those at the highest risk of ongoing transmission [6, 16, 77, 78]. Using HCV treatment uptake data from seven sites in the UK, Martin et al. demonstrated that treating 26 per 1000 HCV-infected PWID per annum with DAA therapy could achieve a 15–50% decrease in chronic HCV prevalence within 10 years [78]. Despite the high cost of DAA therapy, treating recent PWID and HIV-positive MSM with early liver disease appears to be cost-effective compared to delaying until cirrhosis, given the reduction in liver-related complications and additional benefit of averting secondary infections [7, 8, 79]. Modelling estimates support broad access to DAA therapy, without limitations based on disease stage or drug use, to gain the greatest individual- and population-level benefits.

The potential for broad access to highly effective, well-tolerated interferon-free DAA regimens has stimulated discussion around HCV treatment-as-prevention (TasP). HCV treatment scale-up will have a population-level prevention benefit by reducing the size of the HCV viraemic reservoir. However, ongoing risk behaviour following successful HCV therapy will contribute to reinfection. As shown in Fig. 1, rapid scale-up of DAA therapy (>8% per year) among PWID markedly increases the aviraemic proportion and as such increases the proportion susceptible to HCV reinfection [80]. While initially this leads to an increase in the number of people with HCV reinfection, as the viraemic prevalence decreases overall, the number of people with reinfection also decreases. A slower scale-up of DAA therapy (≤4% per year) has more limited impact on the viraemic prevalence and reinfection.

Ongoing risk behaviours associated with HCV transmission and high HCV reinfection rates may compromise the population-level benefits of TasP among recent PWID and HIV-positive MSM commencing DAA therapy. For PWID, access to interventions known to prevent HCV infection, including OST and high-coverage needle and syringe access programs [81–85], is crucial. Education regarding the potential for reinfection by health providers, peer-support workers, and community drug user organisations should be offered.

Using data from the UK Collaborative HIV Cohort (UK CHIC), mathematical modelling predicted that over the next decade, 94% of HCV infections in HIV-positive MSM would occur among high-risk individuals. As such, the greatest impact on HCV incidence and prevalence would be achieved if DAA treatment scale-up was prioritised to those with recently diagnosed (<1 year) HCV infection and occurred in combination with behavioural interventions [6]. Similarly, modelling within the Swiss HIV Cohort Study (SHCS) suggested that DAA treatment scale-up will need to occur in concert with behavioural risk reduction or stabilisation to achieve reductions in HCV incidence and prevalence [86]. Stabilisation of rates of high-risk behaviour combined with increased treatment uptake and the use of DAAs was predicted to reduce HCV incidence by 77% (from 2.2 per 100 py in 2015 to 0.5 per 100 py in 2030) and prevalence by 81% (from 4.8% in 2015 to 0.9% in 2030). However, most importantly, the model highlighted that a decrease in high-risk behaviour alone could rapidly reduce HCV incidence, independent of treatment uptake or efficacy. With serosorting of sexual partners by HIV status and increasing use of pre-exposure prophylaxis to prevent HIV transmission in HIV-negative MSM, there is the potential for increased sexual risk behaviour and transmission of HCV among MSM populations [71, 87, 88].

Prioritising treatment to those at risk of HCV transmission, including recent PWID and HIV-positive MSM engaging in high-risk behaviour, is consistent with international guidelines

**Fig. 1** Rate of HCV reinfection following HCV treatment scale-up assuming various rates of treatment uptake. *Each line* represents the expected number of individuals with HCV reinfection (*left axis*) in subsequent years based on an assumed annual treatment rate scenario. Permission to reproduce the image has been obtained from the author [80]
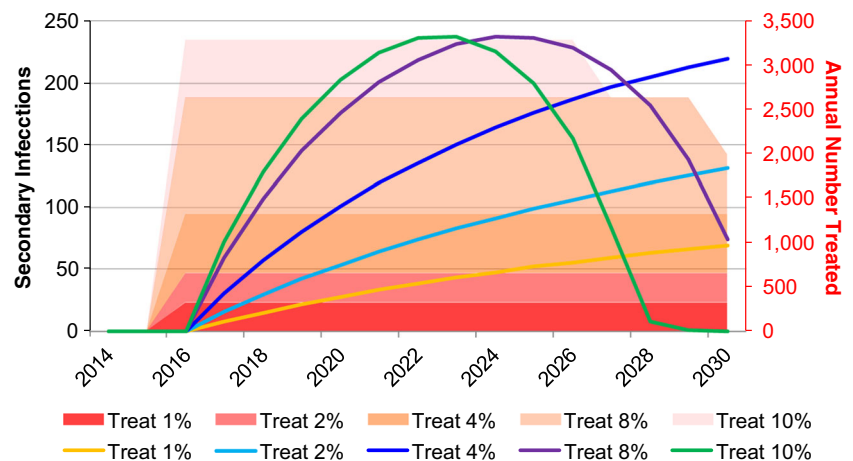
[89–92]. However, while there is evidence supporting interventions for HCV prevention among PWID [81–85], evidence supporting sexual behavioural interventions for HCV prevention among MSM is lacking. If reinfection does occur, retreatment should be made available.

## Future Directions

To date, clinical trials have largely excluded those at the highest risk of ongoing transmission, including those with recent HCV infection, those reporting recent injecting drug use, and those who are incarcerated. Further evidence is required in these populations to assess DAA efficacy, long-term outcomes, and crucially, reinfection incidence. A 3-year post-treatment extension of the C-EDGE COSTAR study is underway, evaluating drug use behaviours and the incidence of HCV reinfection (NCT02105688).

Among recent PWID (defined as injecting drug use within 3 or 6 months of enrolment), ongoing clinical trials assessing the efficacy of sofosbuvir/velpatasvir include HERO (NCT02824640) and SIMPLIFY (NCT02336139). Among people receiving OST and reporting recent injecting drug use (defined as injecting drug use within 6 months of enrolment), D3FEAT (NCT02498015) is examining the efficacy of paritaprevir/ritonavir/ombitasvir and dasabuvir (with or without ribavirin). Among people who are incarcerated, large trials are being conducted in Australia (STOP-C; NCT02064049) and Spain (JAILFREE-C; NCT02768961). In those with recent HCV infection (duration of HCV infection 4–12 months), the efficacy and feasibility of short-duration (6–8 weeks) DAA therapy are being assessed (DAHHS-2, NCT02600325; REACT, NCT02625909; SWIFT-C, NCT02128217; TARGET3D, NCT02634008).

Among HIV-positive MSM in the Swiss Cohort Study, a comprehensive approach to HCV care involving the combination of treatment and behavioural intervention is being trialled ("The Swiss HCVfree trial", NCT02785666). The treatment intervention includes grazoprevir/elbasvir for those with HCV GT 1 or 4 and the behavioural intervention involves targeted counselling about sexual risk behaviour and recreational drug use in participants reporting inconsistent condom use with casual male partners. All participants will receive "standard of care" (written and oral) information regarding the risk of HCV reinfection following successful treatment.

In an effort to expand access, different models of care are being assessed. In Scotland, a cluster randomised trial is assessing the impact of pharmacy-led directly observed HCV DAA therapy versus conventional nurse-led HCV therapy for people receiving OST (SuperDOT-C, NCT02706223). In Melbourne, Australia, the TAP study (NCT02363517) is assessing a social network-based approach ("bring a friend") to HCV treatment among PWID. In a multicentre randomised US study, the feasibility and acceptability of a patient-led model of care are being compared with directly observed therapy in active PWID (HERO; NCT02824640).

## Conclusions

The treatment paradigm for individuals with HCV infection is evolving rapidly [2–4, 26]. High interferon-free DAA efficacy demonstrated in clinical trials appears to be translating into the "real world", even among populations considered "high risk".

The incidence of HCV reinfection following DAA-based treatment is unknown and needs careful evaluation as access to treatment among populations at risk of ongoing transmission increases. There is some uncertainty around current reinfection estimates following interferon-based therapy given small sample sizes, retrospective study designs, exclusion of recent PWID from clinical trials, varied definitions for recent injecting drug use and time at risk for reinfection, and the inability to accurately distinguish relapse from reinfection. Particularly in the setting of interferon-based therapy, there may have been considerable selection bias in those PWID deemed suitable, or willing, for treatment. While injecting risk behaviour among PWID appeared to decline during and after interferon-based treatment [93], it is possible that expanded HCV treatment access and DAA therapeutic optimism may be associated with increased risk behaviour, as seen among MSM following the introduction of HIV combination antiretroviral therapy [94].

With DAA treatment scale-up among traditionally marginalised or "high-risk" populations, implementation and evaluation of novel prevention strategies should be a priority. Populations at high risk of HCV transmission, such as PWID and HIV-positive MSM, are not mutually exclusive, with implications for public health strategies. Treatment should occur in concert with education and harm minimisation. Good-quality evidence supporting interventions for HIV and HCV prevention including needle and syringe access programs, OST, and supervised injection facilities exists [81–85]; broad implementation of these interventions is required. Similarly, education regarding high-risk sexual practices and behavioural risk reduction consistent with currently recommended HIV prevention strategies is warranted, although evidence supporting the success of these strategies in limiting HCV transmission is lacking [95]. Screening protocols for acute HCV in PWID and HIV-positive MSM should be employed to enhance early HCV diagnosis, linkage to care, and access to treatment [89–92]. Future research should evaluate the incidence of reinfection following DAA therapy and the feasibility of HCV prevention and retreatment strategies.

Ultimately, the population-level impact of DAA therapy will relate to facilitating global access to HCV screening, care,

and treatment. Overcoming barriers imposed by high drug pricing, drug use, and liver disease stage restrictions and stigma will be central to this [96]. The risk of HCV reinfection following treatment in individuals with ongoing risk behaviour emphasises the need for post-treatment surveillance, harm reduction strategies, and education, but must not be considered an impediment to treatment, if HCV elimination is to be achieved.

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