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RESEARCH REPORT

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A transient positive association between direct-acting antiviral therapy for hepatitis C infection and drug-related hospitalization among people who inject drugs: Self-controlled case-series analysis of national data

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Abstract

Background and aims: Direct-acting antiviral (DAA) treatment has an established positive effect on liver outcomes in people with hepatitis C infection; however, there is insufficient evidence regarding its effects on the 'extra-hepatic' outcomes of drug-related hospitalization and mortality (DRM) among people who inject drugs (PWID). We investigated associations between these outcomes and DAA treatment by comparing post-treatment to baseline periods using a within-subjects design to minimize selection bias concerns with cohort or case–control designs.

Design: This was a self-controlled case-series study.

Setting: Scotland, 1 January 2015–30 November 2020.

Participants: The study population of non-cirrhotic, DAA-treated PWID was identified using a data set linking Scotland's hepatitis C diagnosis, HCV clinical databases, national inpatient/day-case hospital records and the national deaths register. Three principal outcomes (drug overdose admission, non-viral injecting related admission and drug-related mortality) were defined using ICD codes.

Measurements: Self-controlled case-series methodology was used to estimate the relative incidence (RI) of each outcome associated with time on treatment and up to six 90-day exposure risk periods thereafter.

Findings: A total of 6050 PWID were treated with DAAs in the sampling time-frame. Compared with the baseline period, there was a significantly lowered risk of a drug overdose hospital admission in the second to fifth exposure risk periods only [relative incidence (RI) = 0.86, 95% confidence interval (CI) = 0.80–0.99; 0.89, 95% CI = 0.80–0.99; 0.86, 95% CI = 0.77–0.96; 0.88, 95% CI = 0.78–0.99, respectively]. For non-viral injecting-related admission, there was a reduced risk in the first, third and fourth exposure risk periods (RI = 0.76, 95% CI = 0.64–0.90; 0.75, 95% CI = 0.62–0.90; 0.79, 95% CI = 0.66–0.96, respectively). There was no evidence for reduced DRM risk in any period following treatment end.

Conclusions: Among people who inject drugs in Scotland, direct-acting antiviral treatment appears to be associated with a small, non-durable reduction in the risk of drug-related hospital admission, but not drug-related mortality. Direct-acting antiviral therapy, despite high effectiveness against liver disease, does not appear to offer a panacea for reducing other drug-related health harms.

KEYWORDS
Direct-acting antiviral therapy, hepatitis C virus, hospital admission, mortality, overdose, people who inject drugs

INTRODUCTION

The availability of interferon (IFN)-free direct-acting antiviral (DAA) therapies for treating people who inject drugs (PWID) and others for hepatitis C virus (HCV) infection has had a significant population-level impact on the incidence of severe stages of liver disease in Scotland [1] and elsewhere, and is also anticipated to have a positive impact on liver-related mortality. In contrast to this improved outlook with respect to death from liver disease, mortality from drug-related causes among the PWID population—many of whom are still living with chronic HCV infection—has been rising steeply over the past decade [2].

As more HCV-infected PWID are initiated on DAA therapy and resolve their infection, the question has arisen regarding the existence of an association between DAA treatment and a lowered risk of 'extra-hepatic' outcomes drug-related mortality (DRM) and morbidity. Previous research has hypothesized that the process of drug users engaging with health/drug services (e.g. community pharmacies, primary care, nurse-led community clinics, addiction treatment centres, injecting equipment provision and other harm reduction services) can provide stability and also induce life-style and behavioural changes that, in turn, leads to a reduction in the incidence of drug-related outcomes [3–5]. Although, to date, research on the association between HCV treatment and injecting-related behaviours has been limited, one study among 190 Australian PWID found that sharing of injecting equipment decreased during a period of up to 96 weeks following end of DAA treatment, although drug and alcohol use remained stable or slightly decreased [6]. A much larger population-based cohort study conducted in British Columbia, Canada, reported a substantial protective effect of DAA therapy on drug-related mortality [approximately a 75% reduced risk; hazard ratio = 0.26; 95% confidence interval (CI) = 0.21–0.32] comparing sustained virological response (SVR) attaining DAA-treated with matched untreated individuals [3].

It is plausible that PWID who are initiated on IFN-free DAA treatment differ in important respects from those who do not enter treatment. Consequently, a higher DRM rate may be observed among DAA treatment-naive PWID because of risk behaviours that increase the chance of a fatal overdose and that also lower engagement (possibly due to stigma) with health/drug services at which treatment could be obtained. Standard between-individual designs, such as case–control or cohort studies, may be vulnerable to selection bias; even if every effort is made to control for this using the available methodological tools, unmeasured confounding may persist, which could yield a protective effect of DAA therapy on DRM. The case-only self-controlled case-series (SCCS) analysis offers the advantage of effectively removing the effects of time-constant confounders, as individuals serve as their own controls [7, 8]. We used SCCS to investigate whether there is a temporal relationship between commencement on IFN-free DAA therapy and both DRM and drug-related hospital admission by quantifying the relative incidence of the outcome occurring in earlier compared with later exposure risk periods following the end of DAA treatment. Note that such a comparison will not establish whether or not there is an overall protective effect of DAAs, as perfectly matched untreated PWID are not included in the analysis.

Our objective was to address the following research questions: among chronically HCV-infected PWID, is IFN-free DAA treatment associated with a (potentially transient) positive effect on drug-related harms: (i) hospital admission for drug intoxication (i.e. overdose), (ii) admission for non-viral injecting-related disease and (iii) death from a drug-related cause, following DAA treatment?

METHODS

Three outcomes that serve as indicators for risks associated with ongoing (injecting) drug use were investigated using self-controlled case-series analysis: admission for drug overdose, admission with non-viral injecting-related disease [9] and drug-related mortality. As a negative control, we also evaluated the association between DAA treatment and hospital admission with a cardiovascular ICD-10 code. If a transient effect is seen for this extrahepatic outcome—for which a sustained effect would be expected, given evidence for a beneficial, potentially durable, impact of viral clearance [10, 11] and plausible biological/pharmacological mechanisms [5, 12, 13]—then this would suggest that any transient effects observed for the outcomes of interest may be attributable to an unknown source of bias rather than to a reduction of drug use risks. Analyses were not pre-registered and results should be considered exploratory.

Outcome definitions

All outcomes were classified based on ICD-10 codes in any discharge diagnosis position (hospital admissions) or ICD-10 codes provided as

the underlying or a contributing cause of death (mortality). For drug overdose hospital admissions, these were: mental and behavioural disorders due to psychoactive substance use (F11–16, F19) and poisoning by narcotics and psychodysleptics (T40). For non-viral injecting-related disease hospital admissions, codes were adopted from those used in a previous study [14]: cutaneous abscess (L02), cellulitis (L03), phlebitis or thrombophlebitis (I80), endocarditis (I011, I39, I33.0, I40.0, I41.0), septicaemia (A40–41), osteomyelitis or septic arthritis (M86, M00, M46.5) and necrotizing fasciitis (M76.2). For cardiovascular hospital admissions, the ICD-10 codes from [5] were adopted (see Supporting information, Table S2), and for DRM, the code-set in McDonald *et al.* [15] was used (Supporting information, Table S2).

Design of data analysis

The SCCS method [7, 8] is a type of within-individual analysis, which implicitly controls for all time-invariant confounders. Statistical power is similar to that for cohort studies, and typically greater than for a case–control study. SSCS analysis involves first carefully defining the time-frame for the sampling of cases (i.e. outcomes) within the defined population of interest. Note that one only censors observation time for each person for migration or (non-outcome event) death. The exposure, initiation on IFN-free DAA therapy, must have occurred within the person's observation time. Analysis was restricted to only those people with the outcome and with the exposure; thus, 'risk' periods associated with the exposure can be compared within the same person relative to unexposed, or baseline, periods of follow-up. A fundamental assumption of the SCCS approach is that the occurrence of an outcome does not affect the probability of exposure; that is, we assumed that hospital admission for drug overdose or non-viral injecting-related disease does not lead to initiation on IFN-free DAA therapy.

Unlike hospital admission outcomes, the DRM outcome requires a non-standard SCCS analysis, as exposure cannot occur after the outcome. This 'event-dependence' of exposure is handled using a counterfactual history approach, where each of the defined risk periods (see below) are comparisons with respect to the unexposed (or baseline) period which, for the DRM outcome, is subsequent to the final defined exposure risk period. In the counterfactual history approach, analysis is conducted using the (planned) end-point of observation time for each individual, i.e. had the outcome event not occurred [14].

Data source, participants and sampling frame

A linked data set was constructed using routinely conducted record-linkage between Scotland's hepatitis C diagnosis and HCV clinical databases, national inpatient/day-case hospital records (SMR01) and the national deaths register. Linkage of these data sources to the Scottish HCV clinical database was approved by Public Health Scotland Privacy Public Benefit Panel (application no. 1516-0457). The time-frame for sampling of cases (i.e. the observation period) was set to 1 January 2015 to 30 November 2020 (i.e. the last date of availability of cause-specific mortality data). As the first IFN-free DAA treatment was licensed in June 2014 in Scotland [16], almost all DAA-treated PWID to date will be captured within this sampling time-frame. Next, the observation time for each person was defined to begin at the later of HCV diagnosis date or 1 January 2015, and to end at the earlier of date of death from any cause or 30 November 2020. Criteria for eligibility were PWID (according to aggregated risk information on the HCV diagnosis and HCV clinical databases: PWID status was determined if the route of probable acquisition of HCV infection was indicated as injecting drugs), chronic HCV infection and no diagnosis with cirrhosis by the start of observation time.

For the drug overdose and non-viral injecting-related disease admission outcomes, the study population consisted of all PWID aged between 15 and 54 years (the upper age limit was set a priori as the cessation rate of injecting drug use increases with age), who were chronically HCV-infected and had not been diagnosed with cirrhosis from the start of their observation time, who had a record of at least one hospital admission with an outcome-relevant ICD-10 discharge diagnosis code and had ever been initiated on IFN-free DAAs during the observation period. People who were on treatment for fewer than 6 weeks (and treatment duration was not truncated because of death or administrative censoring), and whose HCV clinical database record noted the reason for this short duration as 'incomplete' or 'unknown', were excluded. The same definitions and exclusion criteria were applied for the cardiovascular admission (negative control) outcome, as well as for the DRM outcome. For the drug overdose outcome only, admissions that were immediately followed by death from a drug-related cause were excluded, as censoring should be independent of the outcome event for application of SCCS analysis.

Exposure risk periods

Risk period sizes were defined to consist of time on treatment (set at 12 weeks), followed by six 90-day periods following end of treatment (Figure 1). For the hospital admission outcomes, a pre-exposure risk period of 45 days (i.e. the 45-day period preceding commencement on treatment) was included in the analysis to address possible event-dependent exposure; i.e. a recent hospital admission may delay the start of DAA therapy, leading to fewer than expected outcomes occurring in a short period of time before therapy commenced [17]. Conversely, if an admission served as a triggering event for being initiated on treatment, a greater than expected number of admissions shortly before treatment would be observed, which would bias effect estimates; specifying a distinct pre-exposure period can also reduce such bias. We assessed the assumption that exposure is not event-dependent using previously proposed graphical means [18], and using sensitivity analysis by varying the size of the pre-exposure window (additionally testing 0, 15, 30, 60 and 90 days). The first three 90-day exposure risk periods are useful for detection of a possible transient

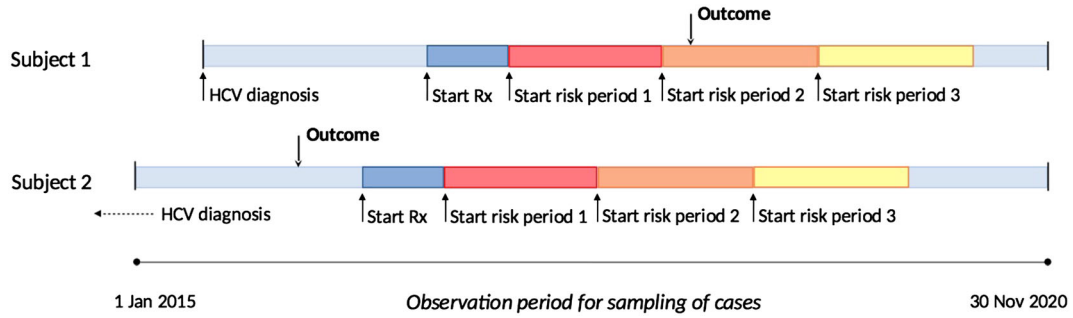

FIGURE 1 Example of observation time for hospital admission outcomes with three defined exposure risk periods, for two hypothetical subjects. The light-shaded segments indicate baseline risk periods. HCV, hepatitis C virus; Rx, DAA treatment.

effect; the next three 90-day periods will assist in determining if any observed effect on the risk of the outcome event occurring in the preceding period(s) is persistent or if it reverts to baseline incidence. All other observation time was defined as unexposed (i.e. baseline). For the DRM outcome, we defined five instead of six 90-day exposure risk periods following end of treatment, due to fewer observed outcomes compared with hospital admissions.

We used the SCCS method to examine whether outcomes occurred less frequently within each exposure risk period than during unexposed (baseline) time-periods. We calculated the relative incidence (RI) of each outcome using conditional Poisson models, comparing the incidence of the outcome during the above pre-specified exposure risk periods to the unexposed period. We included an indicator variable for calendar year in the analyses of the drug-related outcomes, as time is a potential confounder: access to DAA HCV treatment expanded over time, and the risk of DRM (and plausibly also the risks of hospital admission for non-fatal overdose and non-viral injecting-related disease) within Scotland's HCV-diagnosed PWID increased between 2015 and 30 November 2020 [15]. Finally, we conducted supplementary analyses on the drug overdose and non-viral injecting admission and DRM outcomes, stratifying by treatment setting (hospital versus non-hospital/unknown). The setting in which PWID received DAA therapy potentially serves as a proxy for aspects of risk-taking behaviours, as provision of treatment outside the hospital environment—namely, in community settings including prisons—has facilitated scale-up to people who actively inject drugs [19]. This is a subgroup with a potential continued risk of drug-related outcomes post-treatment, consistent with evidence showing higher HCV reinfection rates among those treated in community and prison compared with hospital settings [20]; however, PWID treated in hospital and in community settings may differ in other respects that are unrelated to drug use risks.

Power calculation

To detect an effect size of 0.26 (the adjusted subdistribution hazard ratio for the association of SVR-attainment—compared to an untreated group matched via inverse probability treatment weighting—and drug-related mortality reported by Janjua *et al.* [3]) at the 0.05 level of significance and with 80% power, we determined that a sample size of 64 exposed cases would be needed. Note that this estimate applies for events occurring in a 270-day exposure period within an average observation time of 5.3 years. For a smaller effect size of 0.52, 202 exposed cases are required for the same criteria, and for a modest effect size of 0.78, 1175 cases would be required.

All statistical analysis was conducted in R version 3.5.1 [21], with the SCCS package [22] used for fitting regression models.

RESULTS

In the data linkage a total of 14 857 eligible PWID (i.e. aged 15–54 years and inferred to be chronically HCV infected and non-cirrhotic at start of observation time) were identified. Of these, 6050 PWID (40.7%) were ever initiated on IFN-free DAA treatment (i.e. 'exposed') during their observation time and thus were included in analyses. Table 1 shows the number of events and people for each outcome definition. Throughout all outcomes, three-quarters of individuals were male, were aged approximately 40 years at start of observation time and 42–51% were treated in hospital settings. For the drug overdose cases the mean observation time was 5.3 years, and the majority of DAA treatments commenced in 2018 (26% of all PWID) or 2019 (31% of all PWID). Twelve (< 0.5%) drug overdose outcomes were excluded because they were immediately followed by DRM.

Adjusting for calendar year, there was a significantly lowered risk of a drug overdose hospital admission in the second exposure risk period (91–180 days following end of therapy): RI = 0.86 (95% CI = 0.80–0.99), as well as in the third to fifth exposure risk periods (RI = 0.89, 95% CI= 0.80–0.99; 0.86, 95% CI = 0.77–0.96; 0.88, 95% CI = 0.78–0.99, respectively), compared with the baseline period, but admission risk was not distinguishable from baseline in the sixth period (Table 2). Stratification by treatment setting category did not indicate any difference in the pattern of relative incidence (Supporting information, Figure S2).

For the non-viral injecting-related admission outcome, there was a reduced risk in the first, third and fourth 90-day periods following

TABLE 1 Exposed study population characteristics, and number of drug overdose, non-viral injecting-related disease, cardiovascular first admissions or drug-related deaths, among chronically hepatitis C virus (HCV)-infected, non-cirrhotic PWID who received interferon (IFN)-free DAA therapy; observation period: 1 January 2015 to 30 November 2020.

Variable	Drug overdose admission	Non-viral injecting-related disease admission	Cardiovascular admission (negative control)	Drug-related death
Total eligible DAA-treated PWID	6050	6050	6050	6050
Total number of events	9483	3849	3324	341
Mean; median number of events per individual (IQR)	3.7; 2 (1–4)	3.2; 2 (1–4)	3.2; 2 (1–4)	NA
Total exposed (DAA-treated) PWID	2535	1192	1044	341
Sex				
Male (col %)	1883 (74.3)	849 (71.2)	358 (76.8)	263 (77)
Female (col %)	652 (25.7)	343 (28.8)	108 (23.2)	78 (23)
Mean age (years) at start of observation time (SD)	39.2 (7.2)	39.0 (7.1)	40.9 (7.4)	41.2 (6.7)
Treatment setting				
Hospital (col %)	1058 (41.7)	507 (42.5)	524 (50.2)	173 (50.7)
Other/unknown (col %)	1477 (58.3)	685 (57.5)	520 (49.8)	168 (49.3)
Period initiated treatment				
< 2017 (col %)	317 (12.5)	133 (11.2)	160 (15.3)	90 (25)
2017 (col %)	427 (16.8)	186 (15.6)	178 (17.0)	74 (22)
2018 (col %)	647 (25.5)	312 (26.2)	277 (26.5)	94 (28)
2019 (col %)	795 (31.4)	376 (31.5)	287 (27.5)	73 (21)
2020 (col %)	349 (13.8)	185 (15.5)	142 (13.6)	10 (3)

Abbreviations: DAA = direct-acting antiviral; IQR = interquartile range; PWID = people who inject drugs; SD = standard deviation; NA = not applicable.

end of treatment (RI = 0.76, 95% CI = 0.64–0.90; 0.75, 95% CI = 0.62–0.90; 0.79, 95% CI = 0.66–0.96, respectively); the effect size was attenuated and non-significant in the fifth and sixth 90-day risk periods. The results of the treatment setting category-stratified analyses indicated a diverging pattern of relative incidence between hospital and non-hospital settings for the fifth and sixth exposure risk periods (Supporting information, Figure S2); relative incidences in these periods were higher for PWID treated in hospital settings compared with non-hospital settings, with non-overlapping 95% CIs. No risk period effects were apparent for cardiovascular admissions, except for lower RI observed during time on treatment (Table 2).

During follow-up a total of 341 drug-related (DR) deaths occurred, of which 179 occurred within the five 90-day risk periods following end of treatment; this varied between 31 and 40 deaths per risk period (Table 3). Conventionally-calculated unadjusted DRM incidence rates (among DAA-treated PWID only) were not consistent with a reduced risk of DRM following treatment (Supporting information, Figure S1). In the SCCS analysis, a statistically significant raised relative incidence of DRM compared to the baseline period was observed in the fourth and fifth 90-day risk periods following end of treatment (RIs of 1.48, 95% CI = 1.04–2.09; 1.52, 95% CI = 1.06–2.17, respectively) (Table 3). Stratification by treatment-setting category indicated a raised risk of DRM in those treated in hospital settings (total of 173 DR deaths) in the first, third and fourth 90-day risk periods following the treatment period (RIs of 3.03, 95% CI = 1.79–5.14; 2.16, 95% CI = 1.24–3.77; 2.46, 95% CI = 1.48–4.09, respectively) (Supporting information, Table S1, Figure S3). This pattern differed for the non-hospital settings (total of 168 DR deaths); namely, compared with baseline there was a significantly lowered RI of DRM during the first risk period and a raised RI in the fifth risk period (RIs of 0.41, 95% CI = 0.21–0.83; 1.64, 95% CI = 1.04–2.58, respectively).

Graphical exploration of the assumption that events do not influence exposure did not show an increased number of events in the short period prior to exposure. Histograms of the time between exposure and each outcome indicated a decreased number of admissions in the 45-day pre-exposure period before starting DAAs (Supporting information, Figure S4), also apparent when stratifying by year of treatment (Figure S5). In the 60-day period prior to starting DAA treatment, 6.9, 5.6 and 5.7% of treated PWID had at least one admission with a drug overdose, non-viral injecting-related and cardiovascular diagnosis code, respectively. Results for all three admission outcomes appeared robust to the length of the pre-exposure period (Figure S6).

DISCUSSION

The pattern of relative incidence for the two categories of hospital admissions conceivably associated with (injecting) drug-related risk behaviours was consistent with a small, but non-durable association between these outcomes and IFN-free DAA therapy. This transient

TABLE 2 Results for the three hospital admission outcomes. Relative incidence (RI) estimated using univariate and multivariable (adjusting for calendar year) regression analysis. Observation period 1 January 2015 to 31 November 2020.

	No. events	Univariable RI (95% CI)	Multivariable RI (95% CI)
Drug overdose (*n* = 2535 exposed individuals with at least one drug overdose admission)			
Exposure risk period			
Baseline	6704	Ref.	Ref.
Pre-Rx period (45 days)	200	0.83 (0.72–0.95)	0.75 (0.65–0.86)
On Rx	352	0.80 (0.72–0.89)	0.72 (0.65–0.81)
0–90 days following end of Rx	447	1.01 (0.92–1.12)	0.91 (0.82–1.00)
91–180 days following end of Rx	413	0.96 (0.87–1.06)	0.86 (0.77–0.95)
191–270 days following end of Rx	399	0.99 (0.90–1.10)	0.89 (0.80–0.99)
271–360 days following end of Rx	344	0.96 (0.86–1.07)	0.86 (0.77–0.96)
361–450 days following end of Rx	313	0.99 (0.88–1.11)	0.88 (0.78–1.00)
451–540 days following end of Rx	311	1.14 (1.01–1.28)	1.01 (0.90–1.14)
Calendar year			
2015	955	–	Ref.
2016	1382	–	1.32 (1.21–1.43)
2017	1518	–	1.37 (1.26–1.48)
2018	1680	–	1.44 (1.33–1.57)
2019	2202	–	1.79 (1.65–1.94)
2020	1746	–	1.44 (1.32–1.56)
Non-viral injecting-related disease (*n* = 1192 exposed individuals)			
Exposure risk period			
Baseline	2840	Ref.	Ref.
Pre-Rx period (45 days)	72	0.67 (0.53–0.85)	0.65 (0.51–0.83)
On Rx	137	0.71 (0.59–0.84)	0.69 (0.58–0.82)
0–90 days following end of Rx	151	0.77 (0.65–0.90)	0.76 (0.64–0.90)
91–180 days following end of Rx	173	0.90 (0.77–1.05)	0.90 (0.77–1.06)
191–270 days following end of Rx	130	0.73 (0.61–0.87)	0.75 (0.62–0.90)
271–360 days following end of Rx	122	0.77 (0.64–0.93)	0.79 (0.66–0.96)
361–450 days following end of Rx	121	0.88 (0.73–1.06)	0.92 (0.76–1.11)
451–540 days following end of Rx	103	0.87 (0.72–1.06)	0.91 (0.74–1.11)
Calendar year			
2015	504	–	Ref.
2016	652	–	1.17 (1.04–1.32)
2017	603	–	1.01 (0.90–1.14)
2018	654	–	1.01 (0.90–1.14)
2019	859	–	1.25 (1.11–1.41)
2020	577	–	0.85 (0.75–0.97)
Cardiovascular (*n* = 1044 exposed individuals)			
Exposure risk period			
Baseline	2334	Ref.	
Pre-Rx period (45 days)	82	0.96 (0.77–1.20)	0.91 (0.73–1.14)
On Rx	107	0.69 (0.57–0.84)	0.65 (0.54–0.79)
0–90 days following end of Rx	154	0.99 (0.84–1.17)	0.93 (0.79–1.10)
91–180 days following end of Rx	137	0.91 (0.76–1.08)	0.85 (0.71–1.01)
191–270 days following end of Rx	153	1.08 (0.91–1.27)	1.02 (0.86–1.21)
271–360 days following end of Rx	127	0.97 (0.81–1.16)	0.92 (0.77–1.11)

TABLE 2 (Continued)

	No. events	Univariable RI (95% CI)	Multivariable RI (95% CI)
361–450 days following end of Rx	120	1.02 (0.85–1.23)	0.98 (0.81–1.18)
451–540 days following end of Rx	110	1.04 (0.86–1.26)	0.99 (0.82–1.21)
Calendar year			
2015	504	–	Ref.
2016	652	–	1.20 (1.05–1.37)
2017	603	–	1.13 (0.99–1.29)
2018	654	–	1.09 (0.95–1.25)
2019	859	–	1.49 (1.31–1.69)
2020	577	–	1.11 (0.97–1.28)

Abbreviations: CI = confidence interval; Ref. = reference; Rx = DAA treatment.

TABLE 3 Results for the drug-related mortality outcome (n = 341 exposed individuals). Relative incidence (RI) is estimated using multivariable regression analysis, adjusting for calendar year.

	No. events	Univariable RI (95% CI)	Multivariable RI (95% CI)
Exposure risk period			
On Rx	22	0.70 (0.44–1.11)	0.78 (0.49–1.24)
0–90 days following end of Rx	31	0.91 (0.61–1.38)	1.02 (0.68–1.52)
91–180 days following end of Rx	36	1.06 (0.72–1.56)	1.17 (0.80–1.70)
181–270 days following end of Rx	33	1.04 (0.71–1.53)	1.13 (0.77–1.65)
271–360 days following end of Rx	40	1.37 (0.96–1.96)	1.48 (1.04–2.09)
361–450 days following end of Rx	38	1.43 (0.99–2.06)	1.52 (1.06–2.17)
Baseline (> 450 days following Rx)	141	Ref.	Ref.
Calendar year			
2015	0	–	Ref.
2016	15	–	1.29 (1.03–1.63)
2017	22	–	1.45 (1.17–1.81)
2018	52	–	1.59 (1.27–1.98)
2019	118	–	1.81 (1.46–2.24)
2020	134	–	1.70 (1.37–2.11)

Note: Fitting of the calendar year covariate requires the inclusion of non-exposed cases (e.g. Farrington *et al.* [17]). The 'No. events column' shows the number of deaths among treated people (there are, however, non-zero deaths among all cases in the year 2015, which are used in regression model fitting).
Abbreviations: CI = confidence interval; Ref. = reference; Rx = DAA treatment.

protective effect—most profound while on treatment—lasted approximately 1 year, as the risk of admission with a drug overdose or non-viral injecting related code occurring more than 12–15 months following the end of treatment was not statistically distinguishable from the risk in baseline periods.

Within Scotland's PWID population, and considering only our investigated outcomes, a positive effect of recent IFN-free DAA treatment appeared to be restricted to drug/injecting-related outcomes—and, by inference, drug-using risk behaviours—as the only reduction in hospital admission risk for the cardiovascular negative control outcome was observed for the on-treatment period. Although we have no supporting data, the positive effect for drug/injecting-related outcomes observed while on treatment and in the first part of the post-treatment period may be attributed to engagement with the treatment provider [4], as until at least 12 weeks following treatment end date there would be regular interaction with nursing staff [e.g. for administration of DAAs while on treatment and following the completion of therapy, for the polymerase chain reaction (PCR) test to determine SVR].

We did not observe any reduction in DRM in the exposure risk periods after the end of DAA treatment; in fact, in the fourth and fifth exposure risk periods (i.e. 271–360 and 361–450 days following end

of treatment), RIs were significantly raised (1.5 and 1.6, respectively). These results are not consistent with previous reports of a large beneficial association with SVR attainment [3]. Power for our SCCS analysis was adequate to detect their reported DRM effect size [adjusted hazard ratio of 0.26 (95% CI = 0.21–0.32) comparing 10 426 SVR-attaining DAA-treated with 10 851 matched untreated individuals, over a median follow-up of 2.2 years]. Our SCCS approach, being restricted to exposed (i.e. DAA-treated) PWID, cannot address differences in mortality risk between treated and never-treated people; however, the expected temporal relationship—i.e. a decreasing risk of DRM with time following treatment, reflecting greater engagement with drug treatment and a reduction in drug use risk—was not observed in our data. These differing analysis approaches entail that rather than comparing DRM risk between exposed and unexposed (never DAA-treated) people using a cohort or case–control design, with SCCS one estimates the relative DRM incidence in a defined finite time-period following DAA treatment. Interpretation of the SCCS results must bear in mind a fundamental assumption of the counterfactual-history method for event-dependent exposures; namely, that mortality risk returns to a baseline level following the last defined exposure risk period.

Although, for DRM, mortality risk cannot be estimated prior to starting treatment (i.e. due to event-dependence of exposure), our findings regarding the relative incidence of hospitalization for drug overdose should plausibly also carry over to the counterfactual estimating the relative incidence of overdose death, and thus suggests that—for our study population and available length of follow-up—DAA therapy was probably not associated with a durable reduction in the risk of either non-fatal overdose or mortality from overdose. In this aspect, our findings are consistent with those of Keen *et al.* [23], who also used a SCCS design and reported a transient reduction in the incidence of non-fatal overdose among people receiving medication for opioid use disorder; in their study, risk was reduced while on medication but returned to baseline from the third week post-discontinuation of medication.

Interestingly, although the estimated RIs for DRM in the community (i.e. non-hospital) treatment setting generally followed the overall pattern, for PWID treated in the hospital setting there was a transient raised risk of DRM (RIs ranging between 2.2 and 3.0) in the first, third and fourth exposure risk periods (Supporting information, Table S1, Figure S3). This pattern may indicate a short-term increase in drug use risks that eventually resolves over the longer term, and which would be broadly consistent with Janjua *et al.*'s [3] results. More work is required to understand the potential behavioural and other differences between PWID treated in hospital versus other settings. For instance, it could be that hospital-treated PWID have a higher prevalence of comorbidities.

We adopted the SCCS analysis approach because of its main advantage over other designs: the within-individual analysis effectively addresses unmeasured, time-invariant confounding to which conventional cohort and case–control designs remain susceptible. The principal disadvantage of the SCCS approach is that it cannot easily address the research question of whether there is an overall reduced risk of DRM or drug-related hospitalization associated with DAA treatment; however, it can address the related question regarding the existence of a plausible temporal relationship. Namely, do any reductions in risk of the outcome following DAA treatment persist? By comparing the relative incidence in earlier with later periods subsequent to DAA treatment, clinically useful inferences regarding the association between DAA treatment and drug use risks—with potentially fatal consequences—can be made.

Are the present findings consistent with residual confounding at least partly explaining reported associations between successful DAA therapy and a reduced risk of drug-related (or other) outcomes among PWID [3, 5]? As far as liver-related outcomes are concerned (i.e. outcomes for which a plausible biological mechanism exists), this is unlikely, given compelling data from population-level analyses and large cohort studies showing the effects of the introduction of DAA treatment regimens on liver disease, such as reductions in the incidence of severe outcomes and liver transplantation rates, among countries/regions [1, 24–27]. Although barrier-free access to and engagement with health/drug services may underlie some of the association between DAA-treatment (versus non-treatment) and a durable reduced risk of drug-related outcomes, including DRM, our analysis using the self-controlled design suggests that once treatment has commenced any benefits for behaviour might be time-limited. The BC and Scotland study populations differed in one important respect; namely, the substantial population-level DRM risk for BC (43.6 per 100 000 in 2021 [28]), 78% higher than the overall DRM risk in Scotland (24.5 per 100 000 in 2021; NRS, 2022).

Other potential limitations of our analysis concern unmeasured time-varying confounders. The observed calendar year effect showed clear evidence of variation over time in Scotland, which is consistent with studies showing increasing DRM risk (since at least 2010 [2, 29]) and changes in environmental risk (e.g. polydrug and benzodiazepine use [2]). Although the number of PWID initiated on DAA treatment, particularly in the community setting, has increased over time, if the patient risk profile has also changed (which is entirely plausible, as more difficult-to treat PWID are brought into the care pathway) then the relationship between exposure and outcome may change. Adjustment for calendar year will control for this to an extent; however, if, for instance, DAA treatment was coupled with opioid agonist therapy (OAT), then OAT could be a confounder.

In summary, for the drug-related hospitalization outcomes experienced in Scotland's PWID population, although a reduction in risk was observed while on IFN-free DAA treatment and in a period of 12–15 months subsequent to end of treatment, evidence was consistent with a return to baseline admission risk thereafter. In contrast, DRM risk was relatively stable following commencement of therapy. The implications are that DAA therapy, despite its high effectiveness for liver disease, does not offer a panacea for reducing other drug-related health harms.

AUTHOR CONTRIBUTIONS

Scott A. McDonald: Conceptualization (equal); formal analysis (lead); methodology (lead); writing—original draft (lead); writing—review and

editing (lead). **Matthew Hickman:** Formal analysis (supporting); investigation (equal); writing—review and editing (supporting). **John F. Dillon:** Resources (equal); writing—review and editing (supporting). **Alan Yeung:** Methodology (supporting); writing—review and editing (supporting). **Andrew McAuley:** Investigation (supporting); writing—review and editing (supporting). **Andrew Fraser:** Resources (equal); writing—review and editing (supporting). **Peter C. Hayes:** Resources (equal); writing—review and editing (supporting). **Sharon J. Hutchinson:** Conceptualization (equal); formal analysis (supporting); investigation (equal); supervision (lead); writing—review and editing (supporting).

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DECLARATION OF INTERESTS

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicy available; application to the Public Health Scotland Privacy Public Benefit Panel is required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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