Hepatitis C reinfection by treatment pathway among people who inject drugs in Tayside, Scotland

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Significance Statement

This study adds to the important body of research concerning the monitoring of Hepatitis C (HCV) reinfection among people who inject drugs in order to achieve global elimination. Results found varying reinfection incidence rates across six specialised treatment pathways in Tayside Scotland, with different subpopulations of patients at varying risk of reinfection post sustained virologic response (SVR). This emphasises the importance of defining the characteristics of patients in different care pathways to allow for reliable comparison of reinfection rates. Moreover, our study found comparable rates of reinfection following interferon-based and DAA-based therapies, providing support for widening access to treatment services.

Abstract

The efficacy of direct acting antivirals (DAA) provides an excellent opportunity to scale up HCV diagnosis and treatment, achieving the WHO target of HCV elimination by 2030. However, HCV reinfection among people who inject drugs (PWID) remains a concern and may impede elimination efforts. We assessed reinfection rates among PWID across six specialised treatment pathways, following DAA-based and interferon-based therapies in Tayside, Scotland. Data was collected retrospectively for every treatment episode that resulted in a sustained viral response (SVR) after undergoing treatment. Reinfection rates were calculated for each treatment pathway: hospital outpatient clinic; community pharmacy; drug treatment outreach; prison clinic; nurse led outreach clinic; and injection equipment provision site. Reinfection is defined as a positive RNA test result after SVR. Incidences of reinfection are expressed in 100 person-years (PYs). In total, 916 treatment episodes met selection criteria. Of these, 100 reinfections were identified, generating an overall reinfection rate of 5.27 per 100 PYs (95%CI: 4.36- 6.38). The hospital outpatient clinic had the lowest reinfection incidence (1.81 per 100 PYs, 95%CI: 1.11- 2.93), with the injection equipment provision site treatment pathway having the highest reinfection incidence (19.89 per 100 PYs, 95%CI: 14.91-

26.54). The incidence of reinfection amongst those treated with interferon-based therapies and those treated with DAA-based therapies was 4.93 per 100 PYs (95%CI: 3.97- 6.11) and 7.17 per 100 PYs (95%CI: 4.75- 10.82), respectively. Specialised treatment pathways in Tayside yield varying reinfection incidence rates, with different subpopulations of patients at varying risk of reinfection post SVR. Results suggest that resources should be targeted at the injection equipment provision site pathway in order to reduce the incidence of reinfection and achieve elimination targets. The study found comparable rates of reinfection following interferon-based and DAA-based therapies, providing support for widening access to treatment services.

Keywords

Hepatitis C virus, people who inject drugs, reinfection, injecting drug use, treatment as prevention

Conflict of interest statement: No authors declare any conflicts of interest.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Introduction

Hepatitis C (HCV) is a blood borne virus which affects around 71 million people globally[1]. The most common method of transmission is through injecting drug use behaviour, such as the sharing of needles, syringes and other ancillary injecting equipment, with around 39.2% of people who inject drugs (PWID) currently living with HCV infection worldwide[2]. The World Health Organisation (WHO) has set a target of global HCV elimination by the year 2030, with 80% of those eligible treated, and a 90% reduction in incidence of new infections[3]. The efficacy of pan-genotypic direct acting antivirals (DAA) provides an excellent opportunity to scale up HCV diagnosis and treatment to achieve this goal, with research supporting the treatment of active injecting drug users for HCV[4.5].

The scaling up of treatment services to reduce the prevalence of the disease could be accomplished by utilising the concept of "treatment as prevention" (TasP)[6]. TasP models of elimination are underpinned by the premise that HCV elimination could be achieved by treating PWID for HCV as they are the most at risk population for acquisition of the virus, and sufficient treatment it could reduce the potential for onward transmission[7,8,9]. However, elimination efforts may be impeded by the risk of reinfection after achievement of sustained viral response (SVR) in this population, with concern around reinfection remaining a barrier to treatment accessibility[10]. Therefore, in tandem with providing treatment at scale and speed within at-risk groups, monitoring incidence of reinfection is imperative when striving towards HCV elimination.

A recent meta-analysis investigating the rate of HCV reinfection following treatment estimated an overall reinfection rate of 6.2 per 100 PYs among people recently injecting drugs, and 3.8 per 100 PYs among those on opioid substitution therapy (OST)[11]. This highlights that assessment of different subpopulations of HCV patients generates differing reinfection incidence rates, with those who report recent drug use of higher risk of reinfection than those on OST. The introduction of multidisciplinary managed care networks (MCN) in Tayside, Scotland has improved HCV testing and treatment, and increased access to care[12]. The scaling up of HCV treatment services in Tayside has

involved the introduction of multiple specialised care pathways, utilising numerous healthcare professionals, to enable PWID to access therapy through community pharmacies, drug treatment centres, prisons, injection equipment provision sites (IEP), nurse led outreach clinics, and a hospital outreach clinic[13]. Combined with specialist diagnostic pathways, this scale up in services can prevent transmission and substantially reduce HCV prevalence among the PWID population. Understanding the differential reinfection rates yielded by these pathways will provide greater understanding of the disparate risk of reinfection across subpopulations of the PWID population in Tayside, supplying clarity in regards to the targeting of both testing and treatment resources.

The aim of the current study was to assess incidence of reinfection among people with a risk factor for HCV of injection drug use across the aforementioned six specialised treatment pathways in Tayside, Scotland. A limitation of the previous interferon era of treatment was that treatment was not used across wide spread patient populations, with active injecting behaviour being a contraindication to treatment. Accordingly, the introduction of DAA therapies in HCV care has increased treatment access to HCV patients who would have previously been deemed unsuitable for treatment due to their active injecting behaviour. Concern has arisen that reinfection rates may have increased since the interferon- based treatment era, due to the ease of DAA therapy[10,14]. Therefore, the current study also sought to investigate reinfection rates following DAA based and interferon based therapies.

Methodology

Data sources and identification of cohort

This retrospective study included individuals who were diagnosed with chronic Hepatitis C, attained a sustained virologic response (SVR) after undergoing treatment between 27th April 1998 and 2nd October 2018 in Tayside, Scotland, and whose risk factor for HCV was injection drug use. Therefore, the definition of PWID in our study is people who have “ever injected” drugs, established through

patients' self-report, with no differentiation between recent/active and former PWID. Patients were assigned to one of six pathways based of site of treatment. Individuals who attained SVR after 20th February 2019 were excluded from the cohort to allow for a minimum of six months follow up after SVR. Accordingly, individuals who died less than six months after SVR were excluded due to inadequate follow up time. Finally, individuals who were treated by other boards were excluded as they would not have been allocated treatment pathways in Tayside.

The cohort was identified from the Tayside Hepatitis C Clinical Database which records patients tested for Hepatitis C, awaiting treatment, on treatment, cured, and re-infected in Tayside, Scotland. Data collected from this database included demographic information, risk factors, virology test results, genotype (if available), treatment dates, treatment regimen, treatment pathway, and treatment outcomes. Retrospective virology test data was also sourced from the Sunquest Integrated Clinical Environment (ICE) system, which is an electronic blood test ordering system that displays and records patients' laboratory results. Test data included RNA test dates, RNA results, genotype results, and additional information regarding the specified tests.

Data sources were searched for a negative RNA test result indicating attainment of SVR for each patient in the selected cohort. HCV RNA results were linked to treatment results using patients' Community Health Index (CHI) numbers (unique identification numbers given to every patient registered with a GP in Scotland). SVR was defined as absence of detectable HCV RNA at 12 weeks or more, after completion of treatment (SVR-12). Patients who did not achieve SVR were excluded from the cohort. Data sources were then searched for any test results indicating reinfection, which was defined as a positive RNA test result after attainment of a negative RNA test indicating attainment of SVR. Reinfection was identified by PCR by blood draw. The detection limit for PCR tests used to detect reinfection was 10 international units (IU) of HCV RNA per ml. For each patient,

test results were sourced regarding last known negative RNA test result after attainment of SVR. Study follow up began after attainment of SVR bloods and ended on 20th August 2019.

Study outcomes

Primary outcome: reinfection was defined as a positive PCR result during post treatment follow up for individuals who attained SVR-12. Those who underwent treatment and attained SVR but did not become reinfected will be referred to as "non-reinfections". Accordingly, those who underwent treatment, attained SVR, and became reinfected will be referred to as "reinfections".

Reinfection rates: a) overall reinfection rate for Tayside b) treatment pathway (hospital outpatient clinic; community pharmacy; drug treatment centre; prison clinic; nurse led outreach clinic; and injection equipment provision site); c) treatment regimen (interferon alpha based and directing acting antiviral (DAA) based).

Statistical analysis

All data manipulation and statistical analyses were performed using IBM SPSS Statistics 22. Kaplan Meier survival analysis was performed to investigate differences in the rates of reinfection between treatment pathways. Comparison of survival curves was performed using log rank tests.

Reinfection rate calculations

All individuals who received at least one RNA test during follow up after SVR were considered and included in the calculations. Incidences of reinfection are expressed in 100 person-years (PYs). Time at risk began following attainment of SVR-12 and ended at date of reinfection or date of last PCR

negative test if not reinfected. Time of reinfection was estimated to be the midpoint between last PCR negative test and PCR positive test indicating reinfection.

Results

Study cohort

A total of 1919 HCV treatment episodes were carried out between 27th April 1998 and 2nd October 2018 in Tayside, equating to 1657 individuals treated (see Figure 1). Of these treatment episodes, 1372 resulted in attainment of SVR. After exclusion of individuals with other risk factors, individuals attaining SVR after 20th Feb 2019, individuals treated by other boards, individuals who died less than six months post SVR, and episodes with no RNA tests identified in follow up, 916 treatment episodes met selection criteria. Of these, 816 non-reinfections and 100 reinfections were identified.

Overall incidence rate of reinfection

Of the 916 treatment episodes who met selection criteria, there were 100 reinfections (10.9%).

The total follow up time was 1896 person years (*M*= 2.1 years, range= 0.08- 18.2 years). The overall estimated incidence rate of reinfection was 5.27 per 100 PYs (95%CI: 4.36- 6.38).

A breakdown of treatment episodes per treatment pathway, with number of reinfections, and percentage of treatment episodes carried out with interferon based therapies can be found in Table 1.

The majority of non-reinfections (n= 596, 73.0%) and reinfections (n= 78, 78.0%) were male. The mean age of the two groups differed, with reinfections (*M*= 40.12 ± 8.35) of a younger mean age than non-reinfections (*M*= 47.23 ± 10.17).

Overall, 60.2% of treatment episodes involved interferon alpha based treatment (n= 553), with 74.0% of reinfections previously treated using interferon alpha based treatment (n= 74). The median time between SVR and reinfection was 13.9 months (range= 1.3- 118.1 months), indicating the highest risk period for reinfection is in the first year after SVR.

Incidence of reinfection per treatment pathway

Incidences of reinfection per treatment pathway are displayed in Table 2. The incidence of reinfection among those treated through the hospital outpatient clinic was 1.81 per 100 PYs, (95%CI: 1.11- 2.93). The incidence of reinfection among those treated through the drug treatment outreach clinic was 3.13 per 100 PYs (95%CI: 1.58- 6.18). The incidence of reinfection among those treated through the nurse led outreach clinic was 6.39 per 100 PYs (95%CI: 4.03- 10.12). The incidence of reinfection among those treated through the prison clinic was 8.14 per 100 PYs (95%CI: 4.93- 13.45). The incidence of reinfection among those treated through community pharmacy was 12.12 per 100 PYs (95%CI: 6.33- 23.21). Finally, the incidence of reinfection among those treated through the injection equipment provision site was 19.89 per 100 PYs (95%CI: 14.91- 26.54).

The probability of reinfection per treatment pathway was found to be significantly different, $\chi^2(5) = 72.969$, $p = <.001$ (see Figure 2).

Incidence of reinfection per treatment regimen

Of the 916 treatment episodes that met selection criteria, 550 involved interferon-based therapies, and 366 involved DAA based therapies, respectively.

The incidence of reinfection amongst those treated with interferon-based therapies was 4.93 per 100 PYs (95%CI: 3.97- 6.11). The incidence of reinfection amongst those treated with DAA based therapies was 7.17 per 100 PYs (95%CI: 4.75- 10.82).

The probability of reinfection was not found to be significantly different between treatment regimens, $\chi^2(1) = 0.042$, $p = .84$ (see Figure 3).

Discussion

The aim of the current study was to assess the incidence of reinfection among people with a risk factor for HCV of injection drug use across six specialised treatment pathways. Results show that the various pathways yield differing incidences of reinfection, with the hospital outpatient clinic yielding the lowest incidence of reinfection (1.8 per 100 PYs, 95%CI: 1.1- 2.9), and the injection equipment provision site yielding the highest incidence of reinfection (19.9 per 100 PYs, 95%CI: 14.9- 26.5), respectively. These findings reflect nuances between the pathways, with different subpopulations of patients at varying risk of reinfection post SVR.

These differences in risk of reinfection may be indicative of differences in patients' injecting risk behaviours and injecting status, with some pathways being easier to access for some with high risk behaviours. For example, the low incidence of reinfection observed in the hospital outpatient clinic pathway could be explained by the fact that many of the patients were relatively stable as evidenced by the fact they repeatedly attended a hospital based clinic. Contrastingly, those who are treated on the injection equipment provision site pathway are arguably more active injectors. It is important to note that while the IEP site pathway has found more reinfections, this may be a consequence of increased injecting and risk behaviours or those treated through the IEP site pathway arguably have greater opportunity for retesting on a regular basis due to informal attendance for IEP equipment and being asked by staff about risk behaviours each visit. In contrast, the nurse led care pathways (prison clinic, drug treatment outreach, hospital clinic) are more appointment driven, with less scope for regular discussions around current risk behaviours and retesting. This study reports rates of reinfection post-SVR among PWID that are significantly higher in comparison to estimates published in existing literature[11,15,16]. However, the majority of these studies define active injecting as "injected in the past 6 to 12 months". This is in considerable contrast to the patients treated on the current study's IEP site pathway, who report regular injecting behaviours.

Although the incidence of reinfection of this pathway is high at 19.89 per 100 PYs (95%CI: 14.91-26.54), it is similar to the incidence of reinfection reported in a previous study by our group[17]. The rate of reinfection was assessed among patients who were enrolled on Eradicate, an observational cohort study aimed at assessing the feasibility of interferon based treatment for HCV at the IEP site who actively injected. At 18 months follow up post-SVR, the pathway yielded a reinfection rate of 21.5 per 100 PYs (95%CI: 13.00- 35.65). These findings have meaningful implications for the allocation of HCV testing and treatment resources, with our results suggesting that resources should be targeted at the IEP site treatment pathway in order to reduce the incidence of reinfection and achieve elimination targets. Resources should include testing and treatment resources, and harm

reduction interventions such as OST and high coverage needle and syringe programs (NSP). Also, it is vital to stress the importance of prompt retreatment of reinfections, and the acceptance that reinfection will be identified in high risk cohorts, such as those treated through the IEP site pathway. This highlights the importance of increased treatment volume at speed and scale amongst this population, the significance of reducing community viral load through early detection and early treatment, and the need for greater harm reduction coverage and interventions to minimize reinfection risk amongst this population. Furthermore, risk of reinfection is highest in the first 12 month post treatment, highlighting a period of high risk in need of further intervention.

The study also highlights the importance of access to drug treatment services and OST as a method of preventing reinfection, as evidenced by the lower incidence of reinfection observed in the drug treatment outreach pathway (3.1 per 100 PYs, 95%CI: 1.6- 6.2). The incidence of reinfection in the community pharmacy treatment pathway, where patients also receive OST, was relatively high (12.1 per 100 PYs, 95% CI: 6.3- 23.2). However, this estimate may be inaccurately high as the community pharmacy treatment pathway was only established in Tayside in 2017, with less post-SVR follow up time available for this pathway. It can also be noted that patients treated through the community pharmacy pathway and drug treatment outreach pathway are similar populations, as by definition, they are both in receipt of OST and perhaps engaged with HCV services where they felt most comfortable to do so.

The second aim of the study was to assess reinfection rates following DAA-based and interferon-based treatment regimens. The incidence of reinfection amongst those treated with interferon-based therapies was 4.93 per 100 PYs (95%CI: 3.97- 6.11) and the incidence of reinfection amongst those treated with DAA-based therapies was 7.17 per 100 PYs (95%CI: 4.75- 10.82). However, Kaplan Meier survival analysis found that that the probability of reinfection was not significantly different between treatment regimens, $\chi^2(1) = 0.042$, $p = .84$. These results are in line with findings of a recent meta-analysis, which found that rates of reinfection were comparable following both treatment regimens[5]. These findings address and negate ongoing concern that the widening of DAA-based

treatment access to more high risk patients may result in elevated reinfection rates[10,14]. This is strengthened by the fact that our service treated many active injectors with interferon-based therapy as a result of the Eradicate study which supported treatment of active injectors. Furthermore, it has been proposed that the associated adverse side effects of the interferon era of treatment may have discouraged post SVR injecting risk behaviours to a greater extent than those observed during the side effect free DAA era of treatment. However, recent research has demonstrated there is no significant difference in injecting risk behaviours among PWID following interferon-based and DAA-based treatment[18]. Therefore, the current study provides further evidence of the importance of broad HCV treatment accessibility.

Limitations

The predominant limitation of the current study was the retrospective study design, with limitations in available data. As a result, we were not able to identify factors that may explain the differences in incidence of reinfection across the six treatment pathways, or factors that may overall predict risk of reinfection. Moreover, there was no available data on patients' current injecting status or injecting risk behaviours, which could have given insight into the differential risk of reinfection across the treatment pathways. However, this is the likely explanation for the observed difference. It further emphasises the importance of defining the characteristics of patients in different care pathways to allow for reliable comparison of reinfection rates. Finally, we only included individuals with RNA testing post SVR in our calculations so it is possible that some cases of reinfection have not been detected.

Conclusion

In conclusion, results showed that specialised treatment pathways yield varying reinfection incidence rates, reflecting nuances between the pathways, with different subpopulations of patients at varying risk of reinfection post SVR. It further emphasises the importance of defining the

characteristics of patients in different care pathways to allow for reliable comparison of reinfection rates. The injection equipment provision site treatment pathway yielded the highest incidence of reinfection, suggesting that resources should be targeted at the injection equipment provision site treatment pathway in order to reduce the incidence of reinfection and achieve elimination targets, increasing treatment rates to reduce re-infection. Furthermore this risk is highest in the first 12 month post treatment, highlighting a period of high risk in need of further intervention. The study also found comparable rates of reinfection following interferon-based and DAA-based therapies, providing support for widening access to treatment services. It is imperative that harm reduction services are available, including access to OST and high coverage NSP, and regular post treatment HCV testing is carried out in order to reduce reinfection risk among PWID.

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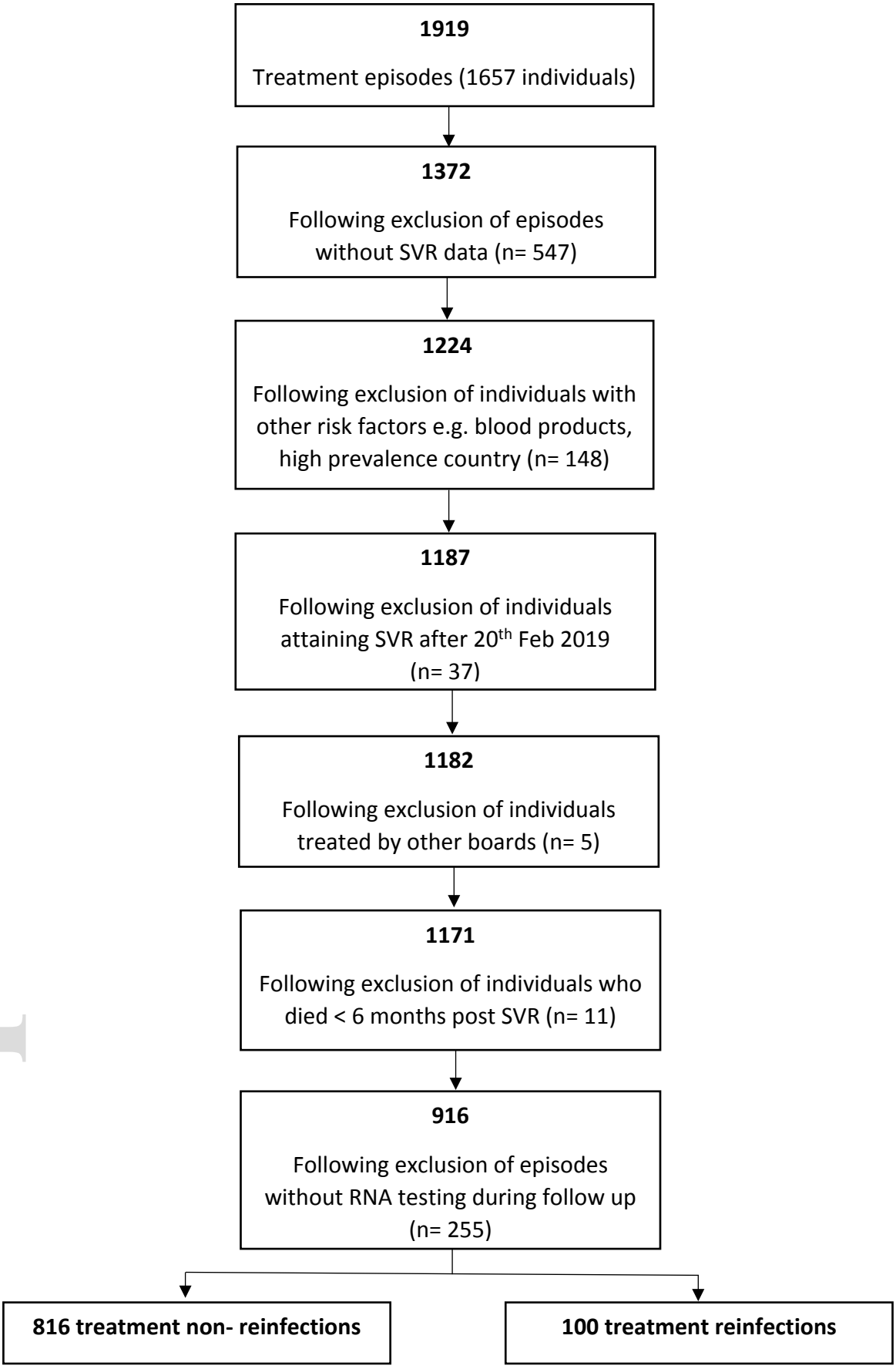

Figure 1. Selection of study cohort based on inclusion/exclusion criteria

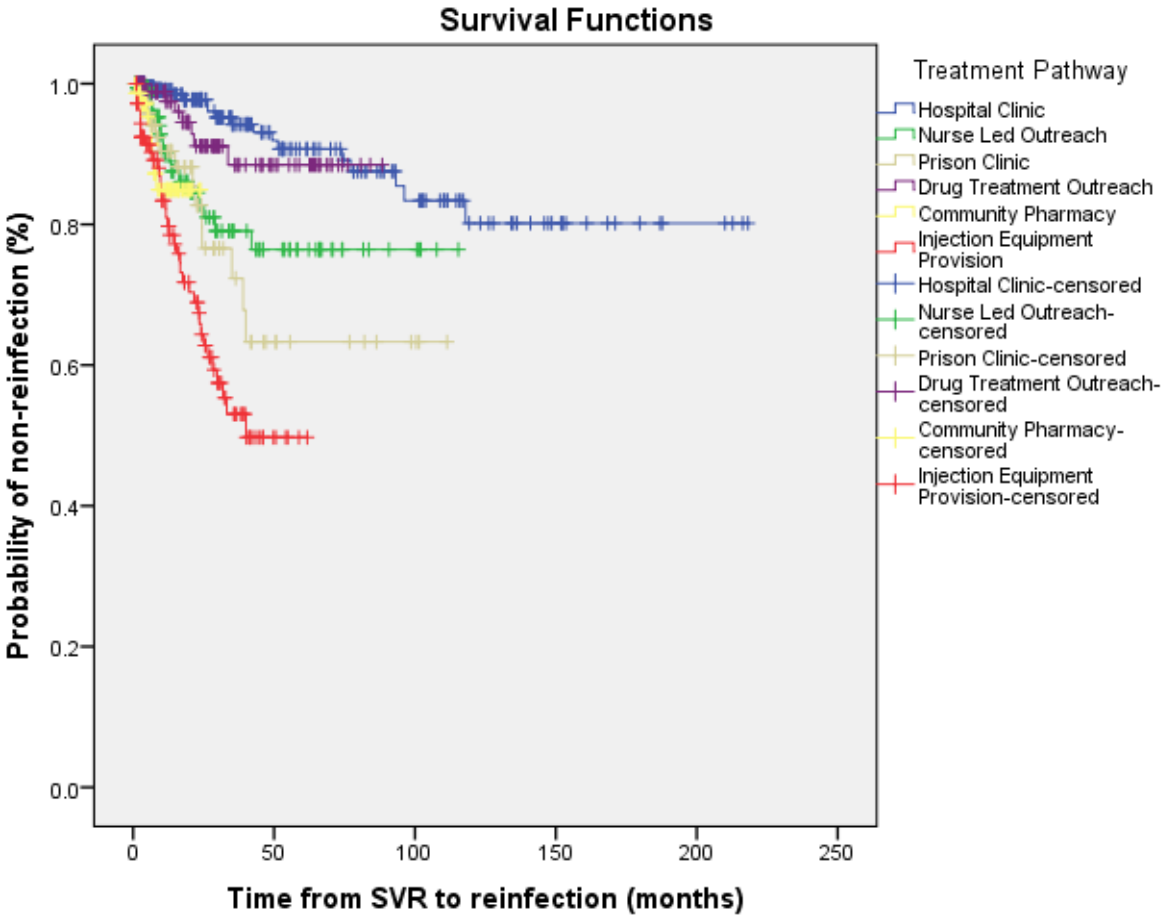

Figure 2. Kaplan Meier survival curve for time from SVR to reinfection per treatment pathway

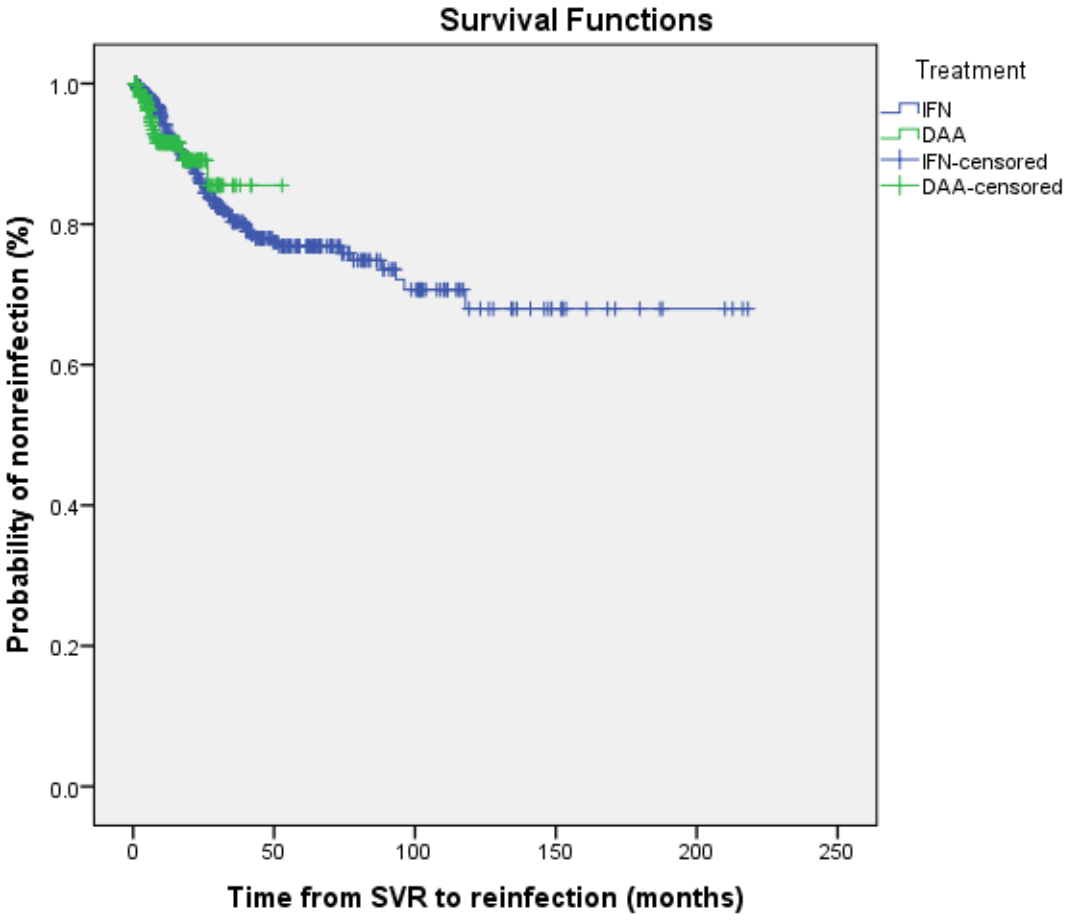

Figure 3. Kaplan Meier survival curve for time from SVR to reinfection per treatment regimen

Table 1. Total number of treatment episodes per treatment pathway with reinfections in parentheses, and percentage of IFN vs DAA treatment episodes

Treatment Pathway	IFN treatment (%)	DAA treatment (%)	Total no. of treatment episodes (reinfections)
Hospital outpatient clinic	233 (65.8%)	121 (34.2%)	354 (16)
Drug treatment outreach	63 (58.9%)	44 (41.1%)	107 (8)
Nurse led outreach	114 (65.5%)	60 (34.5%)	174 (17)
Prison clinic	61 (63.5%)	35 (36.5%)	96 (14)
Community pharmacy	0 (0%)	75 (100%)	75 (8)
Injection equipment provision site	82 (75.0%)	28 (25.0%)	110 (37)

Table 2. Incidence of reinfection per treatment pathway

Treatment Pathway	Reinfection rate per 100 PYs (95%CI)
Hospital outpatient clinic	1.81 (1.11- 2.93)
Drug treatment outreach	3.13 (1.58- 6.18)
Nurse led outreach	6.39 (4.03- 10.12)
Prison clinic	8.14 (4.93- 13.45)
Community pharmacy	12.12 (6.33- 23.21)
Injection equipment provision site	19.89 (14.91- 26.54)