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HCV Treatment as Prevention in People Who Inject Drugs – testing the evidence

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Abstract

Purpose of Review—The majority of HCV infections in UK and many developing countries were acquired through injecting. New clinical guidance suggests that HCV treatment should be offered to people with a transmission risk – such as people who inject drugs (PWID) – irrespective of severity of liver disease. We consider the strength of the evidence base and potential problems in evaluating HCV treatment as prevention among PWID.

Recent Findings—There is good theoretical evidence from dynamic models that HCV treatment for PWID could reduce HCV chronic prevalence and incidence among PWID. Economic evaluations from high-income settings have suggested HCV treatment for PWID is cost-effective, and that in many settings HCV treatment of PWID could be more cost-effective than treating those at an equivalent stage with no ongoing transmission risk. Epidemiological studies of older interferon treatments have suggested that PWID can achieve similar treatment outcomes to other patient groups treated for chronic HCV. Impact and cost-effectiveness of HCV treatment is driven by the potential "prevention benefit" of treating PWID. Model projections suggest that more future infections, End Stage Liver Disease, and HCV related deaths will be averted than lost through re-infection of PWID treated successfully for HCV.

However, there is to date no empirical evidence from trials or observational studies that test the model projections and "prevention benefit" hypothesis. In part this also is because of uncertainty in the evidence base but also because PWID HCV treatment rates historically in most sites have been low, and any scale-up and switch to the new DAA has not yet occurred. There are a number of key uncertainties in the data available on PWID that need to be improved and addressed in order to evaluate treatment as prevention. These include estimates of the prevalence of PWID, measurements of HCV chronic prevalence and incidence among PWID, and how to interpret re-infection rates as potential outcome measures.

Conflicts of Interest: MH and NKM has received research grants from Gilead unrelated to this work and has received honoraria from AbbVie, Gilead, and Jannsen. SH has received consultancy fees from Abbvie, Gilead, Janssen, MSD, Roche, and research grants from Janssen.

Summary—Eliminating HCV through scaling up treatment is a theoretical possibility. But empirical data are required to demonstrate that HCV treatment can reduce HCV transmission which will require an improved evidence base and analytic framework for measuring PWID and HCV prevalence.

Keywords

HCV; injecting drug use; treatment; prevention; evaluation

Introduction

In the UK, as in many developed country settings, over 80% of HCV infection was acquired through injecting drug use(1, 2). The prevalence of HCV among PWID is generally high but heterogeneous, ranging from 20 to 80% in individual countries and sites (3). There is growing evidence that traditional primary prevention such as opiate substitution treatment (OST) and needle and syringe programmes (NSP) can reduce HCV transmission(4-6). For example, recent evidence from Vancouver, Canada (7), Australia (8) and San Francisco in the USA,(9) report that OST can reduce the risk of HCV transmission by 50-80%.

However, epidemiological models and observational data (which report persistently high levels of HCV among PWID despite high intervention coverage) suggest that these interventions are unlikely to achieve substantial reductions in HCV transmission and prevalence among PWID. A recent analysis of the Amsterdam IDU cohort(7) suggested a large proportion of the decline in HIV and HCV may have been due to factors other than the scale of harm reduction, and a modelling study in the UK suggested that further harm reduction scale-up may only achieve modest reductions in prevalence and require several decades (8). Therefore, there is considerable interest in the role of HCV treatment as prevention to enhance other primary interventions and drive HCV transmission and HCV chronic prevalence to negligible levels (i.e. towards elimination). The availability of new highly effective, tolerable, short-course interferon free direct acting antiviral therapies (IFN-free DAAs) (9-13) has added further optimism that HCV treatment could be used for prevention(14) as well as reduce morbidity from liver disease(15).

The prime purpose of HCV treatment is viral clearance from the individual patient which reduces the risk of progression to more severe liver disease and premature HCV related mortality. International guidelines in 2014 recommended treatment prioritisation for moderate to severe liver disease stages (F2-F4) due to the individual's immediate risk of liver disease progression(16). Updated 2015 European guidelines now also recommend providing treatment for people at risk of transmission – such as PWID – irrespective of fibrosis stage(17). Guidelines in the US similarly recommend treatment for people at risk of transmission, but do not specify their ‘priority ranking’, in contrast to other groups which are assigned the ‘highest priority’ (such as F3-F4) and ‘high priority’ (such as F2)(18).

We consider the evidence for HCV treatment as prevention among PWID, including issues of cost-effectiveness and prioritization, and discuss what needs to be addressed in evaluating HCV treatment as prevention in PWID populations.

Empirical evidence vs. modelling evidence

We are unaware of any trials or other evaluation studies that have tested whether HCV treatment can reduce HCV chronic prevalence and transmission in PWID populations. The evidence for the potential of HCV treatment among PWID derives from theoretical modelling studies(19-32), largely assessing the impact of older interferon based treatments and mostly in high-income settings. Modelling studies projecting the impact of HCV treatment among PWID require the use of dynamic transmission models which mechanistically model transmission such that changes in prevalence (for example through scale-up of treatment) are linked to an individual's risk of acquiring infection, and therefore incidence. These models therefore account for both the risk of re-infection and the reduction of HCV risk through averting future/secondary infections(33). These dynamic modelling studies have shown that modest levels of treatment with both traditional interferon based treatments (with lower cure rates), as well as new DAAs, could be effective and reduce HCV chronic prevalence among PWID in most settings – especially when chronic HCV is 40% or below in the PWID population (31) (32). For example, substantial reductions in HCV chronic prevalence among PWID have been projected in UK and France in the future by switching to DAAs and scaling-up to treatment rates achieved in some sites (34) (21).

There is a prevention benefit to HCV treatment if more PWID have avoided HCV infection than became re-infected, and if more health benefit is gained (in terms of reducing End Stage Liver Disease and HCV related deaths) through reducing HCV transmission than are lost through people becoming re-infected. The cost-effectiveness of treating PWID is driven by the prevention benefit as shown with interferon (35) and in a study of the prioritisation of new DAA treatments(36). Without the dynamic element estimating the “prevention benefit” then the cost-effectiveness of HCV treatment and its prioritisation is determined by disease severity(37) with people with severe or moderate disease treated preferentially over people with mild disease.

The key empirical evidence required to underpin these models is to show that HCV treatment for those at risk reduces HCV transmission. However, no epidemiological evidence has yet emerged linking HCV treatment to changes in HCV incidence or prevalence in PWID. One reason for the lack of epidemiological evidence is that studies of HCV treatment rates among PWID estimate that treatment rates tend to be too low to reduce the incidence of End Stage Liver Disease (ESLD) and HCV related mortality - let alone to reduce HCV transmission in key populations such as PWID(2, 38, 39).

Alternative outcomes: SVR and Re-infection rates

The issue of how to best assess impact/measure treatment as prevention outcome (i.e. HCV prevalence and incidence in PWID in the community) remains unresolved. Several alternative outcomes have been proposed to infer treatment as prevention impact.

Trials of the effectiveness of HCV treatment report sustained viral response (SVR) as the outcome. First and second phase clinical trials tend to exclude PWID. There is good evidence that SVR outcomes in PWID, especially if patients are in opiate substitution therapy (OST), are similar to clinical trials (40, 41), and new evidence no doubt will emerge

showing that PWID also can achieve high rates of SVR when treated with new DAAs. For example, some new clinical trials are investigating treatment of PWID on OST. Modelling evidence also has shown that HCV treatment with IFN/RBV is effective and cost-effective even if SVR rates are lower than for other patient groups (because of the potential prevention benefit)(35, 42). Recent modelling work has indicated that early DAA treatment at a moderate stage for PWID is cost-effective in the UK, and treatment at a mild stage for PWID is cost-effective and should be prioritized in settings with chronic prevalence <60% due to primary prevention benefits. However, no studies have looked at the cost-effectiveness of HCV treatment for PWID in low or middle income country settings, and existing studies are not based on real-world DAA SVR outcomes among PWID. Nonetheless, measuring SVR is not an indication alone of the impact of HCV treatment on HCV transmission risk.

Fewer studies have measured HCV re-infection rates which in some cases have been reported as low (<5% per year) (40, 43) which over time could be a cause for concern(44). In model projections re-infection rates are assumed to be similar to primary infection rates (and depending on level of injecting risk and exposure to other interventions such as OST and high coverage NSP). No empirical studies (or modelling studies) have yet compared re-infection rates in PWID with community HCV incidence in order to determine under what circumstances re-infection rates can be used as proxy measures/ unbiased estimates of the impact of HCV treatment on transmission rates in the population.

The HIV analogy

The problem of evaluating effectiveness of public health interventions has been recurrent in the field of HIV for some years. The discussion started with the need to assess the impact of initiatives to change sexual behaviours in developing countries (e.g. see (45)) and the debate has more recently extended to the consideration of ART as prevention, namely as a means of reducing transmission and eventually eliminating HIV(46). Evidence from the HIV Prevention Trial Network 052 (HPTN 052) trial (47, 48) on the ability of ART to substantially reduce HIV transmission in stable HIV serodiscordant couples, has stimulated the development of models (see (49) for a review) suggesting a variety of benefits at population level from an expanded ART programme, including elimination of HIV within a short time scale. The modelling led to several treatment as prevention trials at the community level- including interventions in Botswana and the POPART intervention (50) in Zambia and South Africa(51). POPART involves a combination of increased HIV screening, immediate ART (irrespective of baseline CD4-count) and other primary interventions (such as male circumcision, providing condoms and early treatment of other STI). The trial is currently being carried out in 21 study clusters with the main outcome, HIV incidence, measured over the study period on a population cohort of 2,500 individuals randomly selected from each clusters (52). However, such interventions concern a generalised epidemic in developing countries and although, modelling results suggest that early treatment of HIV in PWID would reduce transmission (53), no analogous evaluation project among PWID is being undertaken. Ecological correlations have been reported between community measures of HIV viral load and HIV incidence in Vancouver and interpreted as evidence that ART could decrease HIV transmission amongst PWID(54). However,

concurrent decreases in HCV incidence suggest that injecting risk may have also decreased, which could represent a further explanation, other than the scale-up of ART, for the decrease in HIV incidence).

There are important distinctions also between HIV and HCV treatment as prevention. HCV treatment has the distinct advantage over HIV treatment that duration of treatment is short and highly efficacious. However, unlike in the HIV generalised epidemic in Africa, HCV transmission in developed countries is mainly driven by the risk in PWID and treatment as prevention outcomes among this hidden population maybe more difficult to measure.

PWID prevalence (and HCV treatment rates)

The size of the PWID population constitutes a critical ingredient for "treatment as prevention" trials as the estimation of the number of PWID with chronic HCV and number of HCV treatments required to reduce HCV transmission to specific levels depends on its knowledge. Sample size calculations and preparatory evaluation work need to characterise the population at risk – which is no easy task as highlighted by Global Burden of Disease estimates of injecting/drug related harm(55, 56).

The PWID population is a "mixture population" of people at risk of acquiring and transmitting infection, encompassing people who currently inject, and people who are in treatment or prison or have recently ceased injecting and are at high risk of relapse. The burden of HCV among PWID in prison and opportunities for prevention is considered in more detail elsewhere (57) (58). Existing PWID prevalence estimates rarely capture the whole population at risk. These estimates typically refer to active injectors (often defined as injected within the last month or 6 months) and exclude those who have temporarily ceased injecting, leading to a potential underestimation. Available estimates are also notoriously uncertain (34, 59), often depending on the methodology used to derive them. PWID estimates for many countries and cities in Europe and elsewhere are out of date, missing, or inconsistent. For instance, in Scotland the estimated number of currently active PWID for has varied from 19,000 to 27,000 (60); and the number of PWID in England varies from 130,000 to 200,000 (1, 61, 62).

Chronic HCV prevalence and incidence

The incidence and prevalence of HCV among PWID, a key outcome in any treatment as prevention trial, also is a composite measure – from PWID in and out of specialist drug treatment, in regular or infrequent contact with needle and syringe programmes (NSP), in and out of stable accommodation and in and out of prison. Routine voluntary HCV testing and public health surveillance systems necessarily only cover very specific subgroups that provide a multiplicity of pieces of information which if simply aggregated together are unlikely to provide an unbiased estimate of HCV transmission(62). Community surveys of PWID, even those recruited through novel recruitment techniques also have been shown to be potentially biased, especially if sampling only a small proportion of the total PWID population (63). In these circumstances, linking and combining the various sources of data while accounting for the biases can be a viable way of producing meaningful estimates. An example of the type of linkage and data synthesis is the recent work conducted in Scotland

where combining data from the Scottish drugs misuse database; the HCV diagnoses register (64); the NESI needle exchange surveillance scheme (65); and a capture-recapture study on a recently infected population (66), it has been possible, through a Bayesian evidence synthesis, to derive estimates of HCV (antibody) prevalence in PWID by age-group, gender in Greater Glasgow & Clyde and the Rest of Scotland(67). A similar exercise may need to be undertaken in small geographical areas to generate the outcome measures for an evaluation of HCV treatment as prevention.

Heterogeneity and Treatment Uptake

It is known that there are heterogeneities in injecting and transmission risk and treatment uptake among PWID. High risk PWID may be more likely to transmit HCV and less likely to enter HCV treatment than low risk PWID. So as treatment is scaled-up will the intervention effect be compromised / reduced by selection bias?

Some models and future trials have considered the impact of delivering treatment through PWID networks in order potentially to maximize treatment as prevention benefits and reduce the number of treatments required to generate an effect (27, 29, 30). These modelling exercises suggest that a “treat your friends” strategy i.e. treating contacts of an infected case could have a greater impact than treating PWID randomly. Further, other modelling analyses assessing whether there is differential impact if HCV treatments are targeted to low or high risk or only to those on OST have generated inconsistent findings (22, 28, 31, 68) due to assumptions surrounding movement between high and low risk states– with some studies concluding that low risk PWID should be targeted in settings where chronic HCV prevalence may be high (28, 31), a further study suggesting that high risk PWID should be targeted (24), and others concluding that if there is movement between high and low risk then targeting is unlikely to make a difference on impact (68).

Part of the problem and difficulty in determining optimal treatment targeting is because of uncertainty over the life course trajectory of injecting (such as the duration of injecting drug use until final cessation, timings of periods in and out of injection, and the time that PWID may stay in or out of a high risk period). Opiate/ PWID cohort studies emphasise opiate dependence is a chronic relapsing problem – whereas information derived from ex-PWID and population surveys suggest that illicit drug use has high rates of remission (supporting an hypothesis that that people “mature” out of drug use)(22, 68-75). One modelling study suggests that HCV treatment will have a greater prevention impact in PWID populations with prolonged durations of injecting – whereas other primary prevention (OST and NSP) strategies are likely to have a greater impact in PWID populations with shorter average injecting durations(42). HCV treatment also may act synergistically with OST and NSP, which if increased or decreased over time could either enhance or reduce the impact of HCV treatment on HCV transmission outcomes(42).

No evaluation of HCV treatment as prevention will be able to resolve uncertainties over the natural history of opiate dependence and injecting drug use – but it will be important that studies follow-up PWID treated for HCV and seek to characterise the PWID population in which the intervention and outcomes are being measured. Moreover, whether HCV

treatment is targeted or delivered through PWID networks, the ultimate arbiter and key outcome will remain HCV prevalence and incidence among PWID.

Conclusions

There is good theoretical evidence from dynamic models that HCV treatment could reduce HCV transmission among PWID – in support of the recent change in clinical recommendations that HCV treatment should be provided to PWID irrespective of severity of liver disease. It is likely also that in high-income settings such as the UK and USA, HCV treatment of PWID is cost-effective and could be more cost-effective than treating other patient groups at the same HCV disease stage who do not have an ongoing transmission risk. The impact and cost-effectiveness of HVC treatment for PWID is driven by the potential "prevention benefit" of treating PWID. However, there is no direct empirical evidence from trials or observational studies that test the model projections and "prevention benefit" hypothesis. In part this is because of uncertainty in the evidence base but also because PWID HCV treatment rates historically in most sites have been low, and any scale-up and switch to the new DAA has not yet occurred.

This means there is a window of opportunity to conduct evaluations of HCV treatment as prevention – as is being undertaken in the HIV field. However, there will be a need (and an opportunity) also to resolve some of the underlying and prevailing issues surrounding measuring the prevalence of PWID and obtaining unbiased estimates of the prevalence and incidence of HCV among PWID in order to test and provide the empirical evidence for HCV treatment as prevention.

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Key points

- Scaling up HCV treatment is an essential component to prevention of HCV transmission among people who inject drugs (PWID).
- There is strong theoretical evidence from modelling studies that treating PWID will be effective and cost-effective in reducing HCV transmission.
- However, there is an absence of any direct evidence from epidemiological studies or trials in support of the “HCV treatment as prevention” hypothesis.
- Future evaluations will need to resolve some problems with measuring outcomes in PWID populations.