Review article

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Published in:
Alimentary Pharmacology & Therapeutics

DOI:
10.1111/apt.13673

Publication date:
2016

Document Version
Peer reviewed version

Alimentary Pharmacology & Therapeutics

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Journal:	*Alimentary Pharmacology & Therapeutics*
Manuscript ID	APT-0137-2016.R2
Wiley - Manuscript type:	Review Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Leask, Jamie; Ninewells Hospital, school of Medicine Dillon, John; Ninewells Hospital, school of Medicine
Keywords:	Hepatitis C < Hepatology, Liver < Organ-based, Statistics < Topics, Screening < Topics, Health economics < Topics

Review Article

Treatment as Prevention: Targeting People who inject Drugs as a Pathway towards Hepatitis C Eradication

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Keywords: Hepatitis C, PWID, treatment as prevention, eradication

Running title: HCV Treatment as prevention

Summary

Background

Hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide. HCV predominates in people who inject drugs (PWID); a group in whom antiviral therapy has previously been withheld on the basis of chaotic life style and associated risks of reinfection. New research has emerged which suggests that by specifically targeting HCV-infected PWID for treatment, the pool of HCV would deplete, thus reducing overall transmission and eventually leading to HCV eradication.

Aim

To outline the requirements for HCV eradication and review the evidence that this is achievable.

Methods

Expert review of the literature.

Results

The achievement of HCV eradication using 'treatment as prevention' is supported by numerous epidemiological modelling studies employing a variety of models in several contexts including PWID, men who have sex with men (MSM) and prisoners. More recent studies also incorporate the newer, more efficacious direct-acting antiviral (DAA) drugs. These drugs have been shown to be safe and effective in PWID in clinical trials. There is no empirical evidence of the impact of treatment as prevention strategies on population prevalence.

Conclusions

This review highlights the efforts to control HCV and evaluates the possibilities of achieving eradication of HCV. Currently, the technologies required to achieve HCV eradication exist, but the infrastructure to deliver them is not generally available or of insufficient scale outside of specific areas. Such areas are yet to demonstrate that elimination is possible but results of studies in these areas are awaited. Such a demonstration would be proof of principle for eradication. Although we are aspiring towards HCV eradication, elimination is the more realistic prospect.

Introduction

Hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide, conferring substantial morbidity and mortality to those infected. Chronically affecting ~3% of the world's population [1], HCV has evolved into a global public health problem. It is estimated that at current treatment rates, HCV will kill 380,000 people worldwide (~13% of those currently infected) by the year 2030; and over one million people by 2060 [2]. However, despite viral hepatitis being responsible for more deaths worldwide than malaria and tuberculosis combined [3], it commands far less international attention.

Clinically, the majority of HCV infections are asymptomatic until late stage disease, often occurring decades after transmission. Liver cirrhosis and hepatocellular carcinoma (HCC) are strongly associated with long-term HCV infection, with the typical interval between HCV exposure and clinical manifestations being around 20-30 years. It is estimated that the prevalence of liver cirrhosis in untreated patients with chronic HCV will increase from 25% in 2010, to 45% in 2030 [4]. HCV-related liver cirrhosis remains the main indication for liver transplantation in developed countries [5, 6, 7]. Chronic HCV infection is also associated with various extra-hepatic manifestations [8].

HCV is a blood borne virus, being absent from most bodily fluids unless they also contain blood. Iatrogenic exposure remains a significant mode of transmission in many developing countries [9], via blood, blood products and re-use of contaminated medical equipment. Significant strides have been made to minimize this route of transmission in developing health care environments. The majority of new HCV

infections worldwide occur within marginalised societal groups, predominating in people who inject drugs (PWID). Acute HCV infection is often difficult to detect given the stigmatisation of at-risk groups and the generally asymptomatic nature of early infection [10]. Previously, treatment for PWID with HCV was withheld on the basis of chaotic lifestyle and associated risks of re-infection, making attempts at treatment futile. This belief has not been substantiated, with the empirical evidence suggesting good outcomes can be achieved, that PWID's display equal, or even superior, HCV treatment outcomes to non-PWID's [12]. This has led to international guidelines now recommending treatment of HCV amongst these high-risk groups following individualized assessment [11]. Although evidence to support such guidelines is growing it is somewhat limited at present. The change in guideline position being in part driven by ensuring equity of access to treatment for those that need it.

Treatment of HCV is fast changing. The arrival of the first generation of direct-acting antiviral drugs (DAA's) in 2011 changed the landscape of HCV therapeutics, with more efficacious and highly tolerable drugs entering the market [13]. The high cost of these DAA's has led to the rationing of therapy based on the degree of liver fibrosis in many healthcare systems. However, research is emerging suggesting that specifically targeting HCV-infected PWID will deplete the pool of HCV within society for transmission, preventing new infections and giving rise to the concept of 'treatment as prevention'. This could ultimately lead to the eradication of HCV.

Treatment as Prevention in HCV

PWID's represent the most at-risk population for acquiring HCV infection. As such, treatment as a means of prevention should focus on PWIDs. As a group, PWID

retain a high rate of morbidity and mortality irrespective of HCV status. However, with the young ages at which PWID acquire HCV infection, the ever increasing longevity of the general population means that the burden of hepatic and extra-hepatic disease will continue to rise [14]. Targeting those at greatest risk of disease acquisition can lead to broader community benefits and long-term cost-effectiveness. Grebely and Dore reported that in 2007 there were 16 million current PWID worldwide, and a 67% HCV prevalence rate amongst PWID. This equates to around 10 million HCV-infected PWID worldwide, not including the additional reservoir of HCV in former PWID [14]. Given that HCV transmission is driven by PWID, efforts to target active PWID for antiviral therapy are strongly supported [15, 16, 17], on the basis that it may prevent virus transmission.

In support of this approach to HCV eradication, modelling studies by Martin and colleagues have indicated that HCV chronic prevalence could be reduced by treating those at risk of ongoing HCV transmission [18, 19]. A more recent study from the same group reviewed a number of similar theoretical modelling studies, this time in a range of global settings and target populations in the context of DAA therapy [20]. They reported that the high incidence of HCV amongst key populations such as PWID, prisoners and men who have sex with men (MSM) represented an ideal opportunity to curb ongoing HCV transmission. However, the authors recognised the need to test these hypotheses empirically [20]. A number of other mathematical models have attempted to explore the preventative value of treating PWID for HCV. A 2013 model proposed that treating as few as 15 out of 1,000 PWID annually could halve HCV prevalence within 15 years [19]. The model was critically dependent on the HCV prevalence in the PWID population with the number needed to treat rising with

increasing prevalence, so that at 25% prevalence 15 treatments per annum achieved this impact but more than 100 treatments per annum were required if HCV prevalence was over 65%. An earlier model by the same authors predicted that for a PWID population with a baseline chronic HCV prevalence of 20%, treatment rates of 5, 10, 20 or 40 per 1,000 PWID annually for 10 years can result in a reduction in prevalence of 15%, 30%, 62% and 72%, respectively [18].

Another 2013 study by Martin and colleagues hypothesised that when antiviral treatment is combined with opiate substitution therapy (OST) and high-coverage needle and syringe programs (HCNSP), significant reductions in HCV could be achieved. Using a HCV transmission model, they estimated that chronic HCV prevalence could be reduced by >50% over a ten-year period. With the newer DAA's, the authors propose that such a target becomes even more attainable [21].

The approach of treatment as prevention carries with it several ethical challenges. Whereas vaccination can be applied universally, curing through drug therapy requires the identification of target populations. Medical screening on such a large scale poses ethical dilemmas. As recently discussed by Hagan *et al* [21], a false positive result can be burdensome on those labelled with such a stigmatizing disease. In addition to being psychologically straining for the patient, it can also lead to unnecessary treatment and resource wastage. Conversely, false negative results only serve to propagate disease transmission as patients are unaware of their true status. Even a true positive result can impose societal repercussions as family relationships, employment opportunities and insurance status are all affected. In a HCV context these concerns are minimized by the high accuracy of the diagnostic

tests and confirmatory lab practices. The authors also mention incentivisation schemes in an effort to combat poor compliance to screening. The follow-on from testing and diagnosis is treatment, with the inconvenience of taking medications and risk of side effects. In conventional treatment pathways the decision for treatment is taken largely by the patient for their individual benefit. However, in the treatment as prevention concept the benefit of treatment is much less for the patient but for society as a whole. Any societal benefit depends on a very high level of uptake, so an individuals' priorities around treatment could be subverted to those of society, with a degree of coercion. However, a balance must be struck between voluntary participation and coercion [22].

Eradication – Can It Be Achieved?

In 2014, *The Lancet* Commission on addressing liver disease in the UK projected that with the advent of these new highly effective IFN-free therapies, chronic HCV infections could be eradicated in the UK by 2030 [23]. It would seem that not only have these new antiviral treatments changed the therapeutic landscape, but they have also altered the horizon for the future of HCV.

The concepts of 'control', 'elimination' and 'eradication' have long been the subject of numerous debates. Writing for the World Health Organisation in 1998, Dowdle proposed the definition of 'control' as being a reduction in disease incidence, prevalence, morbidity or mortality to a locally acceptable level; 'elimination' as a reduction to zero of the incidence of a specified disease in a defined geographical area; and 'eradication' as a permanent reduction to zero of the worldwide incidence of an infection such that interventions are no longer required. To this list, he added

'extinction', defined as being an infectious agent that no longer exists in nature or laboratory conditions [24].

Dowdle went on to describe the three principal indicators of eradicability. Firstly, an intervention must exist to interrupt transmission of the infectious agent. Secondly, diagnostic tools of sufficient sensitivity and specificity must be universally accessible to detect transmissible levels of infection. Lastly, humans must be essential to the life cycle of the infectious agent, with no *ex vivo* amplification [24]. In the context of HCV, the terms 'eradication' and 'elimination' are often used interchangeably, despite regional or national elimination being a more realistic prospect for HCV in the medium term. Regardless, the elimination and eradication of disease, both of which evolve from the concept of control, remain the ultimate goals of public health. To date, only one disease has been successfully eradicated on a global scale; smallpox was declared eradicated in 1980. Polio is now only endemic in a few countries and efforts are ongoing to eradicate it entirely. In both cases, eradication efforts centered on prevention through vaccination and containment. When Dowdle's principles are applied to HCV the evidence generates much hope, but some remaining challenges, to achieve elimination.

HCV Life Cycle and Humans

HCV is exclusively a human pathogen, with very few species capable of being infected even in experimental conditions and no meaningful zoonotic reservoir to infect human hosts [13] or facilitate amplification. So we can regard HCV as having an exclusively human host for it's life cycle and fore filling the first of Dowdle's principles [24].

Diagnostic Tools

The diagnosis of HCV depends on antibody testing and confirmation of active disease by viral nucleic acid detection, usually by a PCR-based test for HCV viral RNA. Both of these tests are widely available as commercial assays validated against international standards. They exist as conventional blood sample-based laboratory analyzed tests, as well as dried blood spot (DBS)-based tests and tests based on analysis of other bodily fluids. Additionally, they can be sent away and batch tested or tested in real time at the point of care; these have been reviewed elsewhere [25]. So the technology to provide accurate diagnosis is widely available. The only remaining challenge is to use it in the most effective way to increase the diagnosis rate and convert this to entry into treatment and cure of HCV. The current failure of diagnosis is evidenced when one considers that 50-70% of those with chronic HCV in the US are unaware of their HCV status [26, 27]. The introduction of sensitive and specific point-of-care testing kits in community settings accessed by at-risk groups would provide healthcare professionals with the tools to rapidly determine HCV status. Many of the available testing kits circumvent the need for venipuncture to be performed. This is advantageous given that PWID generally have poor venous access. The use of such testing would enable case-finding in certain higher prevalence settings. The benefits of point-of-care testing, i.e. result available within thirty minutes as compared to a similar sample being sent to a remote laboratory and available in a few days, are yet to be proven. The most important issue is how diagnosis leads to treatment and cure. The pathway to treatment and cure is going to be one of multiple visits to the point of care or other sites; and the

value of an instant test result as opposed to returning at a later date for said result must be weighed in the context of entry to treatment, which is yet to be evaluated.

Given that over half of PWID in the UK and USA are unaware of their true HCV status [26, 27], testing at-risk populations to raise the number of people being treated for HCV is vital to have any chance of achieving HCV elimination. Previous UK studies evaluating the option of DBS testing within specialist addiction services and prisons found that HCV testing increased almost six-fold [28, 29]. A recent U.S study reported that in IVDU clinics that offer comprehensive screening and assessment for blood borne viruses, diagnostic rates of HCV soar in PWID populations [30]. A 2015 systematic review supports these findings, reporting that the availability of DBS testing appears to increase the uptake of HCV testing in high-risk populations [25].

Hence, DBS is clearly a vital tool in the efforts to increase HCV case-finding amongst PWID. DBS has been proven to be suitable for large-scale screening programs and therapeutic monitoring. As such, it can be employed to increase access to care [30].

A recent cost-utility analysis utilizing a dynamic mathematical model showed that increasing HCV case-finding in addiction services can be cost-effective. However, this does not translate directly to prison settings. Cost-effectiveness of case-finding here depends on continuity of care following release [31]. It has been argued that the U.S criminal justice system represents an ideal focus for HCV case-finding and treatment, given the high volume of HCV-infected individuals currently in contact with correctional facilities [32]. However, some may argue that the way correctional facilities operate would worsen treatment outcomes due to high rates of re-infection, secondary to unacknowledged institutional high risk drug use. Additionally routes of

reimbursement for treatment costs may make it impossible to establish treatment programs in prisons in many countries.

A 2015 Canadian study evaluated the health and economic benefits conferred by incorporating a one-time screening strategy for HCV in various populations. Using a state-transition model, they proposed that a one-time screening program for pre-selected age groups would likely be cost-effective as asymptomatic cases of HCV would be detected. They calculated that this approach could prevent at least 9 HCV-related deaths per 100,000 persons screened over the lifetime of the cohort analysed [33].

So the diagnostic technology to diagnose HCV is reliable, cost-effective and widely available. The evidence base for modes of delivery of testing is substantial and this is being translated into effective detection programs in some countries with France and Australia reporting approximately 80% of their prevalent HCV populations having been diagnosed [34]. So widespread diagnosis of prevalent HCV infection is possible and has already been achieved in some countries.

Interruption of Transmission

There are multiple potential routes at which we could interrupt transmission of HCV, including primary prevention of infection and therapy to prevent further transmission.

In primary prevention of HCV, clean needles and syringes are the mainstay but developments in vaccination offer some hope for the future. In HCV therapy, treatment as prevention is dependent not just on the efficacy of the therapy but also on its effective delivery.

1. Primary prevention of infection.

The main driver for new HCV infection is the injection of drugs with contaminated needles and other injecting paraphernalia [35]. Therefore, the provision of clean needles and other injecting equipment, along with access to opiate replacement therapy (for opiate users), to reduce injecting frequency, should reduce the risk of HCV transmission. It has been estimated that prevalence of HCV in the UK could be up to 60% higher in the absence of OST and HCNSP [36]. Hagan *et al* reported that strategies combining treatment for substance misuse and instruction for safe injecting practices reduced HCV seroconversion by 75%. However, they reported that further research is needed to ascertain what specific interventions are most effective in the different subgroups of PWID [37]. To complement the Hagan study, Turner *et al* estimated that OST and HCNSP reduce HCV transmission by 80% in a UK context [38]. Nonetheless, previous modelling has suggested that OST and HCNSP alone does not prevent incident HCV infections amongst UK PWID [36]. Indeed, such programs have demonstrated higher success rates for HIV prevention compared to HCV [14, 37]. Contributing factors to this are that HCV is ten times more transmissible than HIV, (in the PWID context) and HCV often survives on fomites for prolonged periods of time [39]. Despite this, OST and HCNSP offer other benefits such as reductions in drug-related deaths and drug-related crime as well as protection from other blood borne infections [21, 40].

HCV eradication will likely not be possible without staunch efforts to limit new infections that are fueling the epidemic. Numerous interventions have evolved over the years that serve to decrease transmission rates. As already alluded to,

community-based outreach and education programs, stemming from the HIV epidemic in the 1980's, proved beneficial in reducing the prevalence of blood borne viruses within local populations. Access to free sterile injecting equipment further contributed to reductions in HIV and HCV transmission. Although HCV remains very high amongst PWID, the introduction of anti-HIV interventions had a profound impact on HCV prevalence [14]. However, such effective public health interventions are scarce, even in many developed countries. Even where they exist, funding is poor. Edlin and Winkelstein argue that community interventions must be scaled-up if HCV transmission is to be reduced [39]. In a review on the feasibility of HCV eradication in the United States, they comment that needle and syringe programs only operate in 166 U.S cities, with 20 states not running any such programs at all. They also argue that pharmacies are critical in providing sterile needles as they would reach all populations, not just a fraction of PWID as it currently stands [39]. Current U.S legislation in many states restricts access to sterile needles and syringes for illicit drug-use. This reflects a need for policy change in a concerted effort to stem the tide of HCV. Recent changes to Californian legislation gave more power to local health jurisdictions, with some cities choosing to legalise non-prescription syringe sales in pharmacies. A 2015 analysis demonstrated that where it was legal, more syringes were obtained amongst IVDU populations. Public health policies such as this must be extended to realize the true benefits it would have on HCV transmission in target populations [41]. However, one must take into account the varied transmission profiles now being seen in some developed countries and any public health initiatives for the provision of injecting equipment must ensure it reaches those at risk. Recent trend analysis has revealed an emerging HCV epidemic in the U.S, stemming from chaotic injecting habits and early prescription opioid abuse. Socioeconomic analysis reveals

the epidemic to be concentrated in non-urban white males, who often have very limited access to sterile injecting equipment and injecting advice from experienced IVDU [42] as this is occurring in areas without previous significant injecting drug use. Different patterns of drug abuse may change the benefits of the treatment as prevention approach.

Although needle-sharing is a major aspect of HCV transmission, other injection paraphernalia have been strongly implicated in the spread of the virus. For example, the sharing of cookers, filtration cotton and water can also permit viral transmission [43]. An earlier study calculated that 54% of HCV infections in PWID who did not share needles could be attributed to other injecting equipment [44]. The provision of sterile paraphernalia in Scotland is anticipated to reduce HCV transmission amongst PWID, but results from this natural experiment are awaited [43]. However, earlier studies evaluating the risks of HCV transmission amongst PWID who share injecting equipment have failed to quantify the contribution that this route of infection is having on HCV spread [45]. Indeed, one 2014 study concluded that, although injecting risk behaviour is clearly reduced by OST and NSP, comparatively little review-level evidence exists to support such a trend for HCV transmission amongst PWID's [46].

2. Vaccination

In most infectious diseases that have been considered for elimination a vaccine has been available. However, this is not essential as evidenced by the near eradication of the Guinea worm without even drug therapy [47]. Of course vaccine development seems logical. It can be reasonably argued that due to the asymptomatic nature of the virus, and the fact that most people are unaware of their HCV status, vaccination

is perhaps the most effective way of eradicating HCV [10]. A universal vaccine could not only prevent primary HCV infection, but may also prevent re-infection after cure following DAA therapy. This latter use has implications for those with ongoing risk of HCV exposure, such as PWID [48]. It is estimated that even if pricing of DAA's were 1,000-fold lower to benefit low-income nations, the costs of extensive HCV screening and DAA distribution would exceed those of a universal vaccination program [49]. Results from several vaccine trials are eagerly awaited. In one such study, Swadling *et al* describe the development of a highly immunogenic vaccine for HCV. By utilizing the critical role that T cell immunity plays in antiviral control, they report having produced a potent T cell vaccine that prevents chronic infection by incorporating chimpanzee adenoviral and MVA vectors to prime and boost T cell memory. The first efficacy study of ChAd3NSmut/MVA-NSmut in IVDU's has recently started in the U.S (NCT01436357) [50]. However, results from these studies are forthcoming and historically, such T cell vaccines have had more limited efficacy than antibody based vaccines in clinical trials.

3. HCV therapy

HCV antiviral therapy has undergone a revolution, moving very rapidly from IFN-based therapies with cure rates of 40-70% depending on genotype, to the advent of DAA's achieving cure rates in excess of 90% for all genotypes with treatment duration reduced to as little as eight weeks. The development of these newer DAA's has long been impeded by the lack of an effective cell culture system for HCV proliferation [51]. The availability of high-throughput virological assays to characterise the various stages of the HCV replication cycle have enabled the identification of more specific antiviral targets [52, 53]. This development, combined with changes in the

definition of sustained virological response (SVR), has generated the momentum for the rapid change in the field. The European Association for Study of Liver (EASL) describes the endpoint of therapy as undetectable HCV RNA 24 weeks after the end of the treatment course (SVR24), defined as <15 IU/mL [11]. In a long-term follow-up study of HCV-infected patients treated with PEG-IFN-α2a and ribavirin (n = 1,343), a durable SVR24 of 99.1% was retained once achieved [54]. Such data suggests that HCV recurrence is rare in patients who achieve an SVR, and that from a virologic standpoint, such patients can be regarded as cured. The validity of measuring HCV RNA 12 weeks after completion of treatment (SVR12) has been evaluated and approved by regulators in the U.S and Europe, as an equivalent end point [11].

The currently available new DAA's are split into three classes defined by their HCV target protein: the protease inhibitors targeted against the NS3/4a protease; and the NS5a complex inhibitors and polymerase inhibitors, which are directed against the NS5b protein. This latter class can be further divided into nucleotide and non-nucleotide inhibitors. Initial protease inhibitors, and to a lesser extent NS5a inhibitors, are genotype specific. However, newer pan-genotypic DAA's with superior efficacy, lower adverse effect profiles and shorter therapy durations are constantly emerging [13].

Access to treatment has been widened with the advent of these new drugs. Previously, IFN-based therapy was contraindicated in patients with many co-morbidities including decompensated cirrhosis [35]. Thus, with the new DAA's therapy can now be given to patients in whom it may have previously been contraindicated. This also applies to PWID populations, where concerns about adherence to safety

monitoring was considered a relative contraindication to therapy, despite studies showing this was not an issue. Currently, concerns are expressed about how robust the new all-oral regimens are if adherence is suboptimal in patients with more chaotic lifestyles, leaving them at risk of developing viral resistance. Trials of DAA's in PWID to date have shown treatment remains highly effective in this population [55, 56, 57]. The full impact of DAA's will only be appreciated once innovative approaches to engage more HCV-infected individuals into antiviral therapy are practiced.

4. Delivery of HCV therapy- Pathway to Eradication

The delivery of therapy to patients is key to its efficacy. Complex care pathways, based in, or outreaching from secondary or tertiary care, have been developed to deliver IFN-based therapy to patients. Such care pathways focus on managing the side effects of therapy safely. Chaotic unstable patients such as PWID have not made it through these therapy pathways in significant numbers and such patients that do are atypical. The aim of these pathways has been to prevent advanced liver disease by curing HCV infection before cirrhosis develops. So the episode of treatment can be delayed until the patient is considered suitable, by the constraints of the treatment pathway. This is in marked contrast to the situation if treatment as prevention is the aim of therapy, where early therapy at the earliest possible time in the duration of infection would give the optimum outcome. So the pathway to treatment has to be receptive to the patient.

Clinical networks are a much vaunted solution to the problems associated with treatment of HCV. In England they are a very secondary care-based solution to allow patients to be treated at hospitals closer to their locality, but still controlling

availability of drug therapy centrally. In Scotland's HCV action plan, managed care networks were a central plank to achieve the integration of primary and secondary care with third sector providers of health care around patients with or at risk of HCV into a cohesive and seamless treatment pathway. This integration was fundamental to the success of the Scottish action plan, the implementation of this is described and illustrated in the report by Tait *et al* [58]. Thus networks can achieve improvement in care, particularly when working across healthcare boundaries and accessing difficult-to-reach patient populations. However, all key stakeholders in the area need to be a part of the network, working together to an agreed strategic aim. The MCN model is ideally suited to a treatment as prevention strategy.

PWID are a largely stigmatized group who have limited access to conventional health care. Often as a result of homelessness and deprivation, many patients lack a means of communication with conventional healthcare providers. However, they are often in regular contact with other services in a variety of contexts. For example: needle exchange programs in the community which dispense both sterile injecting equipment and advice on safe injecting practices; and pharmacies which administer methadone to those on opiate substitution programs. These points of contact represent an ideal opportunity to target PWID for HCV treatment. Pilot studies show that with the new DAA's, with their reduced need for regular blood monitoring and fewer side-effects, the clinical and para-clinical staff within these facilities such as pharmacists and drug workers are keen and able to take on a lead role in assessment and provision of anti-HCV therapy as part of managed care networks [59]. These managed care networks provide the clinical supervision they need to deliver a protocol-based HCV treatment pathway. The initial SVR rates from such pathways

match clinical trials and are much more inclusive of a broader group of patients from a PWID background, which is vital to a treatment as prevention strategy.

In addition to OST centers (e.g. pharmacies) and NSP facilities, prisons should also be considered as an opportunity to treat. Given the high numbers and proportions of PWID in correctional facilities, prisoners represent an ideal target population for treatment as prevention. As with targeting PWID's in general, targeting prisoners poses its own challenges and ethical considerations. A 2015 letter by Levy and Larney highlighted the issues of treatment as prevention in correctional settings. They argue that the imbalance of power between prisoners and custodial staff may translate to a curtailing of civil liberties [60]. In such circumstances, how can we be sure that consent to screening and treatment is truly voluntary? Adding to this, Martin and colleagues emphasize the need for continuity of care amongst prisoners after release or transfer for this approach to HCV prevention to be cost-effective [61]. A recent review of treatment outcomes in prisoners treated in Scotland has shown a strong negative correlation between liberation during treatment and SVR. This work was using IFN-based therapy and so should be less of an issue with new DAA-based therapy of shorter duration [62]. In terms of primary prevention Levy and Larney also called for greater access to harm reduction services such as needle exchange programs within prisons, arguing that such services exist in community settings for PWID. As such, those who successfully complete treatment can protect themselves from re-infection and thus increase the effectiveness of this HCV eradication strategy [60]. It should be noted, however, that a 2013 study found that in a sample of 5,076 surveyed prisoners in Scotland, the risk of HCV transmission was lower amongst prisoners compared to Scottish people who inject in the community. The authors

propose that this is due to the low incidence of in-prison injecting, although they concede that some under-reporting is likely. As such, the authors suggest that low HCV incidence amongst prison populations does not depend on the introduction of needle exchange programs [63]. The major issue around provision of needle exchange in prisons is the potential for their use as weapons against staff which has led prison officer unions to object on health and safety grounds.

The major criticism of treatment as prevention strategies in PWID is the impact on injecting behaviour and the risk of re-infection. Regarding the interplay between HCV treatment and PWID behaviour, it has been established that antiviral therapy does not increase illicit drug use. Intermittent injecting during treatment has also been shown to have no influence over regimen adherence, completion of treatment, or SVR attainment. Contrary to this, more regular injecting has been associated with lower SVR rates and discontinuation of treatment [14]. In an effort to better understand injecting behaviours and how they relate to re-infection risk post-SVR, Valerio and colleagues conducted an analysis of 1,170 PWID who attained an SVR over a twenty-year period (1992-2012) [64]. They reported that an increasing minority of PWID who attain an SVR are at an elevated risk of re-infection or death as a result of high intensity injecting behaviour. In agreement with EASL recommendations [11], the authors advocate for the on-going monitoring of high-risk patients post-SVR [64]. However, evidence suggests that PWID who achieve an SVR are more likely to pursue a healthy lifestyle [65]. The Valerio study also voiced concern that re-infection rates amongst PWID will rise as HCV treatment is scaled-up [64]. Commentary from Hellard and Scott (2015) postulated that many of the current models measuring the outcomes of HCV treatment as prevention incorporate high levels of re-infection into

their modelling, thus overstating the re-infection risk. Whilst it is established that HCV re-infection is common out-with treatment settings, re-infection after antiviral therapy is considerably lower [66]. A meta-analysis by Aspinall *et al* calculated the pooled risk of re-infection amongst five cohorts of PWID (n = 131) to be 2.4 (CI = 0.9-6.1) per 100 person years [67]. However, a 2016 study reported an 11% re-infection rate in a multicentre trial follow-up of PWID's infected with genotypes 2 or 3 [68]. This highlights possible variations in the range of reinfections. Emergent data from the ERADICATE trial will provide more information on reinfection rates in PWID's undergoing anti-HCV therapy. A more recent study suggested that targeting HCV treatment by stratifying the level of injection drug-use could enhance benefits at the population level [69]. The authors reported that HCV treatment is best determined by its prevalence within the population; when >50% of all exchanged syringes are contaminated with HCV they recommend treating low-risk PWID first. Conversely, below this threshold, treating high-risk PWID first appeared to produce the greatest societal benefits [69]. Indeed, it has been shown that targeting the injecting network provides greater population health benefit than treating PWID randomly for their HCV [70]. Studies such as this support the idea that PWID's should not be excluded from treatment based on their apparently risky behaviour. A further study by Martin and colleagues suggested that treating current injectors is more cost-effective than treating ex- or non-injectors when the chronic HCV prevalence is less than 60% [71].

Eradication – Is It Cost-Effective?

Relative to the expense of long-term complications associated with HCV infection, the price of DAA's is considered cost-effective [22]. The bulk of the health costs and health consequences associated with HCV infection are due to end stage liver

disease late in the natural history of infection. This has led some to suggest that treatment should be restricted to patients with more advanced disease only. As even in high-income nations the cost of DAA's may prohibit their widespread uptake, due to affordability, relative to other demands on health budgets. Cost-effective evaluations are needed to verify how best to allocate resources and services. A 2015 study aimed to forecast population-level outcomes from alternative treatment strategies in a resource-rich setting [72]. Using a simulation model and projecting outcomes to 2030, trends in HCV incidence and severe liver morbidity was extrapolated according to treatment strategies that prioritised either PWID or patients with moderate/advanced liver fibrosis. The authors concluded that no single approach to the treatment of HCV in an era of IFN-free therapies addressed all public health concerns. Prioritising PWID for treatment results in substantially reduced HCV incidence and transmission rates in the population, but fails to address the impact of liver disease. Conversely, suboptimal reductions in HCV incidence occurs when those with moderate/advanced liver disease are targeted for priority treatment. It is projected that by specifically targeting active PWID, incident HCV infection can be reduced to <50 cases per year by 2025 [72]. The conclusion that can be drawn from this paper was that a twin track strategy that targeted active PWID and those with evidence of hepatic fibrosis would be most cost-effective, but would leave the short fall in treatment on those with mild disease who were not injecting, a strategy that may not be acceptable to the general population. These estimates support the previous modelling studies by Martin and colleagues described above. The high cost of anti-HCV therapy makes a more targeted treatment approach more economically beneficial. As such, epidemiological data on PWID populations must be upgraded on a country by country basis to allow a planned strategy [73]. As already

discussed, it is unlikely that substantial reductions in HCV prevalence would be achievable with OST and HCNSP alone. However, expansion of OST and NSP coverage would reduce the number of PWID requiring HCV treatment, and be highly cost-effective thus making a target HCV prevalence reduction easier to achieve [14]. This supports the idea that HCV eradication policy must be built upon scaled-up community outreach projects. While the health economic analysis supports the idea of treatment as prevention, and shows it to be a cost effective, it may not be achievable due to the affordability issues surround such a relatively common disease with such a currently expensive therapy. There is already prioritisation of HCV therapy for patients with advanced fibrosis in many countries, with patients with milder disease waiting for therapy. To further prioritise active PWID over other patients with mild disease may not be acceptable to health care providers and payers.

Conclusion

The growing burden of chronic HCV infection presents a significant public health concern. With the advent of highly efficacious and tolerable DAA's, the concept of treatment as prevention is gaining credence and efforts to scale-up access to treatment have been developed.

Although global eradication of HCV via targeted treatment is highly desirable, current limitations render it improbable at this point in time; with regional elimination being a more realistic prospect. Sub-optimal coverage of harm reduction services worldwide, the lack of an effective vaccine, and the high baseline HCV prevalence in many places makes HCV eradication very difficult to accomplish. Despite this, modelling

studies by Martin and colleagues show that lower treatment uptake is required to achieve a more substantial reduction in HCV prevalence when the baseline prevalence is below a certain threshold. Increased access to harm reduction services may drive the local HCV prevalence low enough to allow targeted treatment to be successful.

Perhaps the most important prevention strategy is the implementation of HCV testing so as to identify those in need of treatment. Solutions must be formulated to overcome barriers to care. In this way, more patients eligible to be treated are identified and managed accordingly. Early identification, using more accurate diagnostic tools, will be essential to prevent the onward transmission of HCV [10].

Although technically feasible, HCV eradication will require a galvanised effort from not only practitioners and healthcare policy makers, but also the patients themselves. To achieve HCV eradication via treatment on a global scale, PWID must be given increased access to affordable treatment. Ensuring affordability of anti-HCV therapy will be critical in the pursuit of eradicability.

Acknowledgements

The guarantor of the article is Prof JF Dillon

Specific author contributions: Mr Leask performed the initial literature searches under Prof Dillon's direction, the review was jointly written by both authors. Both authors approved the final version of the manuscript.

Disclosures

There was no funding for the writing of this review. Prof Dillon has received honoraria for lectures and advisory boards from Janssen, Roche, Merck, Abbvie and Gilead. Prof Dillon's institution has received research support from Janssen, Roche, Merck, Abbvie and Gilead.

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Review Article: Treatment as Prevention – Targeting People who inject Drugs as a Pathway towards Hepatitis C Eradication

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Keywords: Hepatitis C, PWID, treatment as prevention, eradication

Running title: HCV Treatment as prevention

Summary

Background

Hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide. HCV predominates in people who inject drugs; a group in whom antiviral therapy has previously been withheld on the basis of chaotic lifestyles and associated risks of reinfection. New research has emerged which suggests that by specifically targeting HCV-infected people who inject drugs for treatment, the pool of HCV would deplete, thus reducing overall transmission and eventually leading to HCV eradication.

Aim

To outline the requirements for HCV eradication and review the evidence that this is achievable.

Methods

Expert review of the literature.

Results

The achievement of HCV eradication using 'treatment as prevention' is supported by numerous epidemiological modelling studies employing a variety of models in several contexts including people who inject drugs, men who have sex with men and prisoners. More recent studies also incorporate the newer, more efficacious direct-acting antiviral drugs. These drugs have been shown to be safe and effective in people who inject drugs in clinical trials. There is no empirical evidence of the impact of treatment as prevention strategies on population prevalence.

Conclusions

This review highlights the efforts to control HCV and evaluates the possibilities of achieving eradication of HCV. Currently, the technologies required to achieve HCV eradication exist, but the infrastructure to deliver them is not generally available or of insufficient scale outside of specific areas. Such areas are yet to demonstrate that elimination is possible, but results of studies in these areas are awaited. Such a demonstration would be proof of principle for eradication. Although we are aspiring towards HCV eradication, elimination is the more realistic prospect.

Introduction

Hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide, conferring substantial morbidity and mortality to those infected. Chronically affecting ~3% of the world's population [1], HCV has evolved into a global public health problem. It is estimated that at current treatment rates, HCV will kill 380,000 people worldwide (~13% of those currently infected) by the year 2030; and over one million people by 2060 [2]. However, despite viral hepatitis being responsible for more deaths worldwide than malaria and tuberculosis combined [3], it commands far less international attention.

Clinically, the majority of HCV infections are asymptomatic until late stage disease, often occurring decades after transmission. Liver cirrhosis and hepatocellular carcinoma are strongly associated with long-term HCV infection, with the typical interval between HCV exposure and clinical manifestations being around 20-30 years. It is estimated that the prevalence of liver cirrhosis in untreated patients with chronic HCV will increase from 25% in 2010, to 45% in 2030 [4]. HCV-related liver cirrhosis remains the main indication for liver transplantation in developed countries [5, 6, 7]. Chronic HCV infection is also associated with various extra-hepatic manifestations [8].

HCV is a blood borne virus, being absent from most bodily fluids unless they also contain blood. Iatrogenic exposure remains a significant mode of transmission in many developing countries [9], via blood, blood products and re-use of contaminated medical equipment. Significant strides have been made to minimize this route of transmission in developing health care environments. The majority of new HCV

infections worldwide occur within marginalised societal groups, predominating in people who inject drugs. Acute HCV infection is often difficult to detect given the stigmatisation of at-risk groups and the generally asymptomatic nature of early infection [10]. Previously, treatment for HCV-infected people who inject drugs was withheld on the basis of chaotic lifestyles and associated risks of re-infection, which it was believed maked attempts at treatment futile. This belief has not been substantiated, with the empirical evidence suggesting good outcomes can be achieved; that people who inject drugs display equal, or even superior, HCV treatment outcomes to groups from other routes of infection [12]. This has led to international guidelines now recommending treatment of HCV amongst these high-risk groups following individualized assessment [11]. Although evidence to support such guidelines is growing it is somewhat limited at present. The change in guideline position being in part driven by ensuring equity of access to treatment for those that need it.

Treatment of HCV is fast changing. The arrival of the first generation of direct-acting antiviral drugs in 2011 changed the landscape of HCV therapeutics, with more efficacious and highly tolerable drugs entering the market [13]. The high cost of these newer drugs has led to the rationing of therapy based on the degree of liver fibrosis in many healthcare systems. However, research is emerging suggesting that specifically targeting HCV-infected people who inject drugs will deplete the pool of HCV within society for transmission, preventing new infections and giving rise to the concept of 'treatment as prevention'. This could ultimately lead to the eradication of HCV.

Treatment as Prevention in HCV

People who inject drugs represent the most at-risk population for acquiring HCV infection. As such, treatment as a means of prevention should focus on this population group. As a group, people who inject drugs retain a high rate of morbidity and mortality irrespective of HCV status. However, with the young ages at which intravenous drug users acquire HCV infection, the ever increasing longevity of the general population means that the burden of hepatic and extra-hepatic disease will continue to rise [14]. Targeting those at greatest risk of disease acquisition can lead to broader community benefits and long-term cost-effectiveness. Grebely and Dore reported that in 2007 there were 16 million current intravenous drug users worldwide, and a 67% HCV prevalence rate within this group. This equates to around 10 million HCV-infected people who inject drugs worldwide, not including the additional reservoir of HCV in former injection drug users [14]. Given that HCV transmission is driven by people who inject drugs, efforts to target active injectors of drugs for antiviral therapy are strongly supported [15, 16, 17], on the basis that it may prevent virus transmission.

In support of this approach to HCV eradication, modelling studies by Martin and colleagues have indicated that HCV chronic prevalence could be reduced by treating those at risk of ongoing HCV transmission [18, 19]. A more recent study from the same group reviewed a number of similar theoretical modelling studies, this time in a range of global settings and target populations in the context of direct-acting antiviral therapy [20]. They reported that the high incidence of HCV amongst key populations such as people who inject drugs, men who have sex with men and prisoners

represented an ideal opportunity to curb ongoing HCV transmission. However, the authors recognised the need to test these hypotheses empirically [20]. A number of other mathematical models have attempted to explore the preventative value of treating people who inject drugs for HCV. A 2013 model proposed that treating as few as 15 out of 1,000 people who inject drugs annually could halve HCV prevalence within 15 years [19]. The model was critically dependent on the HCV prevalence within this population, with the number needed to treat rising with increasing prevalence; so that at 25% prevalence 15 treatments per annum achieved this impact, but more than 100 treatments per annum were required if HCV prevalence was over 65%. An earlier model by the same authors predicted that for a population of intravenous drug users with a baseline chronic HCV prevalence of 20%, treatment rates of 5, 10, 20 or 40 per 1,000 drug injectors annually for 10 years can result in a reduction in prevalence of 15%, 30%, 62% and 72%, respectively [18].

Another 2013 study by Martin and colleagues hypothesised that when antiviral treatment is combined with opiate substitution therapy and high-coverage needle and syringe programs, significant reductions in HCV could be achieved. Using a HCV transmission model, they estimated that chronic HCV prevalence could be reduced by >50% over a ten-year period. With the newer direct-acting antiviral drugs, the authors propose that such a target becomes even more attainable [21].

The approach of treatment as prevention carries with it several ethical challenges. Whereas vaccination can be applied universally, curing through drug therapy requires the identification of target populations. Medical screening on such a large scale poses ethical dilemmas. As recently discussed by Hagan *et al* [21], a false

positive result can be burdensome on those labelled with such a stigmatizing disease. In addition to being psychologically straining for the patient, it can also lead to unnecessary treatment and resource wastage. Conversely, false negative results only serve to propagate disease transmission as patients are unaware of their true status. Even a true positive result can impose societal repercussions as family relationships, employment opportunities and insurance status are all affected. In a HCV context these concerns are minimized by the high accuracy of the diagnostic tests and confirmatory lab practices. The authors also mention incentivisation schemes in an effort to combat poor compliance to screening. The follow-on from testing and diagnosis is treatment, with the inconvenience of taking medications and risk of side effects. In conventional treatment pathways the decision for treatment is taken largely by the patient for their individual benefit. However, in the treatment as prevention concept the benefit of treatment is much less for the patient but for society as a whole. Any societal benefit depends on a very high level of uptake, so an individuals' priorities around treatment could be subverted to those of society, with a degree of coercion. However, a balance must be struck between voluntary participation and coercion [22].

Eradication – Can It Be Achieved?

In 2014, *The Lancet* Commission on addressing liver disease in the UK projected that with the advent of these new highly effective IFN-free therapies, chronic HCV infections could be eradicated in the UK by 2030 [23]. It would seem that not only have these new antiviral treatments changed the therapeutic landscape, but they have also altered the horizon for the future of HCV.

The concepts of 'control', 'elimination' and 'eradication' have long been the subject of numerous debates. Writing for the World Health Organisation in 1998, Dowdle proposed the definition of 'control' as being a reduction in disease incidence, prevalence, morbidity or mortality to a locally acceptable level; 'elimination' as a reduction to zero of the incidence of a specified disease in a defined geographical area; and 'eradication' as a permanent reduction to zero of the worldwide incidence of an infection such that interventions are no longer required. To this list, he added 'extinction', defined as being an infectious agent that no longer exists in nature or laboratory conditions [24].

Dowdle went on to describe the three principal indicators of eradicability. Firstly, an intervention must exist to interrupt transmission of the infectious agent. Secondly, diagnostic tools of sufficient sensitivity and specificity must be universally accessible to detect transmissible levels of infection. Lastly, humans must be essential to the life cycle of the infectious agent, with no *ex vivo* amplification [24]. In the context of HCV, the terms 'eradication' and 'elimination' are often used interchangeably, despite regional or national elimination being a more realistic prospect for HCV in the medium term. Regardless, the elimination and eradication of disease, both of which evolve from the concept of control, remain the ultimate goals of public health. To date, only one disease has been successfully eradicated on a global scale; smallpox was declared eradicated in 1980. Polio is now only endemic in a few countries and efforts are ongoing to eradicate it entirely. In both cases, eradication efforts centered on prevention through vaccination and containment. When Dowdle's principles are applied to HCV the evidence generates much hope, but some remaining challenges, to achieve elimination.

HCV Life Cycle and Humans

HCV is exclusively a human pathogen, with very few species capable of being infected even in experimental conditions and no meaningful zoonotic reservoir to infect human hosts [13] or facilitate amplification. So we can regard HCV as having an exclusively human host for it's life cycle and fore filling the first of Dowdle's principles [24].

Diagnostic Tools

The diagnosis of HCV depends on antibody testing and confirmation of active disease by viral nucleic acid detection, usually by a PCR-based test for HCV viral RNA. Both of these tests are widely available as commercial assays validated against international standards. They exist as conventional blood sample-based laboratory analyzed tests, as well as dried blood spot-based tests and tests based on analysis of other bodily fluids. Additionally, they can be sent away and batch tested or tested in real time at the point of care; these have been reviewed elsewhere [25]. So the technology to provide accurate diagnosis is widely available. The only remaining challenge is to use it in the most effective way to increase the diagnosis rate and convert this to entry into treatment and cure of HCV. The current failure of diagnosis is evidenced when one considers that 50-70% of those with chronic HCV in the US are unaware of their HCV status [26, 27]. The introduction of sensitive and specific point-of-care testing kits in community settings accessed by at-risk groups would provide healthcare professionals with the tools to rapidly determine HCV status. Many of the available testing kits circumvent the need for venipuncture to be performed. This is advantageous given that people who inject

drugs generally have poor venous access. The use of such testing would enable case-finding in certain higher prevalence settings. The benefits of point-of-care testing, i.e. result available within thirty minutes as compared to a similar sample being sent to a remote laboratory and available in a few days, are yet to be proven. The most important issue is how diagnosis leads to treatment and cure. The pathway to treatment and cure is going to be one of multiple visits to the point of care or other sites; and the value of an instant test result as opposed to returning at a later date for said result must be weighed in the context of entry to treatment, which is yet to be evaluated.

Given that over half of people who inject drugs in the UK and USA are unaware of their true HCV status [26, 27], testing at-risk populations to raise the number of people being treated for HCV is vital to have any chance of achieving HCV elimination. Previous UK studies evaluating the option of dried blood spot testing within specialist addiction services and prisons found that HCV testing increased almost six-fold [28, 29]. A recent U.S study reported that in clinics that offer comprehensive screening and assessment for blood borne viruses, diagnostic rates of HCV soar within these populations [30]. A 2015 systematic review supports these findings, reporting that the availability of dried blood spot testing appears to increase the uptake of HCV testing in high-risk populations [25]. Hence, dried blood spot testing is clearly a vital tool in the efforts to increase HCV case-finding amongst people who inject drugs. Dried blood spot testing has also been proven to be suitable for large-scale screening programs and therapeutic monitoring. As such, it can be employed to increase access to care [30].

A recent cost-utility analysis utilizing a dynamic mathematical model showed that increasing HCV case-finding in addiction services can be cost-effective. However, this does not translate directly to prison settings. Cost-effectiveness of case-finding here depends on continuity of care following release [31]. It has been argued that the U.S criminal justice system represents an ideal focus for HCV case-finding and treatment, given the high volume of HCV-infected individuals currently in contact with correctional facilities [32]. However, some may argue that the way correctional facilities operate would worsen treatment outcomes due to high rates of re-infection, secondary to unacknowledged institutional high risk drug use. Additionally, routes of reimbursement for treatment costs may make it impossible to establish treatment programs in prisons in many countries.

A 2015 Canadian study evaluated the health and economic benefits conferred by incorporating a one-time screening strategy for HCV in various populations. Using a state-transition model, they proposed that a one-time screening program for pre-selected age groups would likely be cost-effective as asymptomatic cases of HCV would be detected. They calculated that this approach could prevent at least 9 HCV-related deaths per 100,000 persons screened over the lifetime of the cohort analysed [33].

So the diagnostic technology to diagnose HCV is reliable, cost-effective and widely available. The evidence base for modes of delivery of testing is substantial and this is being translated into effective detection programs in some countries with France and Australia reporting approximately 80% of their prevalent HCV populations having

been diagnosed [34]. So widespread diagnosis of prevalent HCV infection is possible and has already been achieved in some countries.

Interruption of Transmission

There are multiple potential routes at which we could interrupt transmission of HCV, including primary prevention of infection and therapy to prevent further transmission. In primary prevention of HCV, clean needles and syringes are the mainstay but developments in vaccination offer some hope for the future. In HCV therapy, treatment as prevention is dependent not just on the efficacy of the therapy but also on its effective delivery.

1. Primary prevention of infection.

The main driver for new HCV infection is the injection of drugs with contaminated needles and other injecting paraphernalia [35]. Therefore, the provision of clean needles and other injecting equipment, along with access to opiate replacement therapy (for opiate users), to reduce injecting frequency, should reduce the risk of HCV transmission. It has been estimated that prevalence of HCV in the UK could be up to 60% higher in the absence of opiate substitution therapy and needle and syringe programs [36]. Hagan *et al* reported that strategies combining treatment for substance misuse and instruction for safe injecting practices reduced HCV seroconversion by 75%. However, they reported that further research is needed to ascertain what specific interventions are most effective in the different subgroups of people who inject drugs [37]. To complement the Hagan study, Turner *et al* estimated that opiate substitution therapy and needle and syringe programs reduce HCV transmission by 80% in a UK context [38]. Nonetheless, previous modelling has

suggested that these interventions alone do not prevent incident HCV infections amongst UK people who inject drug [36]. Indeed, such programs have demonstrated higher success rates for HIV prevention compared to HCV [14, 37]. Contributing factors to this are that HCV is ten times more transmissible than HIV (in the context of people who inject drugs) and HCV often survives on fomites for prolonged periods of time [39]. Despite this, opiate substitution therapy and needle and syringe programs offer other benefits such as reductions in drug-related deaths and drug-related crime as well as protection from other blood borne infections [21, 40].

HCV eradication will likely not be possible without staunch efforts to limit new infections that are fueling the epidemic. Numerous interventions have evolved over the years that serve to decrease transmission rates. As already alluded to, community-based outreach and education programs, stemming from the HIV epidemic in the 1980's, proved beneficial in reducing the prevalence of blood borne viruses within local populations. Access to free sterile injecting equipment further contributed to reductions in HIV and HCV transmission. Although HCV remains very high amongst people who inject drugs, the introduction of anti-HIV interventions had a profound impact on HCV prevalence [14]. However, such effective public health interventions are scarce, even in many developed countries. Even where they exist, funding is poor. Edlin and Winkelstein argue that community interventions must be scaled-up if HCV transmission is to be reduced [39]. In a review on the feasibility of HCV eradication in the United States, they comment that needle and syringe programs only operate in 166 U.S cities, with 20 states not running any such programs at all. They also argue that pharmacies are critical in providing sterile needles as they would reach all populations, not just a fraction of people who inject

drugs as it currently stands [39]. Current U.S legislation in many states restricts access to sterile needles and syringes for illicit drug-use. This reflects a need for policy change in a concerted effort to stem the tide of HCV. Recent changes to Californian legislation gave more power to local health jurisdictions, with some cities choosing to legalise non-prescription syringe sales in pharmacies. A 2015 analysis demonstrated that where it was legal, more syringes were obtained amongst intravenous drug user populations. Public health policies such as this must be extended to realize the true benefits it would have on HCV transmission in target populations [41]. However, one must take into account the varied transmission profiles now being seen in some developed countries and any public health initiatives for the provision of injecting equipment must ensure it reaches those at risk. Recent trend analysis has revealed an emerging HCV epidemic in the U.S, stemming from chaotic injecting habits and early prescription opioid abuse. Socioeconomic analysis reveals the epidemic to be concentrated in non-urban white males, who often have very limited access to sterile injecting equipment and injecting advice from experienced users [42] as this is occurring in areas without previous significant injecting drug use. Different patterns of drug abuse may change the benefits of the treatment as prevention approach.

Although needle-sharing is a major aspect of HCV transmission, other injection paraphernalia have been strongly implicated in the spread of the virus. For example, the sharing of cookers, filtration cotton and water can also permit viral transmission [43]. An earlier study calculated that 54% of HCV infections in people who inject drugs who did not share needles could be attributed to other injecting equipment [44]. The provision of sterile paraphernalia in Scotland is anticipated to reduce HCV transmission amongst people who inject drugs, but results from this natural

experiment are awaited [43]. However, earlier studies evaluating the risks of HCV transmission amongst drug users who share injecting equipment have failed to quantify the contribution that this route of infection is having on HCV spread [45].

Indeed, one 2014 study concluded that, although injecting risk behaviour is clearly reduced by opiate substitution therapy and needle and syringe programs, comparatively little review-level evidence exists to support such a trend for HCV transmission amongst people who inject drugs [46].

2. Vaccination

In most infectious diseases that have been considered for elimination a vaccine has been available. However, this is not essential as evidenced by the near eradication of the Guinea worm without even drug therapy [47]. Of course vaccine development seems logical. It can be reasonably argued that due to the asymptomatic nature of the virus, and the fact that most people are unaware of their HCV status, vaccination is perhaps the most effective way of eradicating HCV [10]. A universal vaccine could not only prevent primary HCV infection, but may also prevent re-infection after cure following direct-acting antiviral therapy. This latter use has implications for those with ongoing risk of HCV exposure, such as in people who inject drugs [48]. It is estimated that even if pricing of direct-acting antivirals were 1,000-fold lower to benefit low-income nations, the costs of extensive HCV screening and drug distribution would exceed those of a universal vaccination program [49]. Results from several vaccine trials are eagerly awaited. In one such study, Swadling *et al* describe the development of a highly immunogenic vaccine for HCV. By utilizing the critical role that T cell immunity plays in antiviral control, they report having produced a potent T cell vaccine that prevents chronic infection by incorporating chimpanzee adenoviral

and MVA vectors to prime and boost T cell memory. The first efficacy study of ChAd3NSmut/MVA-NSmut in IVDU's has recently started in the U.S (NCT01436357) [50]. However, results from these studies are forthcoming and historically, such T cell vaccines have had more limited efficacy than antibody-based vaccines in clinical trials.

3. HCV therapy

HCV antiviral therapy has undergone a revolution, moving very rapidly from IFN-based therapies with cure rates of 40-70% depending on genotype, to the advent of direct-acting antivirals achieving cure rates in excess of 90% for all genotypes with treatment duration reduced to as little as eight weeks. The development of these newer antivirals has long been impeded by the lack of an effective cell culture system for HCV proliferation [51]. The availability of high-throughput virological assays to characterise the various stages of the HCV replication cycle have enabled the identification of more specific antiviral targets [52, 53]. This development, combined with changes in the definition of sustained virological response (SVR), has generated the momentum for the rapid change in the field. The European Association for Study of Liver (EASL) describes the endpoint of therapy as undetectable HCV RNA 24 weeks after the end of the treatment course (SVR24), defined as <15 IU/mL [11]. In a long-term follow-up study of HCV-infected patients treated with PEG-IFN-α2a and ribavirin (n = 1,343), a durable SVR24 of 99.1% was retained once achieved [54]. Such data suggests that HCV recurrence is rare in patients who achieve an SVR, and that from a virologic standpoint, such patients can be regarded as cured. The validity of measuring HCV RNA 12 weeks after completion of treatment (SVR12) has been

evaluated and approved by regulators in the U.S and Europe, as an equivalent end point [11].

The currently available direct-acting antivirals are split into three classes defined by their HCV target protein: the protease inhibitors targeted against the NS3/4a protease; and the NS5a complex inhibitors and polymerase inhibitors, which are directed against the NS5b protein. This latter class can be further divided into nucleotide and non-nucleotide inhibitors. Initial protease inhibitors, and to a lesser extent NS5a inhibitors, are genotype specific. However, newer pan-genotypic direct-acting antivirals with superior efficacy, lower adverse effect profiles and shorter therapy durations are constantly emerging [13].

Access to treatment has been widened with the advent of these new drugs. Previously, IFN-based therapy was contraindicated in patients with many co-morbidities including decompensated cirrhosis [35]. Thus, with the newer antivirals therapy can now be given to patients in whom it may have previously been contraindicated. This also applies to populations of people who inject drugs, where concerns about adherence to safety monitoring was considered a relative contraindication to therapy, despite studies showing this was not an issue. Currently, concerns are expressed about how robust the new all-oral regimens are if adherence is suboptimal in patients with more chaotic lifestyles, leaving them at risk of developing viral resistance. To date, trials of direct-acting antivirals in people who inject drugs have shown that treatment remains highly effective in this population [55, 56, 57]. The full impact of these newer antivirals will only be appreciated once

innovative approaches to engage more HCV-infected individuals into antiviral therapy are practiced.

4. Delivery of HCV therapy- Pathway to Eradication

The delivery of therapy to patients is key to its efficacy. Complex care pathways, based in, or outreaching from secondary or tertiary care, have been developed to deliver IFN-based therapy to patients. Such care pathways focus on managing the side effects of therapy safely. Chaotic unstable patients such as people who inject drugs have not made it through these therapy pathways in significant numbers and such patients that do are atypical. The aim of these pathways has been to prevent advanced liver disease by curing HCV infection before cirrhosis develops. So the episode of treatment can be delayed until the patient is considered suitable, by the constraints of the treatment pathway. This is in marked contrast to the situation if treatment as prevention is the aim of therapy, where early therapy at the earliest possible time in the duration of infection would give the optimum outcome. So the pathway to treatment has to be receptive to the patient.

Clinical networks are a much vaunted solution to the problems associated with treatment of HCV. In England they are a very secondary care-based solution to allow patients to be treated at hospitals closer to their locality, but still controlling availability of drug therapy centrally. In Scotland's HCV action plan, managed care networks were a central plank to achieve the integration of primary and secondary care with third sector providers of health care around patients with or at risk of HCV into a cohesive and seamless treatment pathway. This integration was fundamental to the success of the Scottish action plan, the implementation of this is described

and illustrated in the report by Tait *et al* [58]. Thus networks can achieve improvement in care, particularly when working across healthcare boundaries and accessing difficult-to-reach patient populations. However, all key stakeholders in the area need to be a part of the network, working together to an agreed strategic aim. The MCN model is ideally suited to a treatment as prevention strategy.

People who inject drugs are a largely stigmatized group who have limited access to conventional healthcare. Often as a result of homelessness and deprivation, many patients lack a means of communication with conventional healthcare providers. However, they are often in regular contact with other services in a variety of contexts. For example: needle exchange programs in the community which dispense both sterile injecting equipment and advice on safe injecting practices; and pharmacies which administer methadone to those on opiate substitution programs. These points of contact represent an ideal opportunity to target people who inject drugs for HCV treatment. Pilot studies show that with the new direct-acting antivirals, with their reduced need for regular blood monitoring and fewer side-effects, the clinical and para-clinical staff within these facilities such as pharmacists and drug workers are keen and able to take on a lead role in assessment and provision of anti-HCV therapy as part of managed care networks [59]. These managed care networks provide the clinical supervision they need to deliver a protocol-based HCV treatment pathway. The initial sustained virological response rates from such pathways match clinical trials and are much more inclusive of a broader group of patients from a background of intravenous drug use, which is vital to a treatment as prevention strategy.

In addition to opiate substitution centers (e.g. pharmacies) and needle and syringe program facilities, prisons should also be considered as an opportunity to treat. Given the high numbers and proportions of people who inject drugs in correctional facilities, prisoners represent an ideal target population for treatment as prevention. As with targeting people who inject drugs in general, targeting prisoners poses its own challenges and ethical considerations. A 2015 letter by Levy and Larney highlighted the issues of treatment as prevention in correctional settings. They argue that the imbalance of power between prisoners and custodial staff may translate to a curtailing of civil liberties [60]. In such circumstances, how can we be sure that consent to screening and treatment is truly voluntary? Adding to this, Martin and colleagues emphasize the need for continuity of care amongst prisoners after release or transfer for this approach to HCV prevention to be cost-effective [61]. A recent review of treatment outcomes in prisoners treated in Scotland has shown a strong negative correlation between liberation during treatment and sustained virological response. This work was using IFN-based therapy and so should be less of an issue with new direct-acting antiviral-based therapy of shorter duration [62]. In terms of primary prevention Levy and Larney also called for greater access to harm reduction services such as needle exchange programs within prisons, arguing that such services exist in community settings for people who inject drugs. As such, those who successfully complete treatment can protect themselves from re-infection and thus increase the effectiveness of this HCV eradication strategy [60]. It should be noted, however, that a 2013 study found that in a sample of 5,076 surveyed prisoners in Scotland, the risk of HCV transmission was lower amongst prisoners compared to Scottish people who inject in the community. The authors propose that this is due to the low incidence of in-prison injecting, although they concede that some under-

reporting is likely. As such, the authors suggest that low HCV incidence amongst prison populations does not depend on the introduction of needle exchange programs [63]. The major issue around provision of needle exchange in prisons is the potential for their use as weapons against staff which has led prison officer unions to object on health and safety grounds.

The major criticism of treatment as prevention strategies in people who inject drugs is the impact on injecting behaviour and the risk of re-infection. Regarding the interplay between HCV treatment and the behaviours of intravenous drug users, it has been established that antiviral therapy does not increase illicit drug use. Intermittent injecting during treatment has also been shown to have no influence over regimen adherence, completion of treatment, or attainment of sustained virological responses. Contrary to this, more regular injecting has been associated with lower sustained virological response rates and discontinuation of treatment [14]. In an effort to better understand injecting behaviours and how they relate to re-infection risk post-sustained virological response, Valerio and colleagues conducted an analysis of 1,170 people who inject drugs who attained a sustained virological response over a twenty-year period (1992-2012) [64]. They reported that an increasing minority of people who inject drugs who attain a sustained virological response are at an elevated risk of re-infection or death as a result of high intensity injecting behaviour. In agreement with EASL recommendations [11], the authors advocate for the on-going monitoring of high-risk patients post-sustained virological response [64]. However, evidence suggests that people who inject drugs who achieve a sustained virological response are more likely to pursue a healthy lifestyle [65]. The Valerio study also voiced concern that re-infection rates amongst people who inject drugs will rise

as HCV treatment is scaled-up [64]. Commentary from Hellard and Scott (2015) postulated that many of the current models measuring the outcomes of HCV treatment as prevention incorporate high levels of re-infection into their modelling, thus overstating the re-infection risk. Whilst it is established that HCV re-infection is common out-with treatment settings, re-infection after antiviral therapy is considerably lower [66]. A meta-analysis by Aspinall *et al* calculated the pooled risk of re-infection amongst five cohorts of people who inject drugs (n = 131) to be 2.4 (CI = 0.9-6.1) per 100 person years [67]. However, a 2016 study reported an 11% re-infection rate in a multicentre trial follow-up of intravenous drug users infected with genotypes 2 or 3 [68]. This highlights possible variations in the range of reinfections. Emergent data from the ERADICATE trial will provide more information on reinfection rates in people who inject drugs undergoing anti-HCV therapy. A more recent study suggested that targeting HCV treatment by stratifying the level of injection drug-use could enhance benefits at the population level [69]. The authors reported that HCV treatment is best determined by its prevalence within the population; when >50% of all exchanged syringes are contaminated with HCV they recommend treating low-risk people who inject drugs first. Conversely, below this threshold, treating high-risk intravenous drug users first appeared to produce the greatest societal benefits [69]. Indeed, it has been shown that targeting the injecting network provides greater population health benefit than treating people who inject drugs randomly for their HCV [70]. Studies such as this support the idea that people who inject drugs should not be excluded from treatment based on their apparently risky behaviour. A further study by Martin and colleagues suggested that treating current injectors is more cost-effective than treating ex- or non-injectors when the chronic HCV prevalence is less than 60% [71].

Eradication – Is It Cost-Effective?

Relative to the expense of long-term complications associated with HCV infection, the price of direct-acting antivirals is considered cost-effective [22]. The bulk of the health costs and health consequences associated with HCV infection are due to end stage liver disease late in the natural history of infection. This has led some to suggest that treatment should be restricted to patients with more advanced disease only. As even in high-income nations the cost of direct-acting antivirals may prohibit their widespread uptake, due to affordability, relative to other demands on health budgets. Cost-effective evaluations are needed to verify how best to allocate resources and services. A 2015 study aimed to forecast population-level outcomes from alternative treatment strategies in a resource-rich setting [72]. Using a simulation model and projecting outcomes to 2030, trends in HCV incidence and severe liver morbidity was extrapolated according to treatment strategies that prioritised either people who inject drugs or patients with moderate/advanced liver fibrosis. The authors concluded that no single approach to the treatment of HCV in an era of IFN-free therapies addressed all public health concerns. Prioritising people who inject drugs for treatment results in substantially reduced HCV incidence and transmission rates in the population, but fails to address the impact of liver disease. Conversely, suboptimal reductions in HCV incidence occurs when those with moderate/advanced liver disease are targeted for priority treatment. It is projected that by specifically targeting active intravenous drug users, incident HCV infection can be reduced to <50 cases per year by 2025 [72]. The conclusion that can be drawn from this paper was that a twin track strategy that targeted active injectors and those with evidence of hepatic fibrosis would be most cost-effective, but would leave the short fall in

treatment on those with mild disease who were not injecting, a strategy that may not be acceptable to the general population. These estimates support the previous modelling studies by Martin and colleagues described above. The high cost of anti-HCV therapy makes a more targeted treatment approach more economically beneficial. As such, epidemiological data on injector populations must be upgraded on a country by country basis to allow a planned strategy [73]. As already discussed, it is unlikely that substantial reductions in HCV prevalence would be achievable with opiate substitution therapy and needle and syringe programs alone. However, expansion of these interventions would reduce the number of people who inject drugs requiring HCV treatment, and be highly cost-effective thus making a target HCV prevalence reduction easier to achieve [14]. This supports the idea that HCV eradication policy must be built upon scaled-up community outreach projects. While the health economic analysis supports the idea of treatment as prevention, and shows it to be cost effective, it may not be achievable due to the affordability issues surrounding such a relatively common disease with such a currently expensive therapy. There is already prioritisation of HCV therapy for patients with advanced fibrosis in many countries, with patients with milder disease waiting for therapy. To further prioritise active intravenous drug users over other patients with mild disease may not be acceptable to health care providers and payers.

Conclusion

The growing burden of chronic HCV infection presents a significant public health concern. With the advent of highly efficacious and tolerable direct-acting antivirals, the concept of treatment as prevention is gaining credence and efforts to scale-up access to treatment have been developed.

Although global eradication of HCV via targeted treatment is highly desirable, current limitations render it improbable at this point in time; with regional elimination being a more realistic prospect. Sub-optimal coverage of harm reduction services worldwide, the lack of an effective vaccine, and the high baseline HCV prevalence in many places makes HCV eradication very difficult to accomplish. Despite this, modelling studies by Martin and colleagues show that lower treatment uptake is required to achieve a more substantial reduction in HCV prevalence when the baseline prevalence is below a certain threshold. Increased access to harm reduction services may drive the local HCV prevalence low enough to allow targeted treatment to be successful.

Perhaps the most important prevention strategy is the implementation of HCV testing so as to identify those in need of treatment. Solutions must be formulated to overcome barriers to care. In this way, more patients eligible to be treated are identified and managed accordingly. Early identification, using more accurate diagnostic tools, will be essential to prevent the onward transmission of HCV [10].

Although technically feasible, HCV eradication will require a galvanised effort from not only practitioners and healthcare policy makers, but also the patients themselves. To achieve HCV eradication via treatment on a global scale, people who inject drugs must be given increased access to affordable treatment. Ensuring affordability of anti-HCV therapy will be critical in the pursuit of eradicability.

Acknowledgements

The guarantor of the article is Prof JF Dillon

Specific author contributions: Mr Leask performed the initial literature searches under Prof Dillon's direction, the review was jointly written by both authors. Both authors approved the final version of the manuscript.

Disclosures

There was no funding for the writing of this review. Prof Dillon has received honoraria for lectures and advisory boards from Janssen, Roche, Merck, Abbvie and Gilead. Prof Dillon's institution has received research support from Janssen, Roche, Merck, Abbvie and Gilead.

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