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

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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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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.

For Peer Review

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

1
2
3 infections worldwide occur within marginalised societal groups, predominating in
4
5 people who inject drugs (PWID). Acute HCV infection is often difficult to detect given
6
7 the stigmatisation of at-risk groups and the generally asymptomatic nature of early
8
9 infection ¹⁰. Previously, treatment for PWID with HCV was withheld on the basis of
10
11 chaotic lifestyle and associated risks of re-infection, making attempts at treatment
12
13 futile. This belief has not been substantiated, with the empirical evidence suggesting
14
15 good outcomes can be achieved, that PWID's display equal, or even superior, HCV
16
17 treatment outcomes to non-PWID's ¹². This has led to international guidelines now
18
19 recommending treatment of HCV amongst these high-risk groups following
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21 individualized assessment ¹¹. Although evidence to support such guidelines is
22
23 growing it is somewhat limited at present. The change in guideline position being in
24
25 part driven by ensuring equity of access to treatment for those that need it.
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32 Treatment of HCV is fast changing. The arrival of the first generation of direct-acting
33
34 antiviral drugs (DAA's) in 2011 changed the landscape of HCV therapeutics, with
35
36 more efficacious and highly tolerable drugs entering the market ¹³. The high cost of
37
38 these DAA's has led to the rationing of therapy based on the degree of liver fibrosis
39
40 in many healthcare systems. However, research is emerging suggesting that
41
42 specifically targeting HCV-infected PWID will deplete the pool of HCV within society
43
44 for transmission, preventing new infections and giving rise to the concept of
45
46 'treatment as prevention'. This could ultimately lead to the eradication of HCV.
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48 49 50 51 52 **Treatment as Prevention in HCV**

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54 PWID's represent the most at-risk population for acquiring HCV infection. As such,
55
56 treatment as a means of prevention should focus on PWIDs. As a group, PWID
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1
2
3 retain a high rate of morbidity and mortality irrespective of HCV status. However,
4
5 with the young ages at which PWID acquire HCV infection, the ever increasing
6
7 longevity of the general population means that the burden of hepatic and extra-
8
9 hepatic disease will continue to rise ¹⁴. Targeting those at greatest risk of disease
10
11 acquisition can lead to broader community benefits and long-term cost-effectiveness.
12
13 Grebely and Dore reported that in 2007 there were 16 million current PWID
14
15 worldwide, and a 67% HCV prevalence rate amongst PWID. This equates to around
16
17 10 million HCV-infected PWID worldwide, not including the additional reservoir of
18
19 HCV in former PWID ¹⁴. Given that HCV transmission is driven by PWID, efforts to
20
21 target active PWID for antiviral therapy are strongly supported ^{15, 16, 17}, on the basis
22
23 that it may prevent virus transmission.
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30 In support of this approach to HCV eradication, modelling studies by Martin and
31
32 colleagues have indicated that HCV chronic prevalence could be reduced by treating
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34 those at risk of ongoing HCV transmission ^{18, 19}. A more recent study from the same
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36 group reviewed a number of similar theoretical modelling studies, this time in a range
37
38 of global settings and target populations in the context of DAA therapy ²⁰. They
39
40 reported that the high incidence of HCV amongst key populations such as PWID,
41
42 prisoners and men who have sex with men (MSM) represented an ideal opportunity
43
44 to curb ongoing HCV transmission. However, the authors recognised the need to test
45
46 these hypotheses empirically ²⁰. **A number of other mathematical models have**
47
48 **attempted to explore the preventative value of treating PWID for HCV. A 2013 model**
49
50 **proposed that treating as few as 15 out of 1,000 PWID annually could halve HCV**
51
52 **prevalence within 15 years ¹⁹. The model was critically dependent on the HCV**
53
54 **prevalence in the PWID population with the number needed to treat rising with**
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3 increasing prevalence, so that at 25% prevalence 15 treatments per annum achieved
4 this impact but more than 100 treatments per annum were required if HCV
5 prevalence was over 65%. An earlier model by the same authors predicted that for a
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10 PWID population with a baseline chronic HCV prevalence of 20%, treatment rates of
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12 5, 10, 20 or 40 per 1,000 PWID annually for 10 years can result in a reduction in
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14 prevalence of 15%, 30%, 62% and 72%, respectively ¹⁸.
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18
19 Another 2013 study by Martin and colleagues hypothesised that when antiviral
20
21 treatment is combined with opiate substitution therapy (OST) and high-coverage
22
23 needle and syringe programs (HCNSP), significant reductions in HCV could be
24
25 achieved. Using a HCV transmission model, they estimated that chronic HCV
26
27 prevalence could be reduced by >50% over a ten-year period. With the newer
28
29 DAA's, the authors propose that such a target becomes even more attainable ²¹.
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34 The approach of treatment as prevention carries with it several ethical challenges.
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36 Whereas vaccination can be applied universally, curing through drug therapy
37
38 requires the identification of target populations. Medical screening on such a large
39
40 scale poses ethical dilemmas. As recently discussed by Hagan *et al* ²¹, a false
41
42 positive result can be burdensome on those labelled with such a stigmatizing
43
44 disease. In addition to being psychologically straining for the patient, it can also lead
45
46 to unnecessary treatment and resource wastage. Conversely, false negative results
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48
49 only serve to propagate disease transmission as patients are unaware of their true
50
51 status. Even a true positive result can impose societal repercussions as family
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53 relationships, employment opportunities and insurance status are all affected. In a
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55 HCV context these concerns are minimized by the high accuracy of the diagnostic
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3 tests and confirmatory lab practices. The authors also mention incentivisation
4
5 schemes in an effort to combat poor compliance to screening. The follow-on from
6
7 testing and diagnosis is treatment, with the inconvenience of taking medications and
8
9 risk of side effects. In conventional treatment pathways the decision for treatment is
10
11 taken largely by the patient for their individual benefit. However, in the treatment as
12
13 prevention concept the benefit of treatment is much less for the patient but for
14
15 society as a whole. Any societal benefit depends on a very high level of uptake, so
16
17 an individuals' priorities around treatment could be subverted to those of society,
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19 with a degree of coercion. However, a balance must be struck between voluntary
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21 participation and coercion ²².

Eradication – Can It Be Achieved?

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30 In 2014, *The Lancet* Commission on addressing liver disease in the UK projected
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32 that with the advent of these new highly effective IFN-free therapies, chronic HCV
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34 infections could be eradicated in the UK by 2030 ²³. It would seem that not only have
35
36 these new antiviral treatments changed the therapeutic landscape, but they have
37
38 also altered the horizon for the future of HCV.
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44 The concepts of 'control', 'elimination' and 'eradication' have long been the subject of
45
46 numerous debates. Writing for the World Health Organisation in 1998, Dowdle
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48 proposed the definition of 'control' as being a reduction in disease incidence,
49
50 prevalence, morbidity or mortality to a locally acceptable level; 'elimination' as a
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52 reduction to zero of the incidence of a specified disease in a defined geographical
53
54 area; and 'eradication' as a permanent reduction to zero of the worldwide incidence
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56 of an infection such that interventions are no longer required. To this list, he added
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1
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3 'extinction', defined as being an infectious agent that no longer exists in nature or
4
5 laboratory conditions ²⁴.
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10 Dowdle went on to describe the three principal indicators of eradicability. Firstly, an
11
12 intervention must exist to interrupt transmission of the infectious agent. Secondly,
13
14 diagnostic tools of sufficient sensitivity and specificity must be universally accessible
15
16 to detect transmissible levels of infection. Lastly, humans must be essential to the life
17
18 cycle of the infectious agent, with no *ex vivo* amplification ²⁴. In the context of HCV,
19
20 the terms 'eradication' and 'elimination' are often used interchangeably, despite
21
22 regional or national elimination being a more realistic prospect for HCV in the
23
24 medium term. Regardless, the elimination and eradication of disease, both of which
25
26 evolve from the concept of control, remain the ultimate goals of public health. To
27
28
29 date, only one disease has been successfully eradicated on a global scale; smallpox
30
31 was declared eradicated in 1980. Polio is now only endemic in a few countries and
32
33 efforts are ongoing to eradicate it entirely. In both cases, eradication efforts centered
34
35 on prevention through vaccination and containment. When Dowdle's principles are
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37
38 applied to HCV the evidence generates much hope, but some remaining challenges,
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40
41 to achieve elimination.
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45 **HCV Life Cycle and Humans**

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47 HCV is exclusively a human pathogen, with very few species capable of being
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50 infected even in experimental conditions and no meaningful zoonotic reservoir to
51
52 infect human hosts ¹³ or facilitate amplification. So we can regard HCV as having an
53
54 exclusively human host for its life cycle and fore filling the first of Dowdle's principles
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56 ²⁴.
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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

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3 value of an instant test result as opposed to returning at a later date for said result
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5 must be weighed in the context of entry to treatment, which is yet to be evaluated.
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10 Given that over half of PWID in the UK and USA are unaware of their true HCV
11 status ^{26, 27}, testing at-risk populations to raise the number of people being treated for
12 HCV is vital to have any chance of achieving HCV elimination. Previous UK studies
13 evaluating the option of DBS testing within specialist addiction services and prisons
14 found that HCV testing increased almost six-fold ^{28, 29}. A recent U.S study reported
15 that in IVDU clinics that offer comprehensive screening and assessment for blood
16 borne viruses, diagnostic rates of HCV soar in PWID populations ³⁰. A 2015
17 systematic review supports these findings, reporting that the availability of DBS
18 testing appears to increase the uptake of HCV testing in high-risk populations ²⁵.
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28 Hence, DBS is clearly a vital tool in the efforts to increase HCV case-finding amongst
29 PWID. DBS has been proven to be suitable for large-scale screening programs and
30 therapeutic monitoring. As such, it can be employed to increase access to care ³⁰.
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39 A recent cost-utility analysis utilizing a dynamic mathematical model showed that
40 increasing HCV case-finding in addiction services can be cost-effective. However,
41 this does not translate directly to prison settings. Cost-effectiveness of case-finding
42 here depends on continuity of care following release ³¹. It has been argued that the
43 U.S criminal justice system represents an ideal focus for HCV case-finding and
44 treatment, given the high volume of HCV-infected individuals currently in contact with
45 correctional facilities ³². However, some may argue that the way correctional facilities
46 operate would worsen treatment outcomes due to high rates of re-infection,
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secondary to unacknowledged institutional high risk drug use. Additionally routes of

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3 reimbursement for treatment costs may make it impossible to establish treatment
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5 programs in prisons in many countries.
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10 A 2015 Canadian study evaluated the health and economic benefits conferred by
11 incorporating a one-time screening strategy for HCV in various populations. Using a
12 state-transition model, they proposed that a one-time screening program for pre-
13 selected age groups would likely be cost-effective as asymptomatic cases of HCV
14 would be detected. They calculated that this approach could prevent at least 9 HCV-
15 related deaths per 100,000 persons screened over the lifetime of the cohort
16 analysed ³³.
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28 So the diagnostic technology to diagnose HCV is reliable, cost-effective and widely
29 available. The evidence base for modes of delivery of testing is substantial and this
30 is being translated into effective detection programs in some countries with France
31 and Australia reporting approximately 80% of their prevalent HCV populations having
32 been diagnosed ³⁴. So widespread diagnosis of prevalent HCV infection is possible
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44 **Interruption of Transmission**

45 There are multiple potential routes at which we could interrupt transmission of HCV,
46 including primary prevention of infection and therapy to prevent further transmission.
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50 In primary prevention of HCV, clean needles and syringes are the mainstay but
51 developments in vaccination offer some hope for the future. In HCV therapy,
52 treatment as prevention is dependent not just on the efficacy of the therapy but also
53 on its effective delivery.
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5 1. Primary prevention of infection.
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8 The main driver for new HCV infection is the injection of drugs with contaminated
9 needles and other injecting paraphernalia ³⁵. Therefore, the provision of clean
10 needles and other injecting equipment, along with access to opiate replacement
11 therapy (for opiate users), to reduce injecting frequency, should reduce the risk of
12 HCV transmission. It has been estimated that prevalence of HCV in the UK could be
13 up to 60% higher in the absence of OST and HCNSP ³⁶. Hagan *et al* reported that
14 strategies combining treatment for substance misuse and instruction for safe
15 injecting practices reduced HCV seroconversion by 75%. However, they reported
16 that further research is needed to ascertain what specific interventions are most
17 effective in the different subgroups of PWID ³⁷. To complement the Hagan study,
18 Turner *et al* estimated that OST and HCNSP reduce HCV transmission by 80% in a
19 UK context ³⁸. Nonetheless, previous modelling has suggested that OST and
20 HCNSP alone does not prevent incident HCV infections amongst UK PWID ³⁶.
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22 Indeed, such programs have demonstrated higher success rates for HIV prevention
23 compared to HCV ^{14, 37}. Contributing factors to this are that HCV is ten times more
24 transmissible than HIV, (in the PWID context) and HCV often survives on fomites for
25 prolonged periods of time ³⁹. Despite this, OST and HCNSP offer other benefits such
26 as reductions in drug-related deaths and drug-related crime as well as protection
27 from other blood borne infections ^{21, 40}.
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53 HCV eradication will likely not be possible without staunch efforts to limit new
54 infections that are fueling the epidemic. Numerous interventions have evolved over
55 the years that serve to decrease transmission rates. As already alluded to,
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3 community-based outreach and education programs, stemming from the HIV
4 epidemic in the 1980's, proved beneficial in reducing the prevalence of blood borne
5 viruses within local populations. Access to free sterile injecting equipment further
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8 contributed to reductions in HIV and HCV transmission. Although HCV remains very
9
10 high amongst PWID, the introduction of anti-HIV interventions had a profound impact
11 on HCV prevalence ¹⁴. However, such effective public health interventions are
12 scarce, even in many developed countries. Even where they exist, funding is poor.
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14 Edlin and Winkelstein argue that community interventions must be scaled-up if HCV
15 transmission is to be reduced ³⁹. In a review on the feasibility of HCV eradication in
16 the United States, they comment that needle and syringe programs only operate in
17 166 U.S cities, with 20 states not running any such programs at all. They also argue
18 that pharmacies are critical in providing sterile needles as they would reach all
19 populations, not just a fraction of PWID as it currently stands ³⁹. Current U.S
20 legislation in many states restricts access to sterile needles and syringes for illicit
21 drug-use. This reflects a need for policy change in a concerted effort to stem the tide
22 of HCV. Recent changes to Californian legislation gave more power to local health
23 jurisdictions, with some cities choosing to legalise non-prescription syringe sales in
24 pharmacies. A 2015 analysis demonstrated that where it was legal, more syringes
25 were obtained amongst IVDU populations. Public health policies such as this must
26 be extended to realize the true benefits it would have on HCV transmission in target
27 populations ⁴¹. However, one must take into account the varied transmission profiles
28 now being seen in some developed countries and any public health initiatives for the
29 provision of injecting equipment must ensure it reaches those at risk. Recent trend
30 analysis has revealed an emerging HCV epidemic in the U.S, stemming from chaotic
31 injecting habits and early prescription opioid abuse. Socioeconomic analysis reveals
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3 the epidemic to be concentrated in non-urban white males, who often have very
4 limited access to sterile injecting equipment and injecting advice from experienced
5 IVDU ⁴² as this is occurring in areas without previous significant injecting drug use.
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9 Different patterns of drug abuse may change the benefits of the treatment as
10 prevention approach.
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15 Although needle-sharing is a major aspect of HCV transmission, other injection
16 paraphernalia have been strongly implicated in the spread of the virus. For example,
17 the sharing of cookers, filtration cotton and water can also permit viral transmission
18 ⁴³. An earlier study calculated that 54% of HCV infections in PWID who did not share
19 needles could be attributed to other injecting equipment ⁴⁴. The provision of sterile
20 paraphernalia in Scotland is anticipated to reduce HCV transmission amongst PWID,
21 but results from this natural experiment are awaited ⁴³. However, earlier studies
22 evaluating the risks of HCV transmission amongst PWID who share injecting
23 equipment have failed to quantify the contribution that this route of infection is having
24 on HCV spread ⁴⁵. Indeed, one 2014 study concluded that, although injecting risk
25 behaviour is clearly reduced by OST and NSP, comparatively little review-level
26 evidence exists to support such a trend for HCV transmission amongst PWID's ⁴⁶.
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44 2. Vaccination

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46 In most infectious diseases that have been considered for elimination a vaccine has
47 been available. However, this is not essential as evidenced by the near eradication
48 of the Guinea worm without even drug therapy ⁴⁷. Of course vaccine development
49 seems logical. It can be reasonably argued that due to the asymptomatic nature of
50 the virus, and the fact that most people are unaware of their HCV status, vaccination
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3 is perhaps the most effective way of eradicating HCV ¹⁰. A universal vaccine could
4 not only prevent primary HCV infection, but may also prevent re-infection after cure
5 following DAA therapy. This latter use has implications for those with ongoing risk of
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10 HCV exposure, such as PWID ⁴⁸. It is estimated that even if pricing of DAA's were
11
12 1,000-fold lower to benefit low-income nations, the costs of extensive HCV screening
13 and DAA distribution would exceed those of a universal vaccination program ⁴⁹.
14
15 Results from several vaccine trials are eagerly awaited. In one such study, Swadling
16
17 *et al* describe the development of a highly immunogenic vaccine for HCV. By utilizing
18
19 the critical role that T cell immunity plays in antiviral control, they report having
20
21 produced a potent T cell vaccine that prevents chronic infection by incorporating
22
23 chimpanzee adenoviral and MVA vectors to prime and boost T cell memory. The first
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25 efficacy study of ChAd3NSmut/MVA-NSmut in IVDU's has recently started in the U.S
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29 (NCT01436357) ⁵⁰. However, results from these studies are forthcoming and
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31 historically, such T cell vaccines have had more limited efficacy than antibody based
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33 vaccines in clinical trials.
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39 3. HCV therapy

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41 HCV antiviral therapy has undergone a revolution, moving very rapidly from IFN-
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43 based therapies with cure rates of 40-70% depending on genotype, to the advent of
44
45 DAA's achieving cure rates in excess of 90% for all genotypes with treatment
46
47 duration reduced to as little as eight weeks. The development of these newer DAA's
48
49 has long been impeded by the lack of an effective cell culture system for HCV
50
51 proliferation ⁵¹. The availability of high-throughput virological assays to characterise
52
53 the various stages of the HCV replication cycle have enabled the identification of
54
55 more specific antiviral targets ^{52, 53}. This development, combined with changes in the
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3 definition of sustained virological response (SVR), has generated the momentum for
4 the rapid change in the field. The European Association for Study of Liver (EASL)
5 describes the endpoint of therapy as undetectable HCV RNA 24 weeks after the end
6 of the treatment course (SVR24), defined as <15 IU/mL ¹¹. In a long-term follow-up
7 study of HCV-infected patients treated with PEG-IFN- α 2a and ribavirin (n = 1,343), a
8 durable SVR24 of 99.1% was retained once achieved ⁵⁴. Such data suggests that
9 HCV recurrence is rare in patients who achieve an SVR, and that from a virologic
10 standpoint, such patients can be regarded as cured. The validity of measuring HCV
11 RNA 12 weeks after completion of treatment (SVR12) has been evaluated and
12 approved by regulators in the U.S and Europe, as an equivalent end point ¹¹.
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28 The currently available new DAA's are split into three classes defined by their HCV
29 target protein: the protease inhibitors targeted against the NS3/4a protease; and the
30 NS5a complex inhibitors and polymerase inhibitors, which are directed against the
31 NS5b protein. This latter class can be further divided into nucleotide and non-
32 nucleotide inhibitors. Initial protease inhibitors, and to a lesser extent NS5a
33 inhibitors, are genotype specific. However, newer pan-genotypic DAA's with superior
34 efficacy, lower adverse effect profiles and shorter therapy durations are constantly
35 emerging ¹³.
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48 Access to treatment has been widened with the advent of these new drugs.
49 Previously, IFN-based therapy was contraindicated in patients with many co-
50 morbidities including decompensated cirrhosis ³⁵. Thus, with the new DAA's therapy
51 can now be given to patients in whom it may have previously been contraindicated.
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56 This also applies to PWID populations, where concerns about adherence to safety
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3 monitoring was considered a relative contraindication to therapy, despite studies
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5 showing this was not an issue. Currently, concerns are expressed about how robust
6
7 the new all-oral regimens are if adherence is suboptimal in patients with more
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9
10 chaotic lifestyles, leaving them at risk of developing viral resistance. Trials of DAA's
11
12 in PWID to date have shown treatment remains highly effective in this population ⁵⁵,
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14 ^{56, 57}. The full impact of DAA's will only be appreciated once innovative approaches
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16 to engage more HCV-infected individuals into antiviral therapy are practiced.

21 4. Delivery of HCV therapy- Pathway to Eradication

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23 The delivery of therapy to patients is key to its efficacy. Complex care pathways,
24
25 based in, or outreaching from secondary or tertiary care, have been developed to
26
27 deliver IFN-based therapy to patients. Such care pathways focus on managing the
28
29 side effects of therapy safely. Chaotic unstable patients such as PWID have not
30
31 made it through these therapy pathways in significant numbers and such patients
32
33 that do are atypical. The aim of these pathways has been to prevent advanced liver
34
35 disease by curing HCV infection before cirrhosis develops. So the episode of
36
37 treatment can be delayed until the patient is considered suitable, by the constraints
38
39 of the treatment pathway. This is in marked contrast to the situation if treatment as
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41 prevention is the aim of therapy, where early therapy at the earliest possible time in
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44 the duration of infection would give the optimum outcome. So the pathway to
45
46 treatment has to be receptive to the patient.
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52 Clinical networks are a much vaunted solution to the problems associated with
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55 treatment of HCV. In England they are a very secondary care-based solution to allow
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57 patients to be treated at hospitals closer to their locality, but still controlling
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3 availability of drug therapy centrally. In Scotland's HCV action plan, managed care
4 networks were a central plank to achieve the integration of primary and secondary
5 care with third sector providers of health care around patients with or at risk of HCV
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7
8 into a cohesive and seamless treatment pathway. This integration was fundamental
9
10 to the success of the Scottish action plan, the implementation of this is described
11
12 and illustrated in the report by Tait *et al*⁵⁸. Thus networks can achieve improvement
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14 in care, particularly when working across healthcare boundaries and accessing
15
16 difficult-to-reach patient populations. However, all key stakeholders in the area need
17
18 to be a part of the network, working together to an agreed strategic aim. The MCN
19
20 model is ideally suited to a treatment as prevention strategy.
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28 PWID are a largely stigmatized group who have limited access to conventional
29
30 health care. Often as a result of homelessness and deprivation, many patients lack a
31
32 means of communication with conventional healthcare providers. However, they are
33
34 often in regular contact with other services in a variety of contexts. For example:
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36 needle exchange programs in the community which dispense both sterile injecting
37
38 equipment and advice on safe injecting practices; and pharmacies which administer
39
40 methadone to those on opiate substitution programs. These points of contact
41
42 represent an ideal opportunity to target PWID for HCV treatment. Pilot studies show
43
44 that with the new DAA's, with their reduced need for regular blood monitoring and
45
46 fewer side-effects, the clinical and para-clinical staff within these facilities such as
47
48 pharmacists and drug workers are keen and able to take on a lead role in
49
50 assessment and provision of anti-HCV therapy as part of managed care networks⁵⁹.
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52 These managed care networks provide the clinical supervision they need to deliver a
53
54 protocol-based HCV treatment pathway. The initial SVR rates from such pathways
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3 match clinical trials and are much more inclusive of a broader group of patients from
4
5 a PWID background, which is vital to a treatment as prevention strategy.
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10 In addition to OST centers (e.g. pharmacies) and NSP facilities, prisons should also
11 be considered as an opportunity to treat. Given the high numbers and proportions of
12
13 PWID in correctional facilities, prisoners represent an ideal target population for
14
15 treatment as prevention. As with targeting PWID's in general, targeting prisoners
16
17 poses its own challenges and ethical considerations. A 2015 letter by Levy and
18
19 Larney highlighted the issues of treatment as prevention in correctional settings.
20
21 They argue that the imbalance of power between prisoners and custodial staff may
22
23 translate to a curtailing of civil liberties ⁶⁰. In such circumstances, how can we be
24
25 sure that consent to screening and treatment is truly voluntary? Adding to this, Martin
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27
28 and colleagues emphasize the need for continuity of care amongst prisoners after
29
30 release or transfer for this approach to HCV prevention to be cost-effective ⁶¹. A
31
32 recent review of treatment outcomes in prisoners treated in Scotland has shown a
33
34 strong negative correlation between liberation during treatment and SVR. This work
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36
37 was using IFN-based therapy and so should be less of an issue with new DAA-
38
39 based therapy of shorter duration ⁶². In terms of primary prevention Levy and Larney
40
41 also called for greater access to harm reduction services such as needle exchange
42
43 programs within prisons, arguing that such services exist in community settings for
44
45 PWID. As such, those who successfully complete treatment can protect themselves
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48 from re-infection and thus increase the effectiveness of this HCV eradication strategy
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51 ⁶⁰. It should be noted, however, that a 2013 study found that in a sample of 5,076
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53 surveyed prisoners in Scotland, the risk of HCV transmission was lower amongst
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55 prisoners compared to Scottish people who inject in the community. The authors
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3 propose that this is due to the low incidence of in-prison injecting, although they
4
5 concede that some under-reporting is likely. As such, the authors suggest that low
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7 HCV incidence amongst prison populations does not depend on the introduction of
8
9 needle exchange programs ⁶³. The major issue around provision of needle exchange
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11 in prisons is the potential for their use as weapons against staff which has led prison
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13 officer unions to object on health and safety grounds.
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18 The major criticism of treatment as prevention strategies in PWID is the impact on
19
20 injecting behaviour and the risk of re-infection. Regarding the interplay between HCV
21
22 treatment and PWID behaviour, it has been established that antiviral therapy does
23
24 not increase illicit drug use. Intermittent injecting during treatment has also been
25
26 shown to have no influence over regimen adherence, completion of treatment, or
27
28 SVR attainment. Contrary to this, more regular injecting has been associated with
29
30 lower SVR rates and discontinuation of treatment ¹⁴. In an effort to better understand
31
32 injecting behaviours and how they relate to re-infection risk post-SVR, Valerio and
33
34 colleagues conducted an analysis of 1,170 PWID who attained an SVR over a
35
36 twenty-year period (1992-2012) ⁶⁴. They reported that an increasing minority of
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38 PWID who attain an SVR are at an elevated risk of re-infection or death as a result of
39
40 high intensity injecting behaviour. In agreement with EASL recommendations ¹¹, the
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42 authors advocate for the on-going monitoring of high-risk patients post-SVR ⁶⁴.
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45 However, evidence suggests that PWID who achieve an SVR are more likely to
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47 pursue a healthy lifestyle ⁶⁵. The Valerio study also voiced concern that re-infection
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49 rates amongst PWID will rise as HCV treatment is scaled-up ⁶⁴. Commentary from
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51 Hellard and Scott (2015) postulated that many of the current models measuring the
52
53 outcomes of HCV treatment as prevention incorporate high levels of re-infection into
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2
3 their modelling, thus overstating the re-infection risk. Whilst it is established that HCV
4 re-infection is common out-with treatment settings, re-infection after antiviral therapy
5 is considerably lower ⁶⁶. A meta-analysis by Aspinall *et al* calculated the pooled risk
6
7 of re-infection amongst five cohorts of PWID (n = 131) to be 2.4 (CI = 0.9-6.1) per
8
9 100 person years ⁶⁷. However, a 2016 study reported an 11% re-infection rate in a
11
12 multicentre trial follow-up of PWID's infected with genotypes 2 or 3 ⁶⁸. This highlights
13
14 possible variations in the range of reinfections. Emergent data from the ERADICATE
15
16 trial will provide more information on reinfection rates in PWID's undergoing anti-
17
18 HCV therapy. A more recent study suggested that targeting HCV treatment by
19
20 stratifying the level of injection drug-use could enhance benefits at the population
21
22 level ⁶⁹. The authors reported that HCV treatment is best determined by its
23
24 prevalence within the population; when >50% of all exchanged syringes are
25
26 contaminated with HCV they recommend treating low-risk PWID first. Conversely,
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28 below this threshold, treating high-risk PWID first appeared to produce the greatest
29
30 societal benefits ⁶⁹. Indeed, it has been shown that targeting the injecting network
31
32 provides greater population health benefit than treating PWID randomly for their HCV
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34 ⁷⁰. Studies such as this support the idea that PWID's should not be excluded from
35
36 treatment based on their apparently risky behaviour. A further study by Martin and
37
38 colleagues suggested that treating current injectors is more cost-effective than
39
40 treating ex- or non-injectors when the chronic HCV prevalence is less than 60% ⁷¹.
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Eradication – Is It Cost-Effective?

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51 Relative to the expense of long-term complications associated with HCV infection,
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53 the price of DAA's is considered cost-effective ²². The bulk of the health costs and
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55 health consequences associated with HCV infection are due to end stage liver
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3 disease late in the natural history of infection. This has led some to suggest that
4
5 treatment should be restricted to patients with more advanced disease only. As even
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7 in high-income nations the cost of DAA's may prohibit their widespread uptake, due
8
9 to affordability, relative to other demands on health budgets. Cost-effective
10
11 evaluations are needed to verify how best to allocate resources and services. A 2015
12
13 study aimed to forecast population-level outcomes from alternative treatment
14
15 strategies in a resource-rich setting ⁷². Using a simulation model and projecting
16
17 outcomes to 2030, trends in HCV incidence and severe liver morbidity was
18
19 extrapolated according to treatment strategies that prioritised either PWID or patients
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21 with moderate/advanced liver fibrosis. The authors concluded that no single
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23 approach to the treatment of HCV in an era of IFN-free therapies addressed all
24
25 public health concerns. Prioritising PWID for treatment results in substantially
26
27 reduced HCV incidence and transmission rates in the population, but fails to address
28
29 the impact of liver disease. Conversely, suboptimal reductions in HCV incidence
30
31 occurs when those with moderate/advanced liver disease are targeted for priority
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33 treatment. It is projected that by specifically targeting active PWID, incident HCV
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35 infection can be reduced to <50 cases per year by 2025 ⁷². The conclusion that can
36
37 be drawn from this paper was that a twin track strategy that targeted active PWID
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39 and those with evidence of hepatic fibrosis would be most cost-effective, but would
40
41 leave the short fall in treatment on those with mild disease who were not injecting, a
42
43 strategy that may not be acceptable to the general population. These estimates
44
45 support the previous modelling studies by Martin and colleagues described above.
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47 The high cost of anti-HCV therapy makes a more targeted treatment approach more
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49 economically beneficial. As such, epidemiological data on PWID populations must be
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51 upgraded on a country by country basis to allow a planned strategy ⁷³. As already
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3 discussed, it is unlikely that substantial reductions in HCV prevalence would be
4
5 achievable with OST and HCNSP alone. However, expansion of OST and NSP
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7 coverage would reduce the number of PWID requiring HCV treatment, and be highly
8
9 cost-effective thus making a target HCV prevalence reduction easier to achieve ¹⁴.
10
11 This supports the idea that HCV eradication policy must be built upon scaled-up
12
13 community outreach projects. While the health economic analysis supports the idea
14
15 of treatment as prevention, and shows it to be a cost effective, it may not be
16
17 achievable due to the affordability issues surround such a relatively common disease
18
19 with such a currently expensive therapy. There is already prioritisation of HCV
20
21 therapy for patients with advanced fibrosis in many countries, with patients with
22
23 milder disease waiting for therapy. To further prioritise active PWID over other
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25 patients with mild disease may not be acceptable to health care providers and
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27 payers.
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Conclusion

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37 The growing burden of chronic HCV infection presents a significant public health
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39 concern. With the advent of highly efficacious and tolerable DAA's, the concept of
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41 treatment as prevention is gaining credence and efforts to scale-up access to
42
43 treatment have been developed.
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48 Although global eradication of HCV via targeted treatment is highly desirable, current
49
50 limitations render it improbable at this point in time; with regional elimination being a
51
52 more realistic prospect. Sub-optimal coverage of harm reduction services worldwide,
53
54 the lack of an effective vaccine, and the high baseline HCV prevalence in many
55
56 places makes HCV eradication very difficult to accomplish. Despite this, modelling
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3 studies by Martin and colleagues show that lower treatment uptake is required to
4
5 achieve a more substantial reduction in HCV prevalence when the baseline
6
7 prevalence is below a certain threshold. Increased access to harm reduction
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9 services may drive the local HCV prevalence low enough to allow targeted treatment
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11 to be successful.
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15 Perhaps the most important prevention strategy is the implementation of HCV testing
16
17 so as to identify those in need of treatment. Solutions must be formulated to
18
19 overcome barriers to care. In this way, more patients eligible to be treated are
20
21 identified and managed accordingly. Early identification, using more accurate
22
23 diagnostic tools, will be essential to prevent the onward transmission of HCV ¹⁰.
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30 Although technically feasible, HCV eradication will require a galvanised effort from
31
32 not only practitioners and healthcare policy makers, but also the patients
33
34 themselves. To achieve HCV eradication via treatment on a global scale, PWID must
35
36 be given increased access to affordable treatment. Ensuring affordability of anti-
37
38 HCV therapy will be critical in the pursuit of eradicability.
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49
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51
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53
54 authors approved the final version of the manuscript.

55 Disclosures

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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

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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.

For Peer Review

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

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3 infections worldwide occur within marginalised societal groups, predominating in
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5 people who inject drugs. Acute HCV infection is often difficult to detect given the
6
7 stigmatisation of at-risk groups and the generally asymptomatic nature of early
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9 infection ¹⁰. Previously, treatment for HCV-infected people who inject drugs was
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11 withheld on the basis of chaotic lifestyles and associated risks of re-infection, which it
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13 was believed made attempts at treatment futile. This belief has not been
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15 substantiated, with the empirical evidence suggesting good outcomes can be
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17 achieved; that people who inject drugs display equal, or even superior, HCV
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19 treatment outcomes to groups from other routes of infection ¹². This has led to
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21 international guidelines now recommending treatment of HCV amongst these high-
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23 risk groups following individualized assessment ¹¹. Although evidence to support
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25 such guidelines is growing it is somewhat limited at present. The change in guideline
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27 position being in part driven by ensuring equity of access to treatment for those that
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29 need it.
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38 Treatment of HCV is fast changing. The arrival of the first generation of direct-acting
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40 antiviral drugs in 2011 changed the landscape of HCV therapeutics, with more
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42 efficacious and highly tolerable drugs entering the market ¹³. The high cost of these
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44 newer drugs has led to the rationing of therapy based on the degree of liver fibrosis
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46 in many healthcare systems. However, research is emerging suggesting that
47
48 specifically targeting HCV-infected people who inject drugs will deplete the pool of
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50 HCV within society for transmission, preventing new infections and giving rise to the
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52 concept of 'treatment as prevention'. This could ultimately lead to the eradication of
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54 HCV.
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Treatment as Prevention in HCV

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

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43 In support of this approach to HCV eradication, modelling studies by Martin and
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45 colleagues have indicated that HCV chronic prevalence could be reduced by treating
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47 those at risk of ongoing HCV transmission ^{18, 19}. A more recent study from the same
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49 group reviewed a number of similar theoretical modelling studies, this time in a range
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51 of global settings and target populations in the context of direct-acting antiviral
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53 therapy ²⁰. They reported that the high incidence of HCV amongst key populations
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55 such as people who inject drugs, men who have sex with men and prisoners
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3 represented an ideal opportunity to curb ongoing HCV transmission. However, the
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5 authors recognised the need to test these hypotheses empirically ²⁰. A number of
6
7 other mathematical models have attempted to explore the preventative value of
8
9 treating people who inject drugs for HCV. A 2013 model proposed that treating as
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11 few as 15 out of 1,000 people who inject drugs annually could halve HCV prevalence
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13 within 15 years ¹⁹. The model was critically dependent on the HCV prevalence within
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15 this population, with the number needed to treat rising with increasing prevalence;
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17 so that at 25% prevalence 15 treatments per annum achieved this impact, but more
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19 than 100 treatments per annum were required if HCV prevalence was over 65%. An
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21 earlier model by the same authors predicted that for a population of intravenous drug
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23 users with a baseline chronic HCV prevalence of 20%, treatment rates of 5, 10, 20 or
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25 40 per 1,000 drug injectors annually for 10 years can result in a reduction in
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27 prevalence of 15%, 30%, 62% and 72%, respectively ¹⁸.
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34 Another 2013 study by Martin and colleagues hypothesised that when antiviral
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36 treatment is combined with opiate substitution therapy and high-coverage needle
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38 and syringe programs, significant reductions in HCV could be achieved. Using a
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40 HCV transmission model, they estimated that chronic HCV prevalence could be
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42 reduced by >50% over a ten-year period. With the newer direct-acting antiviral
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44 drugs, the authors propose that such a target becomes even more attainable ²¹.
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50 The approach of treatment as prevention carries with it several ethical challenges.
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52 Whereas vaccination can be applied universally, curing through drug therapy
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54 requires the identification of target populations. Medical screening on such a large
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56 scale poses ethical dilemmas. As recently discussed by Hagan *et al* ²¹, a false
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3 positive result can be burdensome on those labelled with such a stigmatizing
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5 disease. In addition to being psychologically straining for the patient, it can also lead
6
7 to unnecessary treatment and resource wastage. Conversely, false negative results
8
9 only serve to propagate disease transmission as patients are unaware of their true
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11 status. Even a true positive result can impose societal repercussions as family
12
13 relationships, employment opportunities and insurance status are all affected. In a
14
15 HCV context these concerns are minimized by the high accuracy of the diagnostic
16
17 tests and confirmatory lab practices. The authors also mention incentivisation
18
19 schemes in an effort to combat poor compliance to screening. The follow-on from
20
21 testing and diagnosis is treatment, with the inconvenience of taking medications and
22
23 risk of side effects. In conventional treatment pathways the decision for treatment is
24
25 taken largely by the patient for their individual benefit. However, in the treatment as
26
27 prevention concept the benefit of treatment is much less for the patient but for
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29 society as a whole. Any societal benefit depends on a very high level of uptake, so
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31 an individuals' priorities around treatment could be subverted to those of society,
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33 with a degree of coercion. However, a balance must be struck between voluntary
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35 participation and coercion ²².
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Eradication – Can It Be Achieved?

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46 In 2014, *The Lancet* Commission on addressing liver disease in the UK projected
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48 that with the advent of these new highly effective IFN-free therapies, chronic HCV
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50 infections could be eradicated in the UK by 2030 ²³. It would seem that not only have
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52 these new antiviral treatments changed the therapeutic landscape, but they have
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54 also altered the horizon for the future of HCV.
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3 The concepts of 'control', 'elimination' and 'eradication' have long been the subject of
4 numerous debates. Writing for the World Health Organisation in 1998, Dowdle
5 proposed the definition of 'control' as being a reduction in disease incidence,
6 prevalence, morbidity or mortality to a locally acceptable level; 'elimination' as a
7 reduction to zero of the incidence of a specified disease in a defined geographical
8 area; and 'eradication' as a permanent reduction to zero of the worldwide incidence
9 of an infection such that interventions are no longer required. To this list, he added
10 'extinction', defined as being an infectious agent that no longer exists in nature or
11 laboratory conditions ²⁴.

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

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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 hosts¹³ or facilitate amplification. So we can regard HCV as having an exclusively human host for its life cycle and fore filling the first of Dowdle's principles²⁴.

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 elsewhere²⁵. 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

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3 drugs generally have poor venous access. The use of such testing would enable
4 case-finding in certain higher prevalence settings. The benefits of point-of-care
5 testing, i.e. result available within thirty minutes as compared to a similar sample
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8 being sent to a remote laboratory and available in a few days, are yet to be proven.
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10 The most important issue is how diagnosis leads to treatment and cure. The pathway
11 to treatment and cure is going to be one of multiple visits to the point of care or other
12 sites; and the value of an instant test result as opposed to returning at a later date for
13 said result must be weighed in the context of entry to treatment, which is yet to be
14 evaluated.
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24 Given that over half of people who inject drugs in the UK and USA are unaware of
25 their true HCV status ^{26, 27}, testing at-risk populations to raise the number of people
26 being treated for HCV is vital to have any chance of achieving HCV elimination.
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28 Previous UK studies evaluating the option of dried blood spot testing within specialist
29 addiction services and prisons found that HCV testing increased almost six-fold ^{28, 29}.
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31 A recent U.S study reported that in clinics that offer comprehensive screening and
32 assessment for blood borne viruses, diagnostic rates of HCV soar within these
33 populations ³⁰. A 2015 systematic review supports these findings, reporting that the
34 availability of dried blood spot testing appears to increase the uptake of HCV testing
35 in high-risk populations ²⁵. Hence, dried blood spot testing is clearly a vital tool in the
36 efforts to increase HCV case-finding amongst people who inject drugs. Dried blood
37 spot testing has also been proven to be suitable for large-scale screening programs
38 and therapeutic monitoring. As such, it can be employed to increase access to care
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3 A recent cost-utility analysis utilizing a dynamic mathematical model showed that
4 increasing HCV case-finding in addiction services can be cost-effective. However,
5 this does not translate directly to prison settings. Cost-effectiveness of case-finding
6 here depends on continuity of care following release ³¹. It has been argued that the
7 U.S criminal justice system represents an ideal focus for HCV case-finding and
8 treatment, given the high volume of HCV-infected individuals currently in contact with
9 correctional facilities ³². However, some may argue that the way correctional facilities
10 operate would worsen treatment outcomes due to high rates of re-infection,
11 secondary to unacknowledged institutional high risk drug use. Additionally, routes of
12 reimbursement for treatment costs may make it impossible to establish treatment
13 programs in prisons in many countries.
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30 A 2015 Canadian study evaluated the health and economic benefits conferred by
31 incorporating a one-time screening strategy for HCV in various populations. Using a
32 state-transition model, they proposed that a one-time screening program for pre-
33 selected age groups would likely be cost-effective as asymptomatic cases of HCV
34 would be detected. They calculated that this approach could prevent at least 9 HCV-
35 related deaths per 100,000 persons screened over the lifetime of the cohort
36 analysed ³³.
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48 So the diagnostic technology to diagnose HCV is reliable, cost-effective and widely
49 available. The evidence base for modes of delivery of testing is substantial and this
50 is being translated into effective detection programs in some countries with France
51 and Australia reporting approximately 80% of their prevalent HCV populations having
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3 been diagnosed ³⁴. So widespread diagnosis of prevalent HCV infection is possible
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5 and has already been achieved in some countries.
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10 **Interruption of Transmission**

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

29
30 The main driver for new HCV infection is the injection of drugs with contaminated
31
32 needles and other injecting paraphernalia ³⁵. Therefore, the provision of clean
33
34 needles and other injecting equipment, along with access to opiate replacement
35
36 therapy (for opiate users), to reduce injecting frequency, should reduce the risk of
37
38 HCV transmission. It has been estimated that prevalence of HCV in the UK could be
39
40 up to 60% higher in the absence of opiate substitution therapy and needle and
41
42 syringe programs ³⁶. Hagan *et al* reported that strategies combining treatment for
43
44 substance misuse and instruction for safe injecting practices reduced HCV
45
46 seroconversion by 75%. However, they reported that further research is needed to
47
48 ascertain what specific interventions are most effective in the different subgroups of
49
50 people who inject drugs ³⁷. To complement the Hagan study, Turner *et al* estimated
51
52 that opiate substitution therapy and needle and syringe programs reduce HCV
53
54 transmission by 80% in a UK context ³⁸. Nonetheless, previous modelling has
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2
3 suggested that these interventions alone do not prevent incident HCV infections
4
5 amongst UK people who inject drug³⁶. Indeed, such programs have demonstrated
6
7 higher success rates for HIV prevention compared to HCV^{14, 37}. Contributing factors
8
9 to this are that HCV is ten times more transmissible than HIV (in the context of
10
11 people who inject drugs) and HCV often survives on fomites for prolonged periods of
12
13 time³⁹. Despite this, opiate substitution therapy and needle and syringe programs
14
15 offer other benefits such as reductions in drug-related deaths and drug-related crime
16
17 as well as protection from other blood borne infections^{21, 40}.

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22
23 HCV eradication will likely not be possible without staunch efforts to limit new
24
25 infections that are fueling the epidemic. Numerous interventions have evolved over
26
27 the years that serve to decrease transmission rates. As already alluded to,
28
29 community-based outreach and education programs, stemming from the HIV
30
31 epidemic in the 1980's, proved beneficial in reducing the prevalence of blood borne
32
33 viruses within local populations. Access to free sterile injecting equipment further
34
35 contributed to reductions in HIV and HCV transmission. Although HCV remains very
36
37 high amongst people who inject drugs, the introduction of anti-HIV interventions had
38
39 a profound impact on HCV prevalence¹⁴. However, such effective public health
40
41 interventions are scarce, even in many developed countries. Even where they exist,
42
43 funding is poor. Edlin and Winkelstein argue that community interventions must be
44
45 scaled-up if HCV transmission is to be reduced³⁹. In a review on the feasibility of
46
47
48
49 HCV eradication in the United States, they comment that needle and syringe
50
51 programs only operate in 166 U.S cities, with 20 states not running any such
52
53 programs at all. They also argue that pharmacies are critical in providing sterile
54
55 needles as they would reach all populations, not just a fraction of people who inject
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1
2
3 drugs as it currently stands ³⁹. Current U.S legislation in many states restricts access
4
5 to sterile needles and syringes for illicit drug-use. This reflects a need for policy
6
7 change in a concerted effort to stem the tide of HCV. Recent changes to Californian
8
9 legislation gave more power to local health jurisdictions, with some cities choosing to
10
11 legalise non-prescription syringe sales in pharmacies. A 2015 analysis demonstrated
12
13 that where it was legal, more syringes were obtained amongst intravenous drug user
14
15 populations. Public health policies such as this must be extended to realize the true
16
17 benefits it would have on HCV transmission in target populations ⁴¹. However, one
18
19 must take into account the varied transmission profiles now being seen in some
20
21 developed countries and any public health initiatives for the provision of injecting
22
23 equipment must ensure it reaches those at risk. Recent trend analysis has revealed
24
25 an emerging HCV epidemic in the U.S, stemming from chaotic injecting habits and
26
27 early prescription opioid abuse. Socioeconomic analysis reveals the epidemic to be
28
29 concentrated in non-urban white males, who often have very limited access to sterile
30
31 injecting equipment and injecting advice from experienced users ⁴² as this is
32
33 occurring in areas without previous significant injecting drug use. Different patterns of
34
35 drug abuse may change the benefits of the treatment as prevention approach.
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42 Although needle-sharing is a major aspect of HCV transmission, other injection
43
44 paraphernalia have been strongly implicated in the spread of the virus. For example,
45
46 the sharing of cookers, filtration cotton and water can also permit viral transmission
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48
49 ⁴³. An earlier study calculated that 54% of HCV infections in people who inject drugs
50
51 who did not share needles could be attributed to other injecting equipment ⁴⁴. The
52
53 provision of sterile paraphernalia in Scotland is anticipated to reduce HCV
54
55 transmission amongst people who inject drugs, but results from this natural
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2
3 experiment are awaited ⁴³. However, earlier studies evaluating the risks of HCV
4
5 transmission amongst drug users who share injecting equipment have failed to
6
7 quantify the contribution that this route of infection is having on HCV spread ⁴⁵.

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9
10 Indeed, one 2014 study concluded that, although injecting risk behaviour is clearly
11
12 reduced by opiate substitution therapy and needle and syringe programs,
13
14 comparatively little review-level evidence exists to support such a trend for HCV
15
16 transmission amongst people who inject drugs ⁴⁶.

21 2. Vaccination

22
23 In most infectious diseases that have been considered for elimination a vaccine has
24
25 been available. However, this is not essential as evidenced by the near eradication
26
27 of the Guinea worm without even drug therapy ⁴⁷. Of course vaccine development
28
29 seems logical. It can be reasonably argued that due to the asymptomatic nature of
30
31 the virus, and the fact that most people are unaware of their HCV status, vaccination
32
33 is perhaps the most effective way of eradicating HCV ¹⁰. A universal vaccine could
34
35 not only prevent primary HCV infection, but may also prevent re-infection after cure
36
37 following direct-acting antiviral therapy. This latter use has implications for those with
38
39 ongoing risk of HCV exposure, such as in people who inject drugs ⁴⁸. It is estimated
40
41 that even if pricing of direct-acting antivirals were 1,000-fold lower to benefit low-
42
43 income nations, the costs of extensive HCV screening and drug distribution would
44
45 exceed those of a universal vaccination program ⁴⁹. Results from several vaccine
46
47 trials are eagerly awaited. In one such study, Swadling *et al* describe the
48
49 development of a highly immunogenic vaccine for HCV. By utilizing the critical role
50
51 that T cell immunity plays in antiviral control, they report having produced a potent T
52
53 cell vaccine that prevents chronic infection by incorporating chimpanzee adenoviral
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3 and MVA vectors to prime and boost T cell memory. The first efficacy study of
4 ChAd3NSmut/MVA-NSmut in IVDU's has recently started in the U.S (NCT01436357)
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6
7⁵⁰. However, results from these studies are forthcoming and historically, such T cell
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9
10 vaccines have had more limited efficacy than antibody-based vaccines in clinical
11
12 trials.

13 14 15 16 3. HCV therapy

17
18 HCV antiviral therapy has undergone a revolution, moving very rapidly from IFN-
19 based therapies with cure rates of 40-70% depending on genotype, to the advent of
20 direct-acting antivirals achieving cure rates in excess of 90% for all genotypes with
21
22 treatment duration reduced to as little as eight weeks. The development of these
23
24 newer antivirals has long been impeded by the lack of an effective cell culture
25
26 system for HCV proliferation⁵¹. The availability of high-throughput virological assays
27
28 to characterise the various stages of the HCV replication cycle have enabled the
29
30 identification of more specific antiviral targets^{52, 53}. This development, combined with
31
32 changes in the definition of sustained virological response (SVR), has generated the
33
34 momentum for the rapid change in the field. The European Association for Study of
35
36 Liver (EASL) describes the endpoint of therapy as undetectable HCV RNA 24 weeks
37
38 after the end of the treatment course (SVR24), defined as <15 IU/mL¹¹. In a long-
39
40 term follow-up study of HCV-infected patients treated with PEG-IFN- α 2a and
41
42 ribavirin (n = 1,343), a durable SVR24 of 99.1% was retained once achieved⁵⁴. Such
43
44 data suggests that HCV recurrence is rare in patients who achieve an SVR, and that
45
46 from a virologic standpoint, such patients can be regarded as cured. The validity of
47
48 measuring HCV RNA 12 weeks after completion of treatment (SVR12) has been
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3 evaluated and approved by regulators in the U.S and Europe, as an equivalent end
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5 point ¹¹.
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10 The currently available direct-acting antivirals are split into three classes defined by
11 their HCV target protein: the protease inhibitors targeted against the NS3/4a
12 protease; and the NS5a complex inhibitors and polymerase inhibitors, which are
13 directed against the NS5b protein. This latter class can be further divided into
14 nucleotide and non-nucleotide inhibitors. Initial protease inhibitors, and to a lesser
15 extent NS5a inhibitors, are genotype specific. However, newer pan-genotypic direct-
16 acting antivirals with superior efficacy, lower adverse effect profiles and shorter
17 therapy durations are constantly emerging ¹³.
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30 Access to treatment has been widened with the advent of these new drugs.
31 Previously, IFN-based therapy was contraindicated in patients with many co-
32 morbidities including decompensated cirrhosis ³⁵. Thus, with the newer antivirals
33 therapy can now be given to patients in whom it may have previously been
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56, 57. The full impact of these newer antivirals will only be appreciated once

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3 innovative approaches to engage more HCV-infected individuals into antiviral
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5 therapy are practiced.
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10 4. Delivery of HCV therapy- Pathway to Eradication

11
12 The delivery of therapy to patients is key to its efficacy. Complex care pathways,
13
14 based in, or outreaching from secondary or tertiary care, have been developed to
15
16 deliver IFN-based therapy to patients. Such care pathways focus on managing the
17
18 side effects of therapy safely. Chaotic unstable patients such as people who inject
19
20 drugs have not made it through these therapy pathways in significant numbers and
21
22 such patients that do are atypical. The aim of these pathways has been to prevent
23
24 advanced liver disease by curing HCV infection before cirrhosis develops. So the
25
26 episode of treatment can be delayed until the patient is considered suitable, by the
27
28 constraints of the treatment pathway. This is in marked contrast to the situation if
29
30 treatment as prevention is the aim of therapy, where early therapy at the earliest
31
32 possible time in the duration of infection would give the optimum outcome. So the
33
34 pathway to treatment has to be receptive to the patient.
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42 Clinical networks are a much vaunted solution to the problems associated with
43
44 treatment of HCV. In England they are a very secondary care-based solution to allow
45
46 patients to be treated at hospitals closer to their locality, but still controlling
47
48 availability of drug therapy centrally. In Scotland's HCV action plan, managed care
49
50 networks were a central plank to achieve the integration of primary and secondary
51
52 care with third sector providers of health care around patients with or at risk of HCV
53
54 into a cohesive and seamless treatment pathway. This integration was fundamental
55
56 to the success of the Scottish action plan, the implementation of this is described
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3 and illustrated in the report by Tait *et al* ⁵⁸. Thus networks can achieve improvement
4 in care, particularly when working across healthcare boundaries and accessing
5 difficult-to-reach patient populations. However, all key stakeholders in the area need
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7
8 to be a part of the network, working together to an agreed strategic aim. The MCN
9 model is ideally suited to a treatment as prevention strategy.

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16 People who inject drugs are a largely stigmatized group who have limited access to
17 conventional healthcare. Often as a result of homelessness and deprivation, many
18 patients lack a means of communication with conventional healthcare providers.
19 However, they are often in regular contact with other services in a variety of
20 contexts. For example: needle exchange programs in the community which dispense
21 both sterile injecting equipment and advice on safe injecting practices; and
22
23 pharmacies which administer methadone to those on opiate substitution programs.
24 These points of contact represent an ideal opportunity to target people who inject
25 drugs for HCV treatment. Pilot studies show that with the new direct-acting antivirals,
26 with their reduced need for regular blood monitoring and fewer side-effects, the
27
28 clinical and para-clinical staff within these facilities such as pharmacists and drug
29 workers are keen and able to take on a lead role in assessment and provision of
30 anti-HCV therapy as part of managed care networks ⁵⁹. These managed care
31 networks provide the clinical supervision they need to deliver a protocol-based HCV
32 treatment pathway. The initial sustained virological response rates from such
33
34 pathways match clinical trials and are much more inclusive of a broader group of
35 patients from a background of intravenous drug use, which is vital to a treatment as
36 prevention strategy.
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3 In addition to opiate substitution centers (e.g. pharmacies) and needle and syringe
4 program facilities, prisons should also be considered as an opportunity to treat.
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6 Given the high numbers and proportions of people who inject drugs in correctional
7
8 facilities, prisoners represent an ideal target population for treatment as prevention.
9
10 As with targeting people who inject drugs in general, targeting prisoners poses its
11
12 own challenges and ethical considerations. A 2015 letter by Levy and Larney
13
14 highlighted the issues of treatment as prevention in correctional settings. They argue
15
16 that the imbalance of power between prisoners and custodial staff may translate to a
17
18 curtailing of civil liberties ⁶⁰. In such circumstances, how can we be sure that consent
19
20 to screening and treatment is truly voluntary? Adding to this, Martin and colleagues
21
22 emphasize the need for continuity of care amongst prisoners after release or transfer
23
24 for this approach to HCV prevention to be cost-effective ⁶¹. A recent review of
25
26 treatment outcomes in prisoners treated in Scotland has shown a strong negative
27
28 correlation between liberation during treatment and sustained virological response.
29
30 This work was using IFN-based therapy and so should be less of an issue with new
31
32 direct-acting antiviral-based therapy of shorter duration ⁶². In terms of primary
33
34 prevention Levy and Larney also called for greater access to harm reduction
35
36 services such as needle exchange programs within prisons, arguing that such
37
38 services exist in community settings for people who inject drugs. As such, those who
39
40 successfully complete treatment can protect themselves from re-infection and thus
41
42 increase the effectiveness of this HCV eradication strategy ⁶⁰. It should be noted,
43
44 however, that a 2013 study found that in a sample of 5,076 surveyed prisoners in
45
46 Scotland, the risk of HCV transmission was lower amongst prisoners compared to
47
48 Scottish people who inject in the community. The authors propose that this is due to
49
50 the low incidence of in-prison injecting, although they concede that some under-
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3 reporting is likely. As such, the authors suggest that low HCV incidence amongst
4
5 prison populations does not depend on the introduction of needle exchange
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7 programs ⁶³. The major issue around provision of needle exchange in prisons is the
8
9 potential for their use as weapons against staff which has led prison officer unions to
10
11 object on health and safety grounds.
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16 The major criticism of treatment as prevention strategies in people who inject drugs
17
18 is the impact on injecting behaviour and the risk of re-infection. Regarding the
19
20 interplay between HCV treatment and the behaviours of intravenous drug users, it
21
22 has been established that antiviral therapy does not increase illicit drug use.
23
24 Intermittent injecting during treatment has also been shown to have no influence
25
26 over regimen adherence, completion of treatment, or attainment of sustained
27
28 virological responses. Contrary to this, more regular injecting has been associated
29
30 with lower sustained virological response rates and discontinuation of treatment ¹⁴. In
31
32 an effort to better understand injecting behaviours and how they relate to re-infection
33
34 risk post-sustained virological response, Valerio and colleagues conducted an
35
36 analysis of 1,170 people who inject drugs who attained a sustained virological
37
38 response over a twenty-year period (1992-2012) ⁶⁴. They reported that an increasing
39
40 minority of people who inject drugs who attain a sustained virological response are at
41
42 an elevated risk of re-infection or death as a result of high intensity injecting
43
44 behaviour. In agreement with EASL recommendations ¹¹, the authors advocate for
45
46 the on-going monitoring of high-risk patients post-sustained virological response ⁶⁴.
47
48 However, evidence suggests that people who inject drugs who achieve a sustained
49
50 virological response are more likely to pursue a healthy lifestyle ⁶⁵. The Valerio study
51
52 also voiced concern that re-infection rates amongst people who inject drugs will rise
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3 as HCV treatment is scaled-up⁶⁴. Commentary from Hellard and Scott (2015)
4
5 postulated that many of the current models measuring the outcomes of HCV
6
7 treatment as prevention incorporate high levels of re-infection into their modelling,
8
9
10 thus overstating the re-infection risk. Whilst it is established that HCV re-infection is
11
12 common out-with treatment settings, re-infection after antiviral therapy is
13
14 considerably lower⁶⁶. A meta-analysis by Aspinall *et al* calculated the pooled risk of
15
16 re-infection amongst five cohorts of people who inject drugs (n = 131) to be 2.4 (CI =
17
18 0.9-6.1) per 100 person years⁶⁷. However, a 2016 study reported an 11% re-
19
20
21 infection rate in a multicentre trial follow-up of intravenous drug users infected with
22
23 genotypes 2 or 3⁶⁸. This highlights possible variations in the range of reinfections.
24
25 Emergent data from the ERADICATE trial will provide more information on
26
27 re-infection rates in people who inject drugs undergoing anti-HCV therapy. A more
28
29 recent study suggested that targeting HCV treatment by stratifying the level of
30
31 injection drug-use could enhance benefits at the population level⁶⁹. The authors
32
33 reported that HCV treatment is best determined by its prevalence within the
34
35 population; when >50% of all exchanged syringes are contaminated with HCV they
36
37
38 recommend treating low-risk people who inject drugs first. Conversely, below this
39
40 threshold, treating high-risk intravenous drug users first appeared to produce the
41
42 greatest societal benefits⁶⁹. Indeed, it has been shown that targeting the injecting
43
44 network provides greater population health benefit than treating people who inject
45
46 drugs randomly for their HCV⁷⁰. Studies such as this support the idea that people
47
48
49 who inject drugs should not be excluded from treatment based on their apparently
50
51 risky behaviour. A further study by Martin and colleagues suggested that treating
52
53 current injectors is more cost-effective than treating ex- or non-injectors when the
54
55 chronic HCV prevalence is less than 60%⁷¹.
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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-effective²². 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 setting⁷². 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 2025⁷². 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

1
2
3 treatment on those with mild disease who were not injecting, a strategy that may not
4
5 be acceptable to the general population. These estimates support the previous
6
7 modelling studies by Martin and colleagues described above. The high cost of anti-
8
9 HCV therapy makes a more targeted treatment approach more economically
10
11 beneficial. As such, epidemiological data on injector populations must be upgraded
12
13 on a country by country basis to allow a planned strategy ⁷³. As already discussed, it
14
15 is unlikely that substantial reductions in HCV prevalence would be achievable with
16
17 opiate substitution therapy and needle and syringe programs alone. However,
18
19 expansion of these interventions would reduce the number of people who inject
20
21 drugs requiring HCV treatment, and be highly cost-effective thus making a target
22
23 HCV prevalence reduction easier to achieve ¹⁴. This supports the idea that HCV
24
25 eradication policy must be built upon scaled-up community outreach projects. While
26
27 the health economic analysis supports the idea of treatment as prevention, and
28
29 shows it to be cost effective, it may not be achievable due to the affordability issues
30
31 surrounding such a relatively common disease with such a currently expensive
32
33 therapy. There is already prioritisation of HCV therapy for patients with advanced
34
35 fibrosis in many countries, with patients with milder disease waiting for therapy. To
36
37 further prioritise active intravenous drug users ¹⁴ over other patients with mild disease
38
39 may not be acceptable to health care providers and payers.
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47 **Conclusion**

48
49 The growing burden of chronic HCV infection presents a significant public health
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51 concern. With the advent of highly efficacious and tolerable direct-acting antivirals,
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53 the concept of treatment as prevention is gaining credence and efforts to scale-up
54
55 access to treatment have been developed.
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5 Although global eradication of HCV via targeted treatment is highly desirable, current
6
7 limitations render it improbable at this point in time; with regional elimination being a
8
9 more realistic prospect. Sub-optimal coverage of harm reduction services worldwide,
10
11 the lack of an effective vaccine, and the high baseline HCV prevalence in many
12
13 places makes HCV eradication very difficult to accomplish. Despite this, modelling
14
15 studies by Martin and colleagues show that lower treatment uptake is required to
16
17 achieve a more substantial reduction in HCV prevalence when the baseline
18
19 prevalence is below a certain threshold. Increased access to harm reduction
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21 services may drive the local HCV prevalence low enough to allow targeted treatment
22
23 to be successful.
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30 Perhaps the most important prevention strategy is the implementation of HCV testing
31
32 so as to identify those in need of treatment. Solutions must be formulated to
33
34 overcome barriers to care. In this way, more patients eligible to be treated are
35
36 identified and managed accordingly. Early identification, using more accurate
37
38 diagnostic tools, will be essential to prevent the onward transmission of HCV ¹⁰.
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43 Although technically feasible, HCV eradication will require a galvanised effort from
44
45 not only practitioners and healthcare policy makers, but also the patients
46
47 themselves. To achieve HCV eradication via treatment on a global scale, people who
48
49 inject drugs must be given increased access to affordable treatment. Ensuring
50
51 affordability of anti-HCV therapy will be critical in the pursuit of eradicability.
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4
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6
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11
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