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Hepatitis C treatment and prevention in people who inject drugs (PWID) and prisoners: A narrative review of the extant literature

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Summary

Background. Hepatitis C is a curable and preventable disease. People who inject drugs (PWID) and prisoners are at-risk groups for acquisition of Hepatitis C Virus (HCV), yet treatment rates remain low. Agonist Opioid Treatment (AOT) and needle syringe programs (NSP) reduce HCV transmission, yet coverage, particularly in prisons, is inadequate. 'Treatment as prevention' is a key public health strategy to help achieve the World Health Organisation (WHO) goal of HCV elimination by 2030. **Aim:** To review the recent literature on HCV treatment and prevention in PWID and prisoners. **Methods:** Electronic data base (Medline, PubMed, Cochrane library and Embase) and key website search using search terms related to the topic. **Results:** HCV related disease burden in PWID and prisoners is greater than the general population, yet treatment rates remain low. Direct acting anti-virals, mobile elastography, integration of treatment into community and prison settings and less restrictive treatment guidelines have removed many treatment barriers. Treatment adherence and outcomes, among PWID (even current injectors) and prisoners are equivalent to the general population. HCV treatment in both groups is cost-effective but is dependent on up scaling treatment levels, continuing treatment on prison release and preventing re-infection. The public health strategies of treatment as prevention and micro-elimination along with adequate coverage of AOT and NSP has the potential to achieve the WHO goal of HCV elimination by 2030. **Conclusion:** Up-scaling HCV treatment levels and increasing AOT and NSP coverage among PWID and prisoners remains a challenge but is an essential public health strategy to reduce the increasing HCV burden.

Key Words: Hepatitis C; PWID; prisoner; treatment; prevention

1. Introduction

HCV infection is a leading cause of liver related morbidity and mortality across Europe [130]. An estimated 14 million people are chronically infected with this blood borne virus in the European region [61, 130], with over 70,000 dying annually of HCV related liver cirrhosis and cancer [116]. Injecting drug use (IDU) is the major driver of the HCV epidemic in developed countries and now accounts for 80% of new infections in the European Union (EU) [37, 48]. Surveillance data on HCV infection is incomplete which impacts public health efforts to manage this important epidemic [29, 71, 72]. The incidence and prevalence of HCV infection is much higher in PWID and prisoners than the general population [27, 29, 36, 48, 72, 97]. Since 2001 effective treatment with pegylated interferon and ribavirin has been available [59]. More recently the availability of simple and tolerable direct acting antivirals (DAA) have revolutionised the HCV treatment landscape, yet the majority of those infected remain undiagnosed and untreated [30, 53, 87, 123].

PWID and prisoners are some of the most marginalised people in society and despite having high rates of physical and psychiatric morbidity are underserved by traditional health services [40, 41, 48]. PWID include those who have ever injected an illicit

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drug. This population consists of both past injectors and present injectors [71]. A subgroup of PWID will also be receiving agonist opioid treatment (AOT), some of whom will continue to inject drugs [2, 71]. The differentiation between former and current injector is important since those that continue to inject are most at risk of HCV acquisition and transmission and are a key population to target for both treatment and prevention [37, 83].

In the literature, PWID and prisoners are often reported as two distinct groups but artificially so, as HCV infected prison populations typically represent a sub-group of the PWID population [27, 7]. PWID experience high rates of incarceration (56-90% ever being incarcerated), and previous incarceration is associated frequently with HCV infection and increased injecting risk in the community [37, 64, 112]. Recent prison release is also associated with heightened HCV transmission risk which is of particular concern since the majority of prisoners serve short prison sentences (> 12 months) [4, 98, 112, 132]. Managing the transition period between prison and community is seen as crucial to HCV public health strategies targeting prisoners and PWID [57, 112]. Successfully community linkage on release from prison enhances treatment outcomes and cost effectiveness [57, 85].

Understanding the HCV related disease burden and identifying barriers and enablers to treatment uptake are essential to the planning and implementation of public health strategies aimed to HCV elimination [49, 53]. HCV prevention is essential to optimise the benefits of treatment and is also closely associated with re-infection rates and cost-effectiveness of treatment [73]. This review reports on HCV treatment and prevention in PWID and prisoners. It reports on the estimated disease burden, barriers and enablers, treatment guidelines, outcomes, re-infection rates and prevention (including the public health strategies of treatment as prevention and micro-elimination).

2. Methods

A narrative review of the literature was undertaken. The search engines Medline, PubMed, the Cochrane Library and Embase were searched for all articles published in the time frame 2008-2018 and in all languages. Key search terms used were prison, prisoner*, inmate, combined with Hepatitis C and a range of other terms relevant to HCV treatment and prevention, including disease burden, barriers and enablers, outcomes and re-infection rates, cost-effectiveness, treatment as prevention and prevention. The same search was repeating replacing prisoner with PWID.

Due to the recent advances in HCV management, preference was given to systematic reviews and studies published in the last 5 years in high impact peer reviewed journals. The reference lists of the chosen publications were also searched for additional articles that might be relevant to the review. Websites from the following organisations; United Nations Office on Drugs and Crime (UNDOC), World Health Organisation (WHO), European Centre for Disease Prevention and Control (ECDC), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Centre for Disease Control and Prevention (CDC) were searched for relevant reports. Reference lists from these reports were searched for additional articles relevant to this review. Grey and unpublished literature was not included.

The term ‘prison’ is used in this review to encompass all places of detention associated with the criminal justice system, including prisons, remand centres (prisoners awaiting trial) and the American term jail (prisoners on remand and serving sentences of less than one year), juvenile detention facilities, pre-trial detention centres and extra-judicial detention centres for PWID.

3. Results

3.1. HCV-related disease burden

It is difficult to estimate the true extent of the global HCV related disease burden given the asymptomatic nature of HCV infection and the poor access and engagement of those infected with medical services [23, 85, 107, 108]. In some regions as many as 75-90% of HCV positive individuals are unaware of their infection [128]. Globally 71 million people have chronic HCV infection with an estimated 5.6 million of these being PWID [49, 128]. Morbidity and mortality continue to increase among PWID [97, 108].

Those chronically infected remain at risk for onward transmission and frequently progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [32, 108, 111]. An estimated 70-80% of individuals exposed to HCV develop chronic infection; if untreated, 3-11% will develop liver cirrhosis within 20 years, with associated risks of liver failure and HCC [43, 91]. The following factors have been identified to increase progression of liver disease: male gender, co-infection with HBV or HIV and alcohol consumption [79, 106].

The prevalence of HCV related, end-stage liver disease and mortality are increasing [32, 111]. Approximately 27% of cirrhosis and 25% of HCC cases globally can be attributed to HCV [32]. HCV infected individuals have 2.4 times the risk of all-cause mortality compared with the non-infected population (26.5 times the risk of liver-related mortality and 1.8 times the risk of non-liver related mortality) [12, 32].

HCV related mortality surpassed mortality from HIV in the USA, primarily because of end-stage liver disease among members of the 1945-1965 birth cohorts who have been living with HCV infection for 20-30 years [80]. Modeling studies project that without the scaling up of HCV treatment the associated disease burden will increase by 36% to 64% over the next decade [13].

Prioritising patients with advanced liver disease is the most effective strategy to reduce HCV related morbidity and mortality [13, 67]. In jurisdiction were access to DAA is limited by cost, active case finding of patients with liver disease is a priority [125, 128]. The immediate priority across Europe is to scale up HCV treatment in people with severe liver disease to reduce HCV related morbidity and mortality, as rapidly as possible [37].

3.2. HCV treatment

HCV treatment uptake among PWID and prisoners is low [2, 62, 83]. Until 2014, the standard treatment for HCV infection was pegylated interferon (PEG-IFN) and ribavirin (RBV). The length of treatment was dependent on HCV genotype, 48 weeks for HCV genotypes 1, 4, 5, and 6 with expected sustained virologic response (SVR) rates of 40-50% or 24 weeks for HCV genotypes 2 and 3 and 80% SVR response rates [95].

Since 2014 the HCV treatment landscape has changed. The development of non-interferon based DAA therapies has meant a significant reduction in treatment duration (8-12 weeks), adverse side effects experienced and improved treatment outcomes (viral clearance >90%) [13, 39, 49, 100]. In contrast to previous treatments, the new drugs are effective in those with severe liver disease and against all genotypes and have fewer psychiatric side effects [100, 101]. The development of newer pan-genotype DAA has the potential to reduce treatment times even further and reduce the need for genotyping pre-treatment [100, 101]. This may have particular utility in prison populations where short prison sentence length impacts in treatment uptake and completion [6, 53, 87]. However, these treatments remain expensive and challenges remain to scaling up treatment in PWID and prisoners.

3.3. Barriers and enablers

Barriers to HCV treatment among PWID have been identified and include: concerns about side effects, limited knowledge of HCV, worries that treatment will be rationed, experiences of treatment refusal due to drug use, competing priorities, experiencing stigma, criminalisation and difficulty accessing services [49, 63, 114].

In the past, PWID generally had a negative view of interferon, and some physicians hesitated to prescribe this drug because they feared that it may have unacceptable side effects, some resembling opioid withdrawal symptoms [31]. Parenteral application also presented a barrier to interferon use for many PWID [50]. At the practitioner level, perceptions about poor adherence, ongoing substance use, relapse to substance use, risk of exacerbating co-morbid psychiatric disease and potential risk of re-infection have often been used as reasons for withholding therapy [109].

Interventions to enhance linkage to care include; facilitated referral for HCV assessment, scheduling of specialist appointments for clients, integrated HCV care, drug use and psychiatric services delivered by a multidisciplinary team with case management services, with or without non-invasive liver disease assessment [104].

Major barriers exist to the uptake of HCV treatment in prisons. These include the high turnover and movement of incarcerated individuals, and poor linkage to care [9, 131]. In some jurisdictions the high costs of DAA is a further barrier to widespread scale-up of HCV treatment [56, 90].

Enablers to HCV treatment in prisons have been identified and these include; in-reach hepatology services, improved models of health care delivery, nurse-led clinics , telemedicine, increasing prisoners' awareness and understanding of HCV infection and treatment options, educating both operational and clinical staff and involvement of peer educators in increasing knowledge and reducing stigma [17, 79]. Further enablers to HCV treatment uptake include prisoners relinquishing their parole eligibility to commence treatment inside prison. As patients' perceptions of Hepatitis C therapy are influenced by peers, such campaigns should consider involving peers in both planning and implementation [17].

Prison potentially offers a relatively stable environment in which to commence treatment as they usually provide good access to health care providers and are organised around routine and structure [40, 129]. Shorter, more tolerable treatment regimens with less monitoring requirements have the potential to overcome some of the identified barriers including the short length of the majority of prison sentences [101].

The availability of mobile elastography to assess the extent of HCV related liver disease along with movement of HCV treatment out of hospital-based services is further improving HCV treatment uptake and outcomes both in community settings and prisons [3, 117]. In the future this assessment may be further simplified by the use of amino transferase/platelet ratio index (APRI) or FIB-4 test [1, 34]. These tests have further utility in resource limited settings for the assessment of hepatic fibrosis rather than other noninvasive tests that require more resources such as elastography or Fibro Test [59].

3.4. Guidelines

International guidelines recommend the prioritisation of HCV treatment for PWID and prisoners. Clinical guidelines at a European level recommend that current injecting by itself is not a contraindication to HCV treatment access [5, 74] and recommend that treatment be provided to PWID (current) who are at risk of transmitting infection to others, irrespective of disease stage [34]. The recommendation not to exclude PWID who are actively injecting drugs has the potential to remove some of the identified barriers to HCV treatment. Globally, DAA availability is variable with many jurisdictions restricted access to contain cost. In resource limited settings access is often prioritised based on the severity of liver disease. This approach improves morbidity and mortality but does not impact on treatment as a prevention strategy. Treatment decisions need to be individualised taking into consideration social circumstances and the availability of support, as well as the anticipated clinical benefit of achieving an SVR.

3.5. Treatment outcomes

Treatment outcomes are measured by SVR rates; defined as the proportion of patients with undetectable HCV RNA measured at 12 or 24 weeks post treatment. In almost all cases patients achieving SVR remain virus free and are considered cured [34]. It is not clear how many PWID have been treated for HCV infection but the evidence suggests that rates are low [74]. There is increasing evidence that treatment for PWID is highly effective; two systematic reviews suggest that SVR among PWID are comparable to those reported by large randomised controlled trials of pegIFN/RBV treatment [5, 59].

SVR and adherence to treatment of HCV can result in acceptable outcomes in individuals who report current injecting drug use and who meet standard eligibility criteria for commencing HCV treatment [19]. Owing to the small number of studies available, it was not possible to investigate other factors, such as the mode of treatment delivery and the availability of treatment support, that are likely to impact on treatment outcomes. Models of community-based HCV treatment have been established and evaluated for efficacy in various jurisdictions [9. 104]. A recent systematic review concluded that the available data (while limited) supports the efficacy of community-based HCV treatment and the potential for this approach to increase treatment uptake [104]. Among PWID on AOT drug use at baseline and during treatment does not affect adherence or treatment outcomes and active drug use should not exclude PWID from access to DAA [30].

Prison-based HCV treatment achieves similar or better outcomes to community-based treatment, with those not released or transferred during treatment doing particularly well [6]. Inter-prison transfer and release have a negative impact on completion and should be avoided where possible [6, 87, 112]. Linkage to community-based treatment on release improves outcomes and cost-effectiveness and reduces the risk associated with the post-release period [65, 112]. Many of the prison-based treatment outcomes studies are from the interferon area of treatment where many prisoners were excluded from treatment due do stricter eligibility criteria and fears regarding adverse side effects. More recent studies using DAA have also shown very promising outcomes and a number of prisons have reported micro-elimination of HCV from their prison setting [11, 100, 102].

3.6. Re-infection rates

The risk of HCV re-infection among PWID following achieving an SVR is considered relatively low (1–5% per year), but there is considerable uncertainty around this estimate among those who continue to inject after achieving an SVR [6, 19, 33]. Additionally, reported rates of re-infection among PWID are

very likely subject to considerable selection bias for interferon-based treatments [33]. A number of studies have reported higher re-infection rates among current PWID and identified older age and injecting drug use at the end of or post-treatment [89].

However, the rate of HCV re-infection after successful treatment in inmates is high, particularly among those who continue to inject drugs [78, 81]. Studies have reported an overall re-infection rate of 5.27 cases per 100 person-years. Re-infection incidence was significantly higher among active drug users, HIV co-infected and those engaging in more than one risk behaviour after treatment [78, 81]. Preventative interventions at diagnosis and during and after HCV treatment should be strongly reinforced. With less restrictive treatment guidelines and expanding DAA treatment eligibility to increasing numbers of PWID, increasing levels of re-infection are to be expected [54]. Individual- and population-level efforts to address and prevent re-infection should therefore be undertaken when providing HCV care for people with on-going risk behaviour. Constructive strategies include acknowledgement, education and counselling, harm reduction optimisation, scaled-up treatment including treatment of injecting networks, post-treatment screening, and rapid retreatment of re-infections [92].

Re-infection is a major concern and impacts on both the cost effectiveness and prevention benefits of treatment. There is a need for post-treatment surveillance and wide spread implementation of strategies to enhance HCV prevention, such as access to high-coverage needle and syringe programmes (NSP) and AOT to minimise HCV re-infection risk [89].

3.7. Cost-effectiveness

The cost of DAAs, while decreasing, is significant and recognised as a barrier to treatment expansion. Modeling studies show that DAA are cost-effective due to the health care savings associated with reduced HCV related morbidity [25, 46]. Studies have shown that treatment of PWID with interferon-based treatment is cost-effective compared with no treatment [88, 120]. Further modeling studies in the UK have shown that treatment with DAA was cost-effective in models projections of increased uptake of treatment [37, 46, 119] but levels of re-infection could limit the effectiveness of these models.

Similarly, treatment of prisoners with short acting DAA regimes is cost-effective, in particular where treatment uptake is increased and continuity of treatment between community and prison is maintained on release [37]. The economics of prison-based HCV treatment is complicated by the fact that most of the benefits accrued from treatment occur in the community after the prisoner is released. In jurisdictions where the cost of HCV treatment is carried by the prison health care budget there may be reluctance on prison authorities to actively screening and treat HCV infected prisoners. This is of particular importance in US prisons where a number of court cases have supported the rights of HCV infected prisoners to access treatment and where prison budgets are directly responsible for its cost. Increasingly public health specialists recommend that prison health care systems should fall under the remit of national public health care structures and that good prison health is good public health [40, 129].

Changing funding models in some countries have made DAA treatment more cost-effective. Many national governments have negotiated packages based on a maximum drug spend per year which encourages health care systems to actively find and treat those infected. In Australia this model has been shown to be particularly effective [8, 54]. The UK government has developed a model where drug companies provide financial support initiatives to increase screen and HCV treatment in hard to reach groups while agreeing to pay an agreed annual sum for unlimited access to DAA therapies [99].

3.8. 'Treatment as prevention'

Treating HCV infected prisoners and PWID has the potential to cure the individual but also to reduce transmission and disease burden at a population level [47, 60]. The impact on treatment as a prevention strategy is dependent both on the effectiveness and levels of treatment [60, 85, 86, 126]. By inducing a reduction in infectiousness in PWID and prisoners, treatment leads to a reduction in HCV transmission and an eventual decrease in advanced disease and, importantly, potential control of the HCV epidemic. Results from a number of mathematical modelling papers have raised the expectation that a moderate level of HCV treatment in PWID could lead to a significant reduction in the prevalence and incidence of HCV infection [18, 47, 60, 86].

It is hypothesised that an HCV treatment strategy would be especially effective if provided in combination with other primary interventions, such as AOT and NSP, by reducing the risk of spread by removing individuals who have been successfully treated from

'the pool of infected' [47, 51]. The reality is more complex, and real-world evidence of the impact of scaling up HCV treatment is lacking. PWID are a mixed population of individuals at risk of acquiring and transmitting infection, including current injectors, those who are in treatment or prison or have recently ceased injecting and are at high risk of relapse. Furthermore, patterns of drug use along with risk behaviour change over time e.g. emerging psychoactive drugs, HIV outbreaks [44]. Existing estimates of injecting drug use prevalence rarely captures the whole [71]. These factors could change over time (in terms of scaling up or even disinvestment) and impact on the intervention and will need to be measured and incorporated into the analysis.

The public health strategy of treatment as prevention has been driven by the introduction of DAA [51, 60, 77, 87]. There is now a possibility of achieving better treatment retention and outcomes for PWID and prisoners. Research shows that investment in HCV treatment, even for those who continue to inject drugs, is justified on public health grounds [47, 51]. The newer HCV treatment regimens are less complex to administer and, therefore, more appropriate to use in primary care, prison and drug treatment settings [127]. While prisons would seem ideal locations to implement treatment as prevention strategies, concerns have been expressed about associated ethical issues. The unequal relationship between prisoner and health provider may impact on consent issues and those prisoners who have been successfully treated may not have access to appropriate harm reduction measures to protect against re-infection [77]. Furthermore, the short duration of sentences for PWID (predominately incarcerated for drug related crimes) may negatively impact HCV treatment as prevention among prisoners [86, 87].

Peer-involved and peer-led services can help to engage those who are reluctant to draw on traditional services [3, 110, 113, 124]. Concerns have been expressed that an increased impetus on Hepatitis C 'treatment as prevention' might threaten harm reduction 'prevention as prevention' initiatives such as AOT and NSP [16].

3.9. Micro-elimination

Increasingly in the HCV literature the strategy of micro-elimination is reported on [24, 75, 102]. Micro-elimination entails pursuing elimination goals in discrete populations through multi-stakeholder initiatives that tailor interventions to the needs of these populations. Micro-elimination is less daunting, less complex, and less costly than full-scale, country-level initiatives to eliminate HCV, and it can build momentum by producing small victories that inspire more ambitious efforts [75]. The micro-elimination approach encourages stakeholders who are most knowledgeable about specific populations to engage with each other and also promotes the uptake of new models of care. PWID and prisoners are two key populations that could benefit from this approach. A recent study reported on micro-elimination of HCV infection through rapid uptake of government-funded DAA therapy in an Australian prison. During a 22-month period, 119 patients-initiated HCV treatment which reduced the rate of chronic HCV infection from 12% to 1% [11].

3.10. Prevention

The rates of new HCV infections annually are significant (1.7 million in 2015) with a quarter of these attributable to current IDU [128]. HCV exposure is related to the levels of infection in at-risk populations and availability and use of harm reduction [73, 75, 126]. PWID are at particular high-risk of infection during the initial years of injecting [52, 105]. Evidence shows that traditional harm reduction measures such as AOT and NSP are effective in reducing self-reported syringe sharing [7]. Both interventions can reduce transmission of HIV and HCV particularly when provided together [7, 47, 49, 73, 96]. Recently, there has been a further strengthening of the evidence base from non-European countries, with results from the Vancouver Injecting Drug Use Study in Canada and two other prospective studies of PWID, one in Australia and one in San Francisco in the United States all of which reported that AOT can reduce the risk of HCV acquisition by 50-80% [94, 118, 121].

This approach is supported by the newly agreed EU minimum quality standards for prevention [37]. Screening for HCV and educating those who test positive about how to avoid infecting others, treating those who test positive to remove them from the pool of transmitters and changing policies and behaviours to prevent both new infections in the uninfected and re-infection among those successfully treated [37].

NSP and AOT have been increasingly established, with 90 countries having NSP to some degree and 80 at least one AOT programme operational by 2016 [122]. However, coverage remains poor and data on the quality of many of these services is un-

known [37, 73]. These initiatives are fragile, politically unpopular, under-resourced and increasingly undermined by a 'recovery agenda' that prioritises abstinence. In many countries in Europe, particularly in Eastern Europe and Eurasia, interventions such as AOT can be limited or prohibited [37, 38, 73].

In 2017, of 179 countries with evidence of IDU, some level of NSP services was available in 93 countries, and 86 countries had evidence of AOT implementation [73]. 57 countries had data available to estimate NSP coverage, and 60 countries to estimate AOT coverage [73]. Coverage varied widely between countries but was most often low when compared to WHO indicators (<100 needle-syringes distributed per PWID per year; <20 AOT recipients per PWID per year). There are an estimated 33 needle-syringes distributed via NSP per PWID annually, and 16 AOT recipients per 100 PWID globally. Less than 1% of PWID live in countries with high coverage of both NSP and AOT (>200 needle-syringes distributed per PWID and >40 AOT recipients per 100 PWID) [122].

The HCV incidence among general prisoners is estimated to be 1·4 per 100 person-years (py; 95% CI: 0·1, 2·7; k=4), and 16·4 per 100py (95% CI: 0·8, 32·1; k=3) among prisoners with a history of IDU with larger regional and country variations [72]. Although access to HCV screening for PWID seems to be poorer in prison than in the community, access to harm reduction measures is even more limited [14, 73]. Approximately 60 out of more than 10,000 prisons worldwide provide needle exchange. HCV prevention is almost exclusively limited to verbal advice, leaflets and other measures directed to cognitive behavioural change [14]. While the extent of multiple risk behaviours for HCV in prisons is challenging, the setting does offer an ideal opportunity to provide a range of evidence-based interventions that can reduce HCV infection [14, 69, 72]. These include AOT, NSP and condom availability. These have the added advantage of reducing HIV transmission and, in the case of AOT, fatal overdose in the immediate post-release period [15, 20, 96]. Despite the evidence base for the effectiveness of these interventions in the reduction of the transmission of blood borne viruses (BBVs), there is poor coverage of these in prisons globally [14, 38, 129].

Benefits of prison AOT are similar to those in community settings [58]. AOT presents an opportunity to recruit problem opioid users into treatment, to reduce illicit opioid use, injecting and risk behaviours in prison and potentially minimise overdose risks on release [22, 26, 45, 58, 70]. If liaison with community-based programmes exists, prison AOT facilitates continuity of treatment and longer-term benefits can be achieved [58]. For prisoners in AOT before imprisonment, prison AOT provides treatment continuity. Disruption of AOT continuity, especially due to brief periods of imprisonment, is associated with very significant increases in HCV incidence [112].

In Spanish prisons, PWID experience a fivefold lower incidence of HCV if on AOT [82]. Similarly, after introducing prison AOT in Scotland, current coverage of 57% among PWID, evidence suggests HCV incidence among incarcerated PWID reduced, and is now lower than among community PWID [115]. A recent cross-sectional survey of harm reduction coverage in European prisoners found that, twenty-one countries (84%) provide HCV treatment in prison [14]. However, the extent of coverage of these treatment programs varies widely. Two countries (8%) have NSP officially available in prisons in all parts of the country. Eleven countries (44%) provide AOT in prisons in all parts of the country without additional requirements [14].

4. Discussion

Despite PWID and prisoners carrying a disproportionate amount of the HCV disease burden, rates of HCV screening and treatment remain low [27, 72, 87, 97, 108, 128]. Public health strategies aimed at HCV elimination recommend the targeting of these two groups as a priority [49]. This review found that HCV related liver mortality and morbidity is increasing globally and if it remains unchecked will cause 700,000 deaths annually by 2030 [97, 108].

Recent developments in HCV management have increased optimism among health care providers and those infected with HCV and it is now recognised that we have the tools to cure, eliminate and prevent HCV [11, 21, 49]. The treatment of PWID and prisoners is challenging. Central to this challenge is the marginalisation and the associated stigma experienced by these two groups [66, 103, 114, 131]. Despite having much higher levels of physical and psychiatric morbidity, PWID and prisoners do not utilise medical services [40]. Prison can offer the opportunity for this group to engage with services, but benefits can be eroded by the complexity of prison health care delivery, the continuing stigma that prisoners experience while incarcerated and failures in community linkage on release [40, 85, 112, 129, 131].

Despite recent reductions in cost, treatment with DAA remains expensive. Based on modeling stud-

ies this review found that HCV treatment in PWID and prisoners is cost-effective but ultimately this is dependent on real life rates of re-infection [85]. Many high-risk patients for transmission were excluded from interferon-based treatment and with the scaling up of HCV treatment and the use of treatment as prevention these patients will have to be treated but more importantly will have to be protected from re-infection by high coverage of both AOT and NSP [47, 49, 53]. In resource limited jurisdictions the selection of who to treat is challenging. Treating those with advanced HCV-related liver disease will reduce morbidity and mortality but will have little impact on HCV transmission levels [28, 47, 76]. Insufficient treatment levels among PWID, particularly those who continue to inject, will reduce the effectiveness of "treatment as prevention", increase rates of re-infection and limit the cost-effectiveness of treatment [53, 86]. Planning long-term strategies to optimise the benefits of HCV treatment among PWID and prisoners requires that accurate and up to date surveillance data is available to inform the implementation and evaluation of these programs [28, 76].

Despite growing evidence for the benefits of AOT and NSP in reducing HCV transmission, rates of coverage is inconsistent and low across Europe [14, 70, 73, 122]. Present levels are likely to be insufficient to effectively prevent HIV and HCV transmission. This is even more problematic in prison settings [4]. A number of studies reported the protective nature that incarceration provided against HCV acquisition. This protection occurred in jurisdiction with high levels of prison AOT [82, 115]. Scaling up of interventions for PWID and prisoners remains a crucial priority for halting both the HIV and HCV epidemics [73].

The short prison sentence served by the majority of prisoners has been identified as a major block to HCV treatment uptake in this group [84, 87, 112]. The advent of new shorter acting pan-genotypic DAA has the potential to increase the numbers accessing and completing treatment while in prison [100, 101]. Community linkage, facilitating the completion of treatment on release, could have a similar impact [87, 112]. Ongoing criminalisation of PWID across Europe ensures high levels of HCV infections in European prisons [4, 72]. On short-term bases this could be viewed as an opportunity to engage this underserved at risk group with HCV care [87, 98]. Targeted and ambitious screening and treatment strategies including opt-out screening, reflex-RNA testing, in-reach fibroscanning and use of short acting pan-genotypic regimes are required to optimise this opportunity [35, 69, 93, 101]. In the long term, drug policy changes are required to reduce the criminalisation of drug users and the levels of communicable diseases globally [10, 42].

Scaling up of treatment will require the development of effective working partnerships between specialist services working with PWID and prisoners and those offering HCV care [9, 79, 104]. In the past, referral pathways for PWID and prisoners into specialist hepatitis care have represented a critical weak link [63, 114, 131]. This is now changing, and novel approaches have been developed where HCV treatment is provided alongside community AOT and directly in prison settings [11, 104]. There remains a need for these to be expanded and supported so that they become the first line of HCV care for the majority of PWID. While DAA promise more efficacious treatment with limited side effects, social issues including criminalisation, stigma, homelessness and inflexible service provision are likely to continue to impede treatment uptake [49, 55, 68, 103, 131]. Clinical guidance promoting relaxed eligibility criteria holds the potential to break down current barriers to HCV treatment access and uptake for PWID and prisoners [34]. Treatment and prevention of HCV infection in PWID and prisoners must be specifically adapted to these marginalised groups. DAA have the potential to remove many of the identified barriers to treatment but without innovative approaches to treatment delivery treatment uptake and effectiveness will be compromised.

Close collaboration between all professionals involved in HCV care should underpin models of treatment delivery. Evidence based harm reduction measures such as AOT and NSP will need to be scaled up both in the community and prison in order to reduce new HCV infection, minimise the risk of re-infection and necessary if 'HCV elimination' is ever to become a reality. HCV treatment and prevention strategies that view prisons as a key location to target the most marginalised HCV infected PWID are likely to have the greatest impact on the management of this treatable and preventable global epidemic. These strategies will need to be informed and evaluated by appropriate, comprehensive and reliable surveillance data which is presently incomplete and lacking in many jurisdictions.

5. Conclusions

The growing global HCV disease burden carried by PWID and prisoners in developed countries is a major public health concern and one which requires innovative and targeted approaches to combat. Despite having the tools to both cure and prevent this epidemic, major challenges remain to identify and treat those infected. The silent nature of HCV infection coupled with the marginalisation of those most at risk impedes efforts to eliminate HCV as a major public health concern. HCV infected prisoners are a subgroup of HCV infected PWID and prisons remain key locations to target this group for HCV screening, treatment and prevention. Linking community and prison services and supporting transition between these locations has the potential to increase the effectiveness of any public health HCV strategy. The cost of DAA therapies is a major block to expansion of HCV treatment and will need to be addressed if HCV elimination is to become a reality. Medical and political leadership is required to tackle the links between social deprivation, drug use and its criminalisation, marginalisation and stigma. As we strive to overcome the many barriers associated with HCV treatment and prevention, evidence of micro-elimination of HCV in prisons, community drug treatment locations and injecting networks can continue to motivate health care professionals involved in HCV and provide optimism to those infected.

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Conflict of interest

All authors have no conflict of interest.

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