



RESEARCH ARTICLE

Antiviral Treatment to Prevent Transmission of Hepatitis C in People Who Inject Drugs

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Abstract: The hepatitis C virus (HCV) is common among people who inject drugs (PWID) and causes significant morbidity and mortality. Opiate replacement therapy and needle exchange programs have effectively prevented the transmission of the Human immunodeficiency virus (HIV) but have been less effective for HCV. Other HCV prevention strategies are needed. Antiviral therapy with all oral direct acting antivirals is currently available and appears to be highly effective even in PWID and offers a possible strategy to further prevention efforts. This paper will review current evidence for treatment as prevention for HCV in PWID.

Keywords: Access to care, Direct acting antivirals, Injection drug use, Liver Disease, Prevention, Substance use disorder.

INTRODUCTION

The hepatitis C virus (HCV) is a significant public health problem that affects over 140 million people world-wide [1, 2]. HCV is a blood-borne illness and in high income countries the main route of HCV transmission is through injection drug use. The prevalence of HCV antibodies in PWID is approximately 60% [3]. Chronic HCV is associated with significant morbidity including cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC) and increased mortality [4, 5]. In fact, HCC is one of the few cancers that is increasing in frequency in the United States [6]. In addition, HCV is a leading reason for the need for liver transplantation in the United States. Eradication of HCV has been difficult as no vaccine has yet been developed and until recently antiviral treatment rates were low and treatment was effective in only 50-70% of patients. Furthermore, PWID have been typically excluded from antiviral therapy due to stigma and concerns about medication adherence and reinfection (barriers to antiviral therapy are addressed elsewhere in this supplement). However, as treatment success is expected to surpass 90% with the advent of new and direct acting antivirals (DAA's), antiviral treatment may serve as an avenue for limiting the spread of HCV and reducing its prevalence. This article will review the available data regarding "antiviral treatment as prevention" for HCV in people who inject drugs (PWID).

Epidemiology of HCV in PWID

Injection drug use is responsible for over 50% of current HCV infections in the United States [7]. HCV infection occurs rapidly after initiation of drug use behaviors. In one study, the median time from first injection to seroconversion was 3.3 years with greatest risk in the first year [8]. High prevalence rates (64-94%) are found in PWID for 6 years or more [2]. Although needles likely account for most of the HCV infections, data indicate that preparation practices such as "backloading," sharing cotton, cookers and rinse water are also associated with transmission of the virus [9]. Most people who are currently infected were born between 1945 and 1965. However, recent data indicate that there is an emerging epidemic of HCV among young injection drug users. Young injection drug users show prevalence rates of

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20-46% with use of 5 years or less. Many started using alcohol or cannabis before age 13, began opioid use with oral oxycodone and then transitioned to heroin in 1-1.5 years [10 - 14]. One concern about this new epidemiological landscape is that these young people typically do not seek medical care or help for their drug use. Although HCV in PWID is primarily a problem in high income countries, HCV is also emerging in low and middle income countries [3, 15]. Efforts to curb HCV infection will need to account for high rates of HCV in PWID.

Although efforts to curb transmission have been instituted, including harm reduction approaches such as needle exchange programs and opioid substitution treatment, these programs have not been as successful as they have been in HIV prevention. This may be due to higher prevalence rates and easier transmission per injection for HCV [16, 17] compared to HIV [18, 19]. A meta-analysis of studies evaluating prevention strategies for HCV infection in PWID found that no single intervention was associated with HCV seroconversion reductions. However, the analysis did show that multicomponent interventions were effective at reducing the incidence of HCV seroconversion by about 75% in PWID [20]. These multimodal interventions typically consisted of opioid replacement therapy (ORT), needle exchange programs and education. However, given the high HCV prevalence among PWID, it is estimated that these types of programs would need to cover over 80% of the population in order to reduce prevalence to 20% in 20 years [21]. HCV transmission in PWID is still occurring and other prevention approaches are needed, including antiviral treatment as prevention.

Antiviral Treatment in PWID

Multiple studies have shown interferon based treatment regimens can be safely administered to PWID with comparable SVR rates to those without injection drug use [22 - 24]. These studies also report that PWID show good adherence to antiviral therapy of approximately 82%. Although concern for re-infection has always been a factor in restricting access to antiviral therapy in PWID, studies show low rates of re-infection after successful treatment [25, 26]. No studies using interferon free regimens have been performed but given the better tolerability, shorter duration of treatment and significantly improved response rates, it is expected that PWID will respond well.

Although interferon-based treatment is as effective in PWID as for those who do not inject, treatment rates in PWID have been low. In the U.S., Canada and Australia data indicate that approximately 15-20 per 1000 HCV infected (1.5-2.0%) receives antiviral therapy each year in PWID [27]. At the same time studies show that at least 70-80% of PWID's are willing and desire to receive antiviral therapy and desire for treatment is expected to rise with DAA's [28].

Efficacy of interferon-based treatment in PWID has been dependent on integrated or collaborative approaches to care. This has typically involved teams of clinicians including hepatologists, primary care clinicians, and mental health and addiction providers that work together to address the complex needs of this population [29]. Addiction treatment settings including those offering ORT have been successful at helping patients manage and complete interferon based treatments [26, 30, 31]. In order for treatment as prevention to be successful it is likely that expansion of these integrated care approaches will be needed.

Treatment in the Human immunodeficiency (HIV) population has demonstrated that treatment as prevention can be beneficial and effective. Initially data from observational studies suggested that antiretroviral treatment (ART) reduced transmission among couples in which one partner was infected with HIV and the other was not. Randomized controlled trials subsequently confirmed the reduced risk of transmission of HIV between couples who were discordant for HIV [32] as well as in maternal-to-child transmission [33]. Data also suggest that reducing viral load in a community can reduce new HIV infections [34]. These data show that treatment not only can help an individual but may also have an impact on the population at large by limiting transmission and reducing the overall burden of disease. While HIV treatment is chronic and focused on viral suppression, HCV treatment has the potential to be curative. This makes treatment as a method of prevention in HCV attractive as significant reductions in prevalence and transmission can potentially be achieved.

Mathematical Modeling of Treatment as Prevention

Several studies have investigated HCV treatment as prevention in PWID using mathematical models (Table 1). Early models of interferon based treatment using an HCV prevalence of 45%, an annual treatment rate of 10% and a success rate of antiviral treatment of 50% showed that a 32% reduction in HCV prevalence over 10 years was possible [35]. Another study from the United Kingdom using more realistic HCV treatment rates of 2%, 4% and 6% in PWID, an HCV prevalence of 40% and treatment efficacy of 63% showed that HCV prevalence could be reduced by 15%, 33% and 50% respectively over 20 years [36]. Another study showed that with an HCV prevalence of 20%, treatment

efficacy of 62.5% and treatment uptake of 5, 10, 20, 30 or 40 per 1000 PWID reduced HCV prevalence by 15, 31, 62 and 72% over 10 years [37]. In this study reducing antiviral treatment efficacy by 25% (*i.e.* to 45%) had little effect on reductions in HCV prevalence. However, as prevalence rates rise (*i.e.* 20%, 40% or 60% HCV prevalence) and if the treatment rate remains fixed at 10 per 1000 PWID, the ability of antiviral therapy to reduce HCV prevalence falls from 31% to 13% and 7% for each prevalence level, over 10 years [37]. Several other studies show similar effects of HCV antiviral treatment of PWID [38 - 42]. The data suggest that for a fixed treatment rate, the impact of antiviral therapy is greater at lower HCV population prevalence because a greater proportion of the HCV population is treated and thus the risk of re-infection is lower.

Table 1. Selected Studies of “Treatment as Prevention” in PWID.

Author	Year published	Assumptions	Modeled Annual Treatment Rates	Relative prevalence reductions
Zeiler <i>et al.</i>	2010	Number of users starting injecting:4500/yr SVR rate:50% Tx rate: 1% per year Number of individuals starting Tx: 539.362/yr	Increased tx rate to 60% of population of PWID	Reduces chronic infections by ½ in 3.3 yrs and acute infections in ½ in 11.1 yrs.
Martin <i>et al.</i>	2011	Baseline HCV Prevalence: 20% SVR rate (interferon based): 62.5%	5/1000 PWID	15% over 10 yrs
			10/1000 PWID	30% over 10 yrs
			20/1000 PWID	62% over 10 yrs
			40/1000 PWID	72% over 10 yrs
Hellard <i>et al.</i>	2012	Victoria, Australia PWID population: 25,000 HCV positive: 50% Ave duration of infection:14 yrs Current Tx rate: 1/1000 PWID	13/1000 PWID	20% over 30 yrs
			17/1000 PWID	30% over 30 yrs
			25/1000PWID	50% over 30 yrs
Martin <i>et al.</i>	2013	SVR with DAA’s:90% HCV prevalence: Edinburgh, UK:25% Baseline Tx rate: 8/1000 PWID	10/1000 PWID	32% over 15 yrs
			20/1000 PWID	69% over 15 yrs
			40/1000 PWID	90% over 15 yrs
			80/1000 PWID	91% over 15 yrs
		Melbourne, Australia:50% Baseline Tx rate: 3/1000 PWID	10/1000 PWID	9% over 15 yrs
			20/1000 PWID	23% over 15 yrs
			40/1000 PWID	50% over 15 yrs
			80/1000 PWID	90% over 15 yrs
		Vancouver, Canada: 65% Baseline Tx rate:2/1000 PWID	10/1000 PWID	5% over 15 yrs
			20/1000 PWID	9% over 15 yrs
			40/1000 PWID	20% over 15 yrs
			80/1000 PWID	53% over 15 yrs
Innes <i>et al.</i>	2014	Scotland PWID population: 15,300 HCV positive:50% PWID Number treated per year: 120 Total persons treated: 1000/yr	Double treatment rate to 2000/yr Increase Tx of PWID by 20%	Decrease HCV infections by 52.2% over 15 yrs

Direct acting antiviral (DAA) treatment of chronic HCV is now a reality with studies showing high treatment success rates with all genotypes. Recent studies show SVR rates with DAA’s exceeds 90% for all genotypes [43 - 46]. Antiviral therapy with DAA’s is interferon free, all oral and of relatively short duration (*i.e.* 12 weeks). Mathematical modeling of HCV transmission and the impact of antiviral treatment with DAA’s, in three settings with different HCV prevalence (Edinburgh, Scotland, 25%; Melbourne, Australia, 50% and Vancouver, Canada, 65%), shows that HCV prevalence could be halved within 15 years if 15, 38 and 75 per 1000 PWID received antiviral treatment. Alternatively, increasing treatment to 40 per 1000 PWID per year could reduce prevalence by 91% in Edinburgh, 54% in Melbourne and 22% in Vancouver [42].

Hellard and colleagues examined the impact of social networks on HCV transmission and modeled a “treat your

friend's" approach using DAA's in PWID. Models of antiviral treatment as prevention typically assume that injectors have equal contact with other injectors. Using data regarding HCV transmission from PWID followed for 5 years the authors were able to model the "treat your friend's" approach wherein an individual is chosen at random for treatment and all their "infected neighbors" are treated as well. When compared to treatment of randomly selected nodes that does not account for knowledge of the injecting network, the authors found that the "treat your friend's" approach led to greater reductions in HCV prevalence. The authors found that treating 25 per 1000 PWID over 10 years reduced HCV prevalence from 50% to 40% for a random approach and to 33% for a treat your friends approach, further reductions were noted as more PWID were treated and as treatment efficacy was increased [39].

Another study compared antiviral treatment strategies by prioritizing treatment of either PWID or people with moderate to advanced fibrosis. Not surprisingly, prioritizing treatment of people with more advanced liver disease reduced new cases of severe liver disease but had a minimal impact on incident HCV. By prioritizing treatment of PWID, fewer new infections occurred but this strategy had a suboptimal impact on new severe liver disease cases [47]. The data suggest that policy makers in resource constrained settings will need to consider the impact and value of prioritizing the treatment of different populations on health in HCV patients.

In summary, mathematical modeling of the impact of antiviral treatment of PWID with DAA's suggest that significant reductions in HCV prevalence are possible. Effective treatment as prevention is dependent on HCV prevalence, treatment efficacy and treatment uptake. Currently, a significant barrier to reducing HCV prevalence through antiviral treatment is access and treatment uptake among PWID.

Access to Hepatitis Care for PWID

In the U.S. it is estimated that approximately 3.5 million people are infected with HCV but only 50% are aware of their infection. Of those people aware of their infection, approximately 85% have health insurance and thus are able to access care. Furthermore, many people who are aware of their HCV status do not seek care and current estimates indicate that less than 20% of the total HCV population have received antiviral therapy and only 9% have achieved a sustained virologic response (SVR) [48]. In PWID access to care and treatment rates are even lower although when PWID are treated rates of SVR are similar to other populations. Barriers to antiviral treatment exist at the patient, provider and system levels and may include lack of knowledge and awareness, financial difficulties and worries over medication side effects for patients [49, 50]. Clinicians may have concerns about medication adherence, the risk of re-infection and may lack the knowledge or resources to address alcohol and injection drug use [51]. In addition, stigma may reduce care seeking [52].

Many people are unaware of their HCV infection and efforts to increase HCV testing and linkage to care in the injecting population are needed. Substance use treatment settings are an ideal place to provide education and testing of people most at risk for HCV. One study implemented systematic hepatitis education, HCV testing and a facilitated referral to a hepatitis clinic and the authors found that new HCV patients were identified and patients' understanding of hepatitis improved [53]. Once identified, improved access to care and treatment uptake are also needed. Antiviral treatment that takes place in the context of multidisciplinary care with hepatologists, mental health and addiction providers has been shown to be effective during the interferon therapy *era* [29]. Multiple observational studies suggest that integrated or collaborative care approaches to addressing HCV patients with psychiatric and substance use disorders including PWID are effective, both increasing antiviral treatment rates and improving SVR [22, 54]. A recent randomized trial of integrated care showed that HCV patients with psychiatric and substance use disorders were more likely to receive treatment and were more adherent to antiviral therapy in the intervention group than those receiving treatment as usual [55]. Integrated or collaborative care approaches are still warranted in the DAA *era* as patients with HCV and injection drug use remain a complicated group that may require and benefit from enhanced support in order to start and adhere to antiviral therapy [56]. Finally, efforts to improve testing and antiviral treatment will be necessary for treatment as prevention to be maximally effective.

CONCLUSION

Antiviral treatment for HCV has improved significantly over the past several years and offers hope that treatment of hard to reach populations such as PWID may soon become a reality. Studies show that multi-model prevention strategies can significantly reduce HCV prevalence, including needle exchange and ORT. However, in order to potentially eradicate HCV, other prevention strategies are needed. Data from mathematical models suggest that HCV "treatment as prevention" may be one avenue that could further reduce HCV prevalence. Highly effective antiviral

treatment with DAA's may not only help individuals with HCV but may reduce the population burden as well. In order for eradication of HCV to become a possibility, increased testing and linkage to care will be a priority. Unique approaches to providing antiviral therapy may be required, including providing antiviral therapy in substance use disorder treatment settings. Furthermore, methods for engaging and maintaining patients in care, such as integrated or collaborative models of care should continue and may need to be expanded.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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