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Commentary

Can hepatitis C virus infection be eradicated in people who inject drugs?

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ABSTRACT

People who inject drugs (PWID) represent the core of the hepatitis C virus (HCV) epidemic in many countries and HCV-related disease burden continues to rise. There are compelling data demonstrating that with the appropriate programs, treatment for HCV infection among PWID is successful, with responses to therapy similar those observed in large randomized controlled trials in non-PWID. However, assessment and treatment for HCV infection lags far behind the numbers who could benefit from therapy, related to systems-, provider- and patient-related barriers to care. The approaching era of interferon-free directly acting antiviral therapy has the potential to provide one of the great advances in clinical medicine. Simple, tolerable and highly effective therapy will likely address many of these barriers, thereby enhancing the numbers of PWID cured of HCV infection. This commentary will consider why we should strive for the eradication of HCV infection among PWID, whether eradication of HCV infection among PWID is feasible, components that would be needed to achieve eradication of HCV infection in PWID, potential settings and strategies required to establish programs targeted towards eradicating HCV infection among PWID and the feasibility of eradication versus elimination of HCV infection among PWID. This article forms part of a symposium in *Antiviral Research* on "Hepatitis C: next steps toward global eradication."

1. Introduction

The burden of hepatitis C virus (HCV) infection continues to rise. People who inject drugs (PWID) represent the core of the HCV epidemic in many settings particularly high-income countries although also increasingly in low- and mid-income countries (Nelson et al., 2011; Hajarizadeh et al., 2013). Over recent years, the development of simple, tolerable and highly effective directly acting antiviral (DAA)-based therapies for HCV infection has brought great optimism to the sector. The approaching era of interferon-free DAA therapy, with its potential to provide one of the great advances in clinical medicine, has raised the prospect of HCV treatment as prevention (Grebely et al., 2013). An upward trajectory in treatment optimism ultimately leads to the question of whether HCV infection can be eradicated from populations, particularly PWID?

From a public health perspective, eradication refers to the complete and permanent worldwide reduction to zero new cases of an infectious disease through deliberate efforts, with no further control measures required (e.g. smallpox). Elimination refers to the reduction of the incidence of infection caused by a specific agent to zero in a defined geographical area as a result of deliberate efforts, but requires the presence of continued measures to prevent re-establishment of transmission (e.g. measles, poliomyelitis). As such, eradication of HCV infection would represent a considerably greater challenge compared to elimination.

This commentary will consider why we should strive for the eradication of HCV infection among PWID, whether eradication of HCV infection among PWID is feasible, components that would be needed to achieve eradication of HCV infection in PWID and potential settings and strategies required to establish programs targeted towards eradicating HCV infection among PWID. In this commentary PWID refers to people who are actively or currently injecting, unless otherwise stated as former PWID.

2. Why should we strive for eradication of HCV infection among PWID?

2.1. The burden of HCV infection is growing, including among PWID

In high income countries, the majority (80%) of new cases of HCV infection occur among PWID, with most (60%) existing

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infections among former and current PWID (Fig. 1) (Nelson et al., 2011; Hajarizadeh et al., 2013). HCV infection is also emerging as major public health problem among PWID in low and middle income countries (Nelson et al., 2011; Hajarizadeh et al., 2013). In 2007, it was estimated that there were 16 million PWID worldwide (Mathers et al., 2008). Given an estimated global HCV prevalence of 67% among PWID (Fig. 2) (Nelson et al., 2011), around 10 million PWID have been infected with HCV (Table 1), with an additional large reservoir of infection among former PWID.

Given around 25% of people infected with HCV spontaneously clear virus (Micallef et al., 2006), ~50% of PWID will have chronic HCV infection (represents 8 million PWID globally). In those with spontaneous HCV clearance, re-infection in the setting of ongoing HCV exposure is possible (Grebely et al., 2012). Although many of those with re-infection clear repeatedly, others develop persistent infection. Development of chronic HCV infection may lead to progressive hepatic fibrosis, cirrhosis, and complications of liver failure or hepatocellular carcinoma (Seeff, 2009). Progression to advanced liver disease is uncommon in the initial 10–20 years of infection, particularly among PWID who generally acquire infection at a younger age, but becomes more common with each subsequent decade of infection (Thein et al., 2008a,b; Grebely and Dore, 2011; Kirk et al., 2013).

Although younger individuals with HCV infection are at lower risk of HCV-related morbidity and mortality, and drug-related mortality is significant among PWID, the ageing cohort nature of PWID populations means that liver disease-related mortality is increasing (Amin et al., 2006; Grebely et al., 2011; Deans et al., 2013; Walter et al., 2011). There is also increasing evidence that HCV infection is associated with an increase in both hepatic and extra-hepatic disease, including circulatory diseases, renal diseases, and neuropsychiatric disorders (Lee et al., 2012). There is also evidence treatment can attenuate hepatitis C-related disease consequences, including all-cause mortality (van der Meer et al., 2012). Thus, PWID should receive curative HCV therapy simply because it is the right thing to do for the individual, impact on eradication notwithstanding.

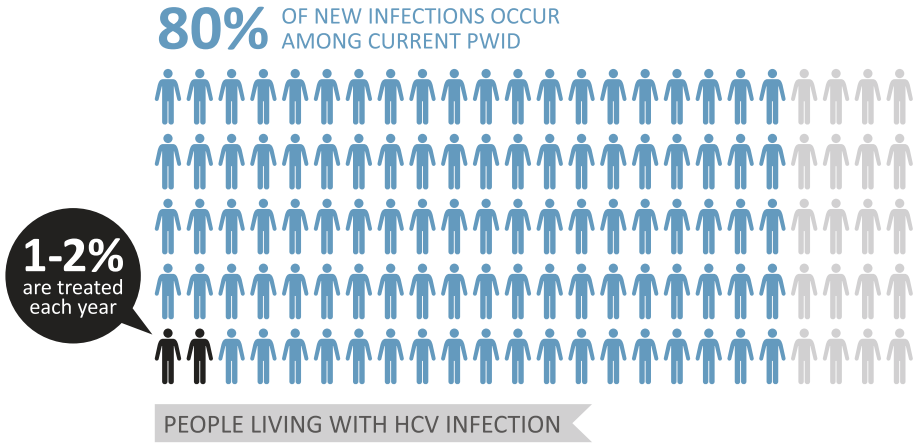

Fig. 1. Despite high burden of HCV infection among PWID, treatment uptake remains low. In many high-income countries (and some low- and medium-income countries), >80% of new cases of HCV infection occur among PWID each year (Hajarizadeh et al., 2013). However, the annual HCV treatment uptake is only 1–2% among PWID (Grebely et al., 2009; NCHECR, 2010a,b; Mehta et al., 2008; Alavi et al., 2013; Iversen et al., 2014).

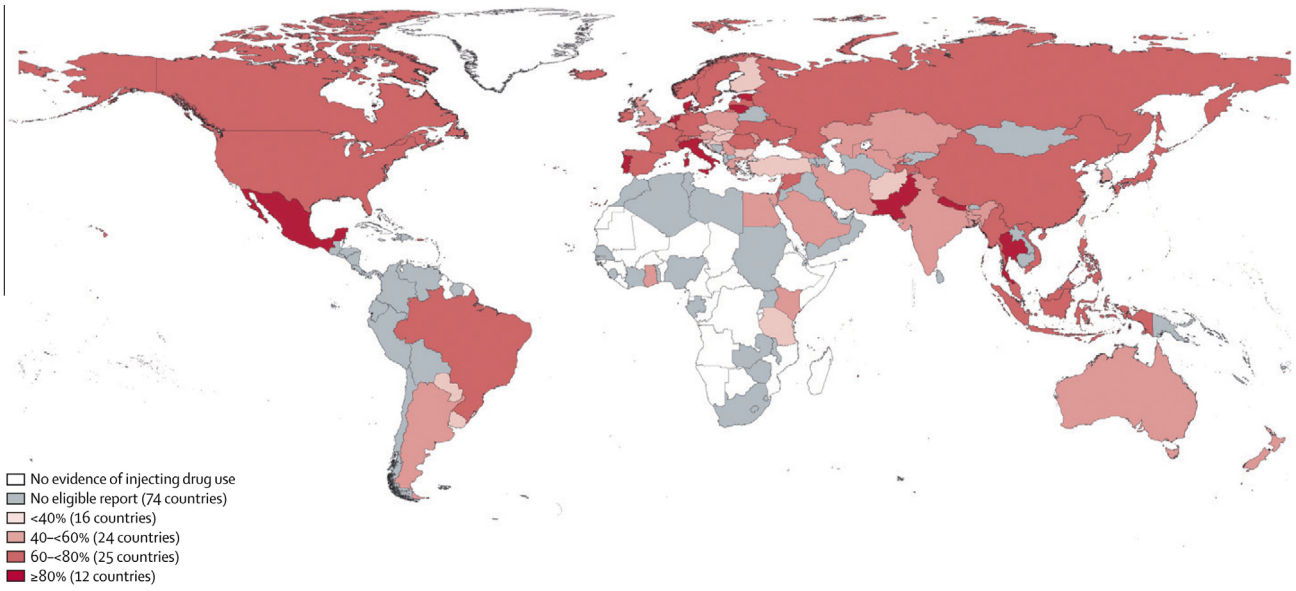

Fig. 2. Prevalence of hepatitis C antibodies in people who use drugs (Permission obtained from Nelson et al. (2011)).

2.2. HCV transmission continues to occur among PWID

In addition to the considerable burdens of HCV infection and liver disease among PWID, HCV transmission remains unabated in most settings (Page et al., 2013). Estimated HCV incidence among PWID ranges from 5% to 45% per annum (Grebely and Dore, 2011). The risk of HCV infection is highest among younger individuals and recent initiates into injecting drug use.

Harm reduction strategies, such as needle syringe programs (NSP) and opioid substitution treatment (OST), that have been successful for HIV prevention among PWID populations, have been less effective for HCV prevention (Hagan, 2011; Sacks-Davis et al., 2012; Turner et al., 2011; Palmateer et al., 2010; Van Den Berg et al., 2007). This is consistent with greater per contaminated injecting exposure transmission (2.5–5.0% for HCV vs. 0.5–2.0% for HIV), and higher prevalence (and thus, risk of exposure) (Grebely and Dore, 2011).

In a recent meta-analysis of studies evaluating strategies to prevent HCV infection among PWID, it was demonstrated that no single intervention has been associated with a reduction in HCV incidence (Hagan, 2011). However, two studies were identified where combined interventions incorporating OST have led to reductions in HCV incidence (Van Den Berg et al., 2007; Abou-Saleh et al., 2008). More recently, pooled data from six studies from the UK has also demonstrated that combined NSP and OST programs were associated with an 80% reduction in HCV infection (Turner et al., 2011). However, mathematical modelling has suggested that in a setting with an HCV prevalence of 40%, reducing the prevalence to below 20% in 20 years would potentially require NSP and OST coverage of $\geqslant$80% (Vickerman et al., 2012). In many countries, low coverage of NSP and OST programs further hinders HCV prevention efforts (Mathers et al., 2010). Given that HCV transmission continues to occur among PWID and an effective HCV vaccine remains remote, alternate strategies to achieve HCV eradication among PWID must be explored.

3. Why is eradication of HCV infection feasible among PWID?

3.1. HCV treatment is effective among PWID

The goal of HCV therapy is viral eradication as represented by a sustained virological response (SVR) [HCV RNA undetectable in the blood six months following treatment]. HCV treatment with pegylated-interferon (PEG-IFN)/ribavirin can achieve SVR in ~50% of individuals.

Initially, HCV treatment guidelines excluded PWID from consideration, citing concerns about adherence, increased susceptibility to side effects (e.g. depression) and re-infection (NIH, 1997). However, there is now compelling evidence that HCV treatment is safe and effective among PWID (Hellard et al., 2009; Aspinall et al., 2013; Dimova et al., 2013). In two systematic reviews of studies assessing treatment for PWID (one specifically focusing on those with recent injecting at the time of treatment initiation), the overall SVR was 56% (Aspinall et al., 2013; Dimova et al., 2013). These response rates are comparable to large randomized controlled trials of PEG-IFN/RBV treatment (Manns et al., 2006). International guidelines now recommend treatment for PWID following individualised assessment (Ghany et al., 2009; EASL Clinical Practice Guidelines, 2011; Robaeys et al., 2013).

Recent international recommendations have reviewed the evidence on drug use and treatment for HCV infection (Robaeys et al., 2013). A history of injecting drug use does not generally compromise adherence, treatment completion, or SVR, although some studies have found lower treatment completion. Recent injecting drug use at treatment initiation has limited impact on adherence, treatment completion, or SVR. Some studies have reported lower treatment completion in those with recent injecting drug use at treatment initiation. In the first randomized controlled trial among active drug users, participants randomized to immediate vs. delayed directly observed PEG-IFN and self-administrated RBV demonstrated a high SVR (65%), but delayed treatment compromised subsequent engagement in HCV treatment (Hilsden et al., 2013). HCV treatment does not have an impact on drug dependency treatment or increase drug use. Occasional injecting drug use during treatment does not seem to impact adherence, treatment completion, or SVR. However, lower adherence and SVR has been observed in persons with frequent injecting drug use (daily/every other day) during treatment. When discontinuation occurs, it often occurs early during therapy.

Although there is concern that HCV re-infection may negate the potential benefits of treatment, the reported rates of reinfection following successful HCV treatment among PWID are low (1–5% per year) Aspinall et al., 2013; Grady et al., 2013. Looking forward, any attempts to eradicate HCV infection among PWID will need to be closely linked to a foundation of enhanced HCV treatment uptake, while optimising adherence and retention in care.

Table 1
Regional and global estimates of the numbers of PWID who were positive for hepatitis C antibodies (anti-HCV) in 2010 (Permission obtained from Nelson et al. (2011)).

	Lower	Mid	Upper
Eastern Europe	1,244,500	2,346,000	3,918,000
Western Europe	497,000	727,500	1,018,000
East and southeast Asia	1,820,000	2,642,000	3,576,500
South Asia	232,500	354,500	532,000
Central Caribbean	91,500 *	146,000	213,000
Latin America	675,500	1,022,000	1,441 000
Canada and USA	1,099,000	1,673,500	2,471,500
Pacific Island states and territories	*		
Australia and New Zealand	44,500	97,000	165,000
Middle East and north Africa	28,500	63,500	115,500
Sub-Saharan Africa†	206,500	800,000	1,524,000
Extrapolated global estimates	6,031,000	10,018,000	15,186,500

All figures rounded to nearest 500 people; global figure totaled from regional estimates prior to rounding. 2010 UN population division estimates were used to derive 2010 estimates of population sizes of PWID.

* Insufficient data to produce a region-specific estimate for populations of PWID in this region; countries in this region were still included in global estimates.

† Numbers of sub-Saharan African PWID and derived population estimates should be viewed with caution because injecting drug user prevalence estimates were derived from three countries in the region (South Africa, Mauritius, and Kenya); the estimated range of PWID was derived by applying the regional observed error (the large error band emphasises the uncertainty around these estimates).

3.2. Although HCV treatment uptake is low, treatment willingness is high among PWID

Despite the high prevalence of HCV infection, favourable HCV treatment responses and guidelines recommending treatment among PWID, very few have received HCV treatment (Fig. 1). Between 2004 and 2005, community-based studies of PWID in Australia, Canada and the United States demonstrated HCV treatment uptake rates ranging from 0.5% to 1.0% per year (5–10 per 1000 infected) (Grebely et al., 2009; NCHECR, 2010a; Mehta et al., 2008). More recently, data from cohorts of current PWID in Canada (Alavi et al., 2013) and Australia in 2010–2011 (Iversen et al., 2014), suggest that HCV treatment uptake in PWID settings has increased to 1.5–2.0% in 2009–2010 (15–20 per 1000 infected) (Iversen et al., 2013). This is consistent with trends in HCV treatment uptake among the general population in Australia (NCHECR, 2010b), Europe (Lettmeier et al., 2008) and US (Volk et al., 2009).

So why is uptake of treatment for HCV infection low among PWID? Many have suggested that it is because PWID are not willing or interested in receiving HCV treatment. However, 53–86% of PWID report a willingness to receive treatment for HCV under current treatment scenarios with PEG-IFN/RBV (Grebely and Tyndall, 2011; Doab et al., 2005; Alavi et al., 2013). The motivation to receive treatment increases as the treatment response increases, with one study demonstrating that willingness increased from 63% to 93% under treatment success scenarios of 40% and 70%, respectively (Doab et al., 2005). Barriers to HCV treatment are multi-factorial and include issues of access to therapy and barriers at the level of the patient, practitioner and the health care system (Grebely and Tyndall, 2011; Grebely et al., 2013, 2008). However, a major barrier to HCV treatment uptake is the toxicity (e.g. anemia, depression, flu-like symptoms), complexity (once-weekly injections and twice-daily pills for 6–12 months), and sub-optimal responses (~50%) of pegylated interferon and ribavirin (PEG-IFN/RBV)-based regimens. In the IFN-free era, HCV treatment willingness should be even higher, and the large gap between willingness and uptake should be narrowed.

3.3. Simple, effective IFN-free DAA-based HCV treatments could substantially improve treatment uptake

Numerous antiviral agents targeting specific HCV viral functions have been developed (direct acting antivirals [DAAs]) (Sarrazin et al., 2012). The first two DAAs approved for treatment of genotype 1 infection in combination with PEG-IFN/ribavirin are the NS3-4A protease inhibitors, telaprevir and boceprevir. Nucleoside/nucleotide analogues and non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase (NS5B) and inhibitors of NS5A are in advanced clinical evaluation. The first Phase 3 studies of IFN-free therapy commenced in 2012 (Dore, 2012) and over the next 2–3 years several combination DAA regimens should be licensed. These regimens offer increased efficacy (>90%), reduced toxicity, shortened treatment durations (8–24 weeks), simplified dosing (all oral, possibly once-daily regimens) and monitoring schedules. The availability of such regimens should markedly improve the feasibility of enhanced HCV treatment uptake and responses among PWID, making eradication of HCV infection among PWID a possibility.

3.4. HIV has taught us that treatment as prevention can be effective

The demonstration that ART is an effective strategy for the prevention of HIV transmission has provided considerable optimism to the field (Cohen et al., 2011). As reviewed elsewhere (The HIV Modelling Consortium Treatment as Prevention Editorial Writing Group, 2012; Cohen et al., 2012), the potential of HIV treatment as a prevention strategy was initially based on findings from observational studies demonstrating that ART reduces transmission risk among HIV-serodiscordant couples (i.e. couples in which one partner is infected and the other is not). These data provided the impetus for a randomized controlled trial to evaluate the magnitude and durability of a prevention effect of ART, the HIV Prevention Trials Network (HPTN) 052 trial Cohen et al., 2011. The HPTN 052 trial enrolled 1763 HIV-1 serodiscordant couples and their HIV-infected partners who were randomized to receive either immediate ART or were delayed to receive ART once their CD4 count dropped < 250 - cells/uL. The early initiation of ART was associated with a 96% reduction [95% confidence interval (95% CI):73–99%] in HIV transmission to uninfected partners as compared to delayed ART, and a 41% (95% CI: 12–60%) reduction in a composite indicator of morbidity and mortality. These findings have potential benefits at the individual level for those provided with these medications and at the population level by limiting transmission and reducing the overall burden of infection (The HIV Modelling Consortium Treatment as Prevention Editorial Writing Group, 2012).

Mathematical modelling provides a framework for estimating the potential impact of treatment as prevention at the population-level (The HIV Modelling Consortium Treatment as Prevention Editorial Writing Group, 2012). Two factors influence the impact of a treatment program on the prevention of infection. First, there are transmission events occurring *prior* to treatment which are dependent on the biology of infection, the prevalence of infection, risk behaviours between partners, the effectiveness of other established prevention programs, the rates of testing, and access to care. Second, there are transmission events occurring *after* treatment initiation, which are dependent on treatment efficacy, adherence and retention in care.

In contrast to HIV, antiviral therapy for HCV infection is both finite in duration and frequently curative. Thus, a reduction in the prevalence of active infection can potentially be achieved in a substantial proportion of cases, in addition to the prevention of secondary transmission events.

3.5. Substantial reductions in HCV prevalence and incidence could be achieved with modest increases in treatment uptake with IFN-free DAA-based regimens

The potential preventative utility of HCV treatment for PWID has been explored in a number of different mathematical modelling studies (Grebely et al., 2013). To evaluate the potential impact of IFN-free DAA-based therapy on HCV prevalence, a deterministic mathematical model of HCV transmission was applied to three different settings with varying HCV prevalence (chronic HCV prevalence: Edinburgh, Scotland-25%; Melbourne, Australia-50%; and Vancouver, Canada-65%) (Martin et al., 2013a). With the introduction of DAA-based therapy (cure rate of 90% and 12 weeks therapy), HCV prevalence could be halved within 15 years if treatment is scaled up to 15, 38 and 75 per 1000 PWID in Edinburgh, Melbourne and Vancouver, respectively. Scaling up HCV treatment to 40 per 1000 PWID annually could achieve a prevalence reduction of 91% in Edinburgh, 54% in Melbourne and 22% in Vancouver over 15 years. These data suggest that if these treatment uptake and response rates to DAA-based therapy can be achieved among PWID, HCV treatment as prevention could achieve substantial reductions in the prevalence of HCV infection, with eradication possible in low HCV prevalence settings.

3.6. Treatment of HCV infection among PWID is cost-effective

Treatment of HCV infection has been demonstrated in a number of global settings to be cost-effective in non-PWID or those without risk of reinfection (Martin et al., 2013b). However, there is also considerable evidence from settings in Australia, Europe, New Zealand and the United States demonstrating that HCV treatment (either PEG-IFN/RBV or PEG-IFN/RBV and a protease inhibitor for those with genotype 1) for current and former PWID is cost-effective (Martin et al., 2013b). To evaluate the cost-effectiveness of providing treatment for PWID as compared to treating ex/non-PWID or no treatment, a dynamic mathematical model of HCV transmission and disease progression was developed by Martin et al. Martin et al. (2012). The results demonstrated that treating chronic HCV infection among both active injectors and ex- or non-injectors is cost-effective, but that the treatment of active injectors may be more cost-effective when the chronic prevalence of HCV infection is below 60% (Martin et al., 2012). Treating PWID prevents onward transmission and results in greater quality adjusted life years gained than are lost through potential HCV reinfection. These data provide convincing evidence to suggest that HCV treatment among PWID should not be withheld (particularly

given concerns of HCV reinfection), but rather prioritized, given the potential prevention and cost-effectiveness benefits. A key issue will be to re-examine the cost-effectiveness of HCV treatment among PWID in the era of IFN-free DAA-based therapy.

4. What are the requirements for achieving eradication of HCV infection among PWID?

4.1. A strong foundation of non-treatment-based HCV prevention strategies

Any attempts to eradicate HCV infection among PWID will require an existing framework of harm reduction interventions for HCV prevention among PWID, such as NSP and OST programmes. Although harm reduction strategies have been less effective for HCV prevention among PWID (Hagan, 2011; Sacks-Davis et al., 2012; Turner et al., 2011; Palmateer et al., 2010; Van Den Berg et al., 2007; Macarthur et al., 2013; Des Jarlais et al., 2013; Abdul-Quader et al., 2013), model projections for countries which have reached and sustained high coverage (such as Australia, the UK and other countries) suggest that considerable infections have been averted (Vickerman et al., 2012). For example, in the UK, the prevalence of HCV infection could be almost 60% higher in the absence of OST and NSP interventions (Vickerman et al., 2012). However, reductions in HCV prevalence through NSP and OST alone may be modest and require many years of sustained intervention coverage to occur.

One strategy might be to couple HCV treatment with OST and NSP to achieve a greater prevention benefit. Further work by Martin and colleagues investigated the impact of modelling a combination of OST, high coverage NSP and HCV treatment on HCV prevalence and incidence among PWID (Martin et al., 2013). They demonstrated that with very feasible HCV treatment rates, large reductions (>45%) in chronic prevalence over 10 years could be achieved when HCV treatment was combined with OST and NSP. Substantial reductions in HCV prevalence (>30% reduction in HCV prevalence in 10 years) were unlikely to be achieved with NSP/OST alone in the absence of HCV treatment. However, greater NSP and OST coverage allowed for a reduction in the number of PWID who would need to be treated for HCV infection annually to achieve a specific target HCV prevalence reduction. As such, any hopes at eradication of HCV infection will need to be built upon the foundation of existing HCV prevention strategies, such as OST and NSP programmes.

4.2. Broad expansion of screening and assessment for HCV infection among PWID

The feasibility of HCV eradication among PWID will rest heavily on the ability to achieve high screening and diagnosis rates of HCV infection among PWID and subsequently link infected individuals into care. Within clinics with large populations of PWID where systematic programs are established for comprehensive screening and diagnosis of HCV infection, uptake of testing and assessment of >85% can be achieved (Lindenburg et al., 2011; Senn et al., 2009; Harris et al., 2010; Hallinan et al., 2007). However, a vast number of HCV-infected PWID remain undiagnosed and unlinked to care.

In the primary care setting, interventions based on targeted case-finding (Cullen et al., 2012), risk-based assessment (Drainoni et al., 2012; Litwin et al., 2012), birth-cohort screening (Litwin et al., 2012) and motivational interviewing with case management (Masson et al., 2013) can be effective in increasing testing for HCV infection. In the first randomized controlled trial to examine the efficacy of a hepatitis care coordination model (including motivational interviewing-enhanced patient navigation and case management services) in the OST setting, participants receiving the intervention were significantly more likely to receive assessment for HCV infection (65% vs. 37%, odds ratio = 4.10, 95% confidence intervals: 2.35, 7.17) (Masson et al., 2013). Enhanced screening could also be achieved through targeted HCV testing initiatives such as rapid finger-prick testing (Wong et al., 2013; Jewett et al., 2012; Smith et al., 2011a,b), oral saliva testing (Jewett et al., 2012; Smith et al., 2011a,b; Drobnik et al., 2011), and dried blood spot testing (Tuaillon et al., 2010; Hickman et al., 2008; Craine et al., 2009; Martin et al., 2013). One study from the UK demonstrated that the introduction of dried blood spot testing in addiction services to increase case-finding for HCV infection can be cost-effective (Martin et al., 2013). The challenge will be to ensure that newly diagnosed individuals are effectively linked with services offering assessment and care for HCV infection.

Assessment of HCV-related liver disease has been long complicated by the fact that liver biopsy is invasive and logistically difficult. However, the availability of non-invasive fibrosis assessment methods such as transient elastography (e.g. Fibroscan®) has greatly improved the ease of liver disease assessment. Transient elastography has excellent utility for the identification of HCV-related cirrhosis (Shaheen et al., 2007), can predict HCV-related survival (Vergniol et al., 2011) and is cost-effective (Liu et al., 2011). Further, there are several studies demonstrating that transient elastography is a useful tool for enhancing liver disease screening among PWID attending addiction clinics (Moessner et al., 2011; Foucher et al., 2009). Increased community-based liver disease screening using transient elastrography might be one useful strategy for engaging PWID in HCV care and triaging those with advanced liver disease who are in most need of immediate treatment.

4.3. Broad expansion of HCV treatment among PWID

The impressive advances in the development of DAA-based therapy, particularly IFN-free regimens, provide the potential to cure HCV infection in the vast majority of treated individuals. However, as shown in Fig. 3, there is a considerable disparity between the potential treatment efficacy (>90%) and the current HCV treatment effectiveness (<10%), given that less than 10% of people have been treated in most countries. Unless the proportion of individuals screened, assessed and treated for HCV infection is substantially increased these anticipated therapeutic advances will have limited impact at the population level.

Barriers at the level of the patient, provider and system need to be overcome to increase HCV treatment uptake among PWID (Grebely and Tyndall, 2011; Grebely et al., 2013, 2008). It is known that patient knowledge around the long-term consequences of HCV infection and its treatment, including the fear of side effects, are major barriers to assessment and treatment (Grebely et al., 2008, 2011; Treloar et al., 2012). Peer support programs offering HCV education may be one strategy to enhance HCV education and improve engagement in HCV assessment and treatment (Crawford and Bath, 2013). At the provider-level, improved patient-provider interactions with health care professionals are needed to enhance HCV assessment. Strategies to address this may include promotion of national HCV testing guidelines, enhanced education and training of general and drug and alcohol practitioners about HCV testing and diagnostic criteria, an improved awareness of programs offering comprehensive multidisciplinary HCV care (particularly for PWID) and improved pathways for referral. The recent development of the first international recommendations for the management of HCV infection among PWID is a key step forward in providing practitioners with an evidence-base for appropriate assessment and treatment of HCV infection in this group (Robaeys et al., 2013).

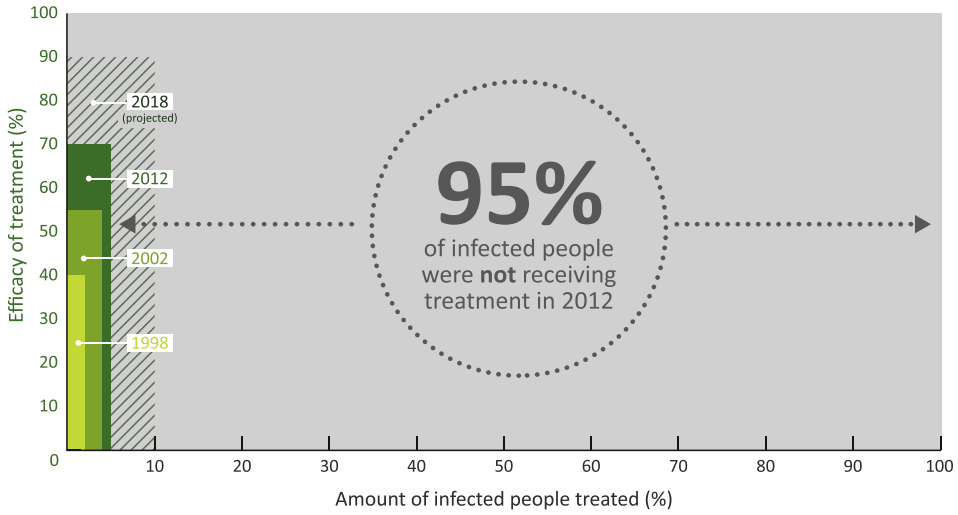

Fig. 3. The disparity between potential HCV treatment efficacy and projected HCV treatment effectiveness. High efficacy of HCV treatment is projected over 5–10 years. SVR has increased from 40% with IFN and RBV in 1998, 55% with PEG-IFN and RBV in 2002, ~70% in the era of PEG-IFN, RBV, and a PI in 2012 (genotype 1 only; patients with HCV genotype 2 or 3 will still have an SVR of ~80% with PEG-IFN-RBV) and IFN-free regimens are anticipated to be available by 2018, with an expected SVR of 90%. However, the global effects of new treatments are negligible without expanded access given the low treatment uptake among people with HCV infection (NCHECR, 2010b; Lettmeier et al., 2008; Volk et al., 2009). Abbreviations: IFN; interferon; PEG-IFN, pegylated-interferon; PI, protease inhibitor; RBV, ribavirin; SVR, sustained virologic response (Modified with permission from Thomas (2013)).

Lastly, improving access to care will require a better understanding of the components of successful assessment and treatment models. Integrated, multidisciplinary models of care that simultaneously address drug dependence, social support (housing, employment, etc.) and HCV care may serve to address these issues (Bruggmann and Litwin, 2013). Further, reducing stigma and discrimination related to HCV infection and drug use is essential (Treloar et al., 2013). Research is needed to better understand why PWID are not being assessed and receiving treatment so that strategies can be designed to enhance treatment assessment and uptake.

4.4. Effective, tolerable, short-duration HCV therapy

Therapeutic regimens that optimize adherence and completion will also be essential. A simplified regimen consisting of combination antiviral agents in one tablet taken once-daily that provides pan-genotypic efficacy and high tolerability would be ideal. As demonstrated in HIV, improved and simplified ART has led to successful treatment outcomes for PWID (Wolfe et al., 2010). Interventions shown to enhance adherence include adherence management strategies (pill boxes, electronic reminders), peer counselling at point of ART delivery, case management and nurse counselling, integrated treatment into existing health services (e.g. prisons, OST clinics, primary care), directly observed therapy and incentives or contributions to food/transport costs. Similar strategies should be explored for HCV treatment among PWID.

4.5. Drug pricing reform and public health advocacy

The rapid scale-up of therapy required to achieve eradication of HCV infection will depend considerably on issues related to cost-effectiveness and government subsidization of IFN-free regimens. HCV treatment for both active and former PWID is cost-effective (driven by the prevention benefit among active PWID) (Martin et al., 2012, 2011). However, it is uncertain whether HCV treatment as prevention for PWID will be cost-effective, particularly in the initial era of DAA-based therapy. Newer, more effective regimens will undoubtedly come at an increased cost. Price reform and enhanced access to therapy for those with HCV infection will require considerable public health advocacy from all sectors in the HCV community, including community organizations representing PWID. The involvement of several pharmaceutical companies in development of DAA-based therapy may enable more competitive drug pricing in high-income countries. In low- and middle-income countries, production of generic DAA regimens will be required, similar to antiretroviral therapy for HIV.

Ultimately, markedly enhanced global public health advocacy and investment along the lines of the Global Fund for HIV, tuberculosis and malaria, will be required to enable broadened access to highly effective HCV therapy, including for PWID.

5. What are the specific settings and strategies for achieving HCV eradication among PWID?

5.1. Programs based in OST, the prison and the community will be essential

A strategy aimed at the eradication of HCV infection among PWID will require targeted programs in settings where there are large numbers of PWID at risk of transmitting infection. As shown in Fig. 4, this will include PWID in the community, those receiving OST and those in prisons. In Australia, among the 230,000 people with chronic HCV infection, it is estimated that 88,000 are PWID (Fig. 4) (The Kirby Institute, 2013). Around 47,000 people in Australia are currently receiving OST through a range of services including public and private clinics and pharmacies, with around half in active PWID and half in former PWID groupings (AIHW, 2012). The prevalence of HCV infection is 75–80% among people on opiate pharmacotherapy (50% chronic HCV prevalence) (Day and Haber, 2009), giving an estimate of 24,000 in the OST setting with chronic HCV infection at any one time, of whom around 12,000 would be active PWID. It is estimated that 50,000 people in Australia are detained in prisons each year (ABS, 2013). The prevalence of chronic HCV infection is estimated to be 20% among people detained in prison, giving an estimate of 10,000 in the prison system each year, the vast majority PWID (Butler and Papanastasiou, 2008). Thus, the proportion (around 25%) of PWID in either prison or OST settings in a given year, and the considerable movements between PWID in the community, OST and prison settings

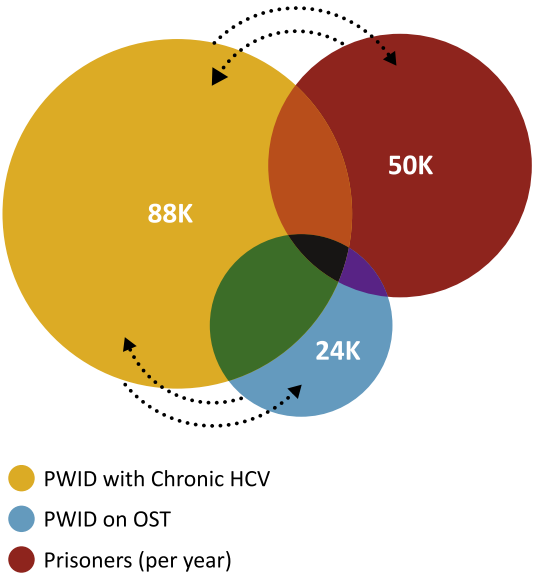

Fig. 4. Specific settings and strategies for achieving HCV eradication among PWID. A strategy aimed at the eradication of HCV among PWID will require targeted programs in settings where there are large numbers of PWID at risk of transmitting infection. This will include PWID in the community, those receiving OST and those in prisons. In Australia, among the 230,000 people with chronic HCV infection, it is estimated that 88,000 are PWID (The Kirby Institute, 2013). The prevalence of HCV is 75–80% among the 47,000 people on opiate pharmacotherapy (50% chronic HCV prevalence) (Day and Haber, 2009), giving an estimate of 24,000 in the OST setting with chronic HCV at any one time, of whom around 12,000 would be active PWID. It is estimated that 50,000 people in Australia are detained in prisons each year (ABS, 2013). The prevalence of chronic HCV is estimated to be 20% among people detained in prison, giving an estimate of 10,000 in the prison system each year, the vast majority PWID (Butler and Papanastasiou, 2008). The considerable movements between PWID in the community, OST and prison settings provides a unique opportunity to capitalize on these settings as HCV treatment access points.

provides a unique opportunity to capitalize on these settings as HCV treatment access points. The simplification of HCV treatment through combination DAA regimens, particularly if treatment duration can be shortened to 8–12 weeks for the majority, should enhance uptake and importantly treatment completion in these dynamic transitioning settings.

Programs most successful in treating HCV infection among PWID have often been built upon existing medical infrastructures for drug user health (e.g. community health centres, OST clinics, general practitioners) (Bruggmann and Litwin, 2013). The common theme from this spectrum of HCV care models among PWID, is that "one size does not fit all". When barriers are systematically addressed within a supportive environment, HCV assessment and treatment among PWID can be very successful. In Australia, the Enhancing the Treatment for Hepatitis C in Opiate Substitution Settings (ETHOS) Study, has demonstrated that when HCV nursing and specialist support are integrated into existing OST or community health clinics, a high proportion of active and former PWID with chronic HCV infection assessed by a nurse can be engaged in HCV specialist assessment and treatment (Alavi et al., 2013). This is consistent with other data from Australia (Hallinan et al., 2007; Lloyd et al., 2013; Alavi et al., 2013), Canada (Grebely et al., 2010), Europe (Lindenburg et al., 2011) and the United States (Harris et al., 2010), demonstrating that when programs are specifically designed to address barriers to care among PWID with an appropriate infrastructure for screening, testing and assessment, PEG-IFN/ribavirin treatment uptake is 3–5% per year (30–50 per 1000 infected) (Lindenburg et al., 2011; Hallinan et al., 2007; Grebely et al., 2010). But, this will need to increase substantially if eradication of HCV infection is to be achieved.

Prison-based settings also provide considerable opportunity for addressing eradication of HCV infection (Post et al., 2013), given the high HCV incidence (Larney et al., 2013; Lloyd et al., 2013), moderate prevalence (25%) Larney et al., 2013; Lloyd et al., 2013, availability of effective screening and treatment programs (Lloyd et al., 2013) and high rates of transitioning between prisons and communities (Post et al., 2013). This presents prisons as an important setting in which to evaluate the feasibility of HCV treatment as prevention. The Surveillance and Treatment of Prisoners with Hepatitis C (SToP-C) Study which is to begin in Australia in 2014 and will explore the hypothesis that a rapid scale-up of HCV treatment with IFN-free DAA-based therapy in prison inmates can achieve a reduction in the incidence of HCV infection.

Lastly, given that the majority of HCV infection occurs in the community, strategies need to also be explored for PWID not directly engaged with health services. One approach that has been proposed is "bring a friend" that would utilise the close social and injecting networks among PWID (Rolls et al., 2013). Recent mathematical modelling indicates that HCV treatment of community-based PWID through assessment and treatment of index cases and their close social network contacts would have a greater impact than treatment of random individual PWID with chronic HCV infection (Rolls et al., 2013). Recent data also indicates close social and injecting networks in low and middle-income countries, with rapid recruitment of PWID into research proposals in India an example of how "bring a friend" strategies may have applicability in diverse settings (Latkin et al., 2011).

5.2. Optimal HCV treatment delivery among PWID

At the population-level (Fig. 5), HCV treatment as prevention may have the greatest impact on reducing the prevalence and incidence of HCV infection in the long term if therapy is targeted to groups and settings associated with the highest risk of transmission (prisons, younger injectors, and newer initiates to injecting). To date, HCV transmission research has generally focused on risk factors for HCV acquisition (Page et al., 2013; Grebely and Dore, 2011). Further research is required to identify HCV-infected individuals with the highest risk of transmitting virus, and social/injecting networks with particularly high rates of HCV spread.

However, at the individual-level (Fig. 5), in the short-term, HCV treatment may have the greatest impact on disease morbidity and mortality if targeted to those PWID who have already been infected with HCV for many years with the greatest risk of disease

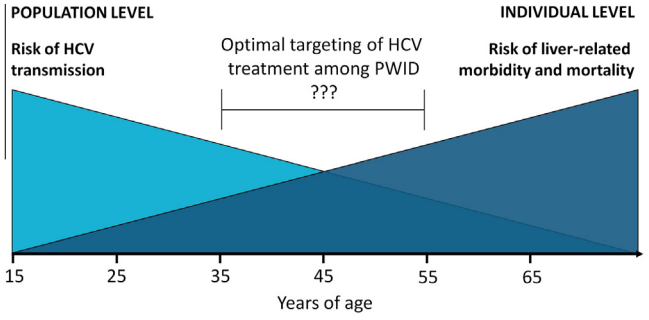

Fig. 5. Optimal targeting of HCV treatment among people who inject drugs (PWID). At the population level, HCV treatment as prevention may have the greatest impact on reducing the prevalence and incidence of HCV infection if therapy is targeted to those at greatest risk of transmitting infection (younger injectors or newer initiates to injecting). However, at the individual level, HCV treatment may have the greatest impact on disease morbidity and mortality if targeted to individuals with the greatest risk of disease progression and death (former PWID who are older and have more advanced disease, but may be at lower risk of transmitting infection) (Modified with permission from Grebely et al. (2013)).

progression and death (Grebely et al., 2013). This population may include those receiving OST (some of whom will also be actively injecting) and PWID who have ceased injecting (although active and former PWID populations are dynamic, given initiation and cessation of injecting). Targeting therapy to these groups might not achieve a large prevention benefit given the lower risk of transmitting infection. However, given higher levels of HCV treatment uptake among former PWID (Gidding et al., 2011; Conway et al., 2005; Bini et al., 2005; Kanwal et al., 2007) and greater healthcare engagement among those receiving OST, HCV assessment and treatment may be more easily targeted towards these groups initially. At the individual level, this approach will clearly limit HCV-related morbidity and mortality, but will have less impact on HCV incidence at the population level. Given this balance of individual-level and population-level health, and the uncertainties related to the cost of future IFN-free DAA-based regimens, further research (including mathematical modelling of cost-effectiveness) is needed to understand the optimal delivery of HCV treatment among PWID in the short- and long-term.

6. Elimination is probably more feasible than eradication among PWID

Although this commentary has suggested a number of reasons why we should strive for global eradication of HCV infection among PWID, there are key limitations which suggest that elimination among this group is more feasible at this point.

6.1. The implementation of harm reduction strategies is still limited in many countries

Despite a number of effective available harm reduction strategies (e.g. NSP and OST), access to and uptake of HCV prevention strategies globally remains suboptimal (Mathers et al., 2010). In a systemic review of available prevention strategies for PWID among 200 countries globally, only 41% ($n = 82$) of countries had implemented NSPs and 35% ($n = 70$) had implemented OST (Mathers et al., 2010). Further, regional and national coverage varied substantially with the highest rates of needle-syringe distribution (up to 202 needle-syringes per PWID per year) in Australasia and the lowest rates in Latin America and the Caribbean, Middle East and north Africa, and sub-Saharan Africa (0.1–0.5 needle–syringes per PWID per year). Western Europe had the highest levels of OST coverage (61 per 100 PWID), but low levels were observed in central Asia, Latin America and sub-Saharan Africa (1 per 100 PWID). Of the 16 million PWID with HCV infection globally, 12 million people are in low- and middle-income countries (Mathers et al., 2008). As Page and colleagues have highlighted, even in a country like the United States, "public health and political efforts to increase clean syringe/needle availability have been met with ideological, social, and political barriers, effectively thwarting the delivery of one of the most efficacious biomedical technologies for preventing injection-related infections" (Page et al., 2013). Global eradication could only be achieved with a substantial increase in the coverage of NSP and OST interventions internationally, and even then elimination is probably the realistic goal.

6.2. Eradication among PWID would likely require an HCV vaccine

The only infectious disease in humans that has been successfully eradicated through deliberate efforts is smallpox (WHO, 1999). In 1796, Edward Jenner successfully demonstrated the efficacy of smallpox vaccination using a challenging inoculation with variola virus, representing the discovery of vaccination (WHO, 1999). Subsequently, it was shown that prophylaxis through a global mass vaccination program using a highly effective smallpox vaccine (consisting of live vaccinia virus) could lead to the eradication of an infectious disease. Key components of success included that smallpox infections are restricted to humans, variola virus cannot establish latent or persistent infections, smallpox was symptomatic and signs were easily noticed, the vaccine induced long-lasting protective immunity and was effective against all strains of variola virus, no variants of variole virus could escape protective immunity and the vaccine was easy to prepare, cheap and stable without refrigeration.

As reviewed elsewhere (Cox and Thomas, 2013), although there are several HCV vaccine candidates in development, there are significant challenges to testing a vaccine among PWID. In 2012, the first HCV vaccine trial in at-risk HCV-uninfected PWID was initiated. The results from this and other ongoing studies will guide vaccine development, which is probably a critical component for achieving global eradication of HCV infection.

The availability of a highly effective HCV vaccine would still require major global investment and advocacy for implementation. Further, inclusion in the childhood immunization schedule would not be inevitable in most countries, and the sub-optimal delivery of HBV vaccine to PWID a lesson in the difficulties of targeted public health interventions in highly marginalized populations.

6.3. Treatment as prevention is less effective in high HCV prevalence settings

There are a number of mathematical modelling studies have illustrated the potential preventative utility of HCV treatment for PWID (Grebely et al., 2013). However, a key theme that has emerged is that the effectiveness of an HCV treatment as prevention strategy is highly dependent on the baseline HCV prevalence. For example, in modelling studies of DAA-based HCV treatment as prevention, in a low chronic HCV prevalence setting (e.g. Edinburgh, Scotland; 25% chronic HCV prevalence) compared to a high chronic prevalence setting (e.g. Vancouver, Canada; 65% chronic HCV prevalence) a lower annual treatment uptake is required to achieve a 50% reduction in HCV prevalence over 15 years (15 vs. 75 per 1000 PWID annually) (Martin et al., 2013a). Similarly, at a treatment uptake of 40 per 1000 PWID, the prevalence reduction would be 91% in Edinburgh as compared to 22% in Vancouver over 15 years. Given an estimated global HCV prevalence of 67% among PWID (Fig. 2) (Nelson et al., 2011), the majority of countries in the world will have difficulty in achieving even elimination among PWID in the short to medium term.

6.4. Reinfection among PWID may compromise DAA-based HCV treatment

Despite successful response to HCV therapy observed among PWID, there are still concerns that re-infection due to recurrent risk behaviours will negate the potential benefit of treatment. In the era of PEG-IFN and RBV combination therapy, the reported rates of reinfection following successful HCV treatment among PWID are low (1–5% per year) Aspinall et al., 2013; Grady et al., 2013. However, studies of reinfection following successful HCV treatment are limited by the small sample sizes, heterogeneous study populations, retrospective study designs and incomplete longitudinal follow-up. Further, little is known about whether the incidence of HCV reinfection will be higher in the DAA-based era, given the potential for broader expansion to PWID with more recent injecting risk behaviours. Although an increase in the rate of HCV reinfection would be concerning, given the lack of available evidence, it is certainly not justifiable to withhold HCV treatment to PWID based on the potential concern of HCV reinfection. Nonetheless, education and counselling about the risk of reinfection and

potential strategies for risk reduction should be a key component for PWID initiating treatment for HCV infection as reinfection can occur. If very high rates of HCV reinfection would be observed among PWID in the DAA-based era, it would certainly compromise efforts to eradicate HCV infection in this group.

7. Conclusions

Eradication of HCV infection, defined as the complete and permanent worldwide reduction to zero new cases through deliberate efforts, with no further control measures required (e.g. smallpox), is a considerable challenge. Elimination of HCV infection, defined as the reduction of the incidence of infection caused by a specific agent to zero in a defined geographical area, requiring the presence of continued measures to prevent re-establishment of transmission (e.g. measles, poliomyelitis), is probably much more feasible. It is likely that the incidence of HCV infection could be reduced to zero in defined geographical areas with continued interventions to prevent re-emergence of infection (e.g. NSP and OST), rather than a complete and permanent worldwide reduction to zero.

This is an exciting era for the field of HCV. As newer IFN-free DAA agents become available, HCV treatment as prevention may be an attractive option to reduce the future burden of HCV-related disease. Any strategy will need to build upon the existing foundation of prevention and care for PWID. HCV treatment as prevention is part of a larger challenge to expand access to HCV testing and care. Both individual-level and population-based strategies will be required for a comprehensive approach for the control and eventual elimination of HCV transmission and disease. Cost-effectiveness evaluations are needed to determine how services can be optimally allocated. Future research in this area will help better understand the role of HCV treatment as prevention in the hope of eradicating HCV infection, or at least eliminating the virus in specific population groups such as PWID populations in many settings.

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Conflict of interest

JG is a consultant/advisor and has received grants from Merck and Gilead. GD is a consultant/advisor and has received research grants from Roche, Merck, Janssen, Gilead, and Bristol Myers Squibb.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.antiviral.2014.01.002.

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