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Candidate hepatitis C vaccine trials and people who inject drugs: Challenges and opportunities

Lisa Maher[a,*], **Bethany White**[a], **Margaret Hellard**[b], **Annie Madden**[c], **Maria Prins**[d], **Thomas Kerr**[e], and **Kimberly Page**[f]

Lisa Maher: LMaher@nchecr.unsw.edu.au

[a]Viral Hepatitis Epidemiology and Prevention Program, National Centre in HIV Epidemiology and Clinical Research and School of Public Health and Community Medicine, University of New South Wales, Centre for Immunology, Corner Boundary and West Streets, Darlinghurst, NSW 2010, Australia [b]Centre for Population Health, The Macfarlane Burnet Institute for Medical Research, 85 Commercial Road, Melbourne, Victoria 3004, Australia [c]Australian Intravenous and Injecting League (AIVL), Sydney Building, Level 1/112-116 Alinga Street, Canberra, ACT 2600, Australia [d]Academic Medical Centre, University of Amsterdam and Infectious Disease Cluster, GGD Amsterdam Public Health Service, Department of Research, Amsterdam 1000 CE, The Netherlands [e]Urban Health Research Elective, British Columbia Centre for Excellence in HIV/AIDS, St Paul's Hospital, 806-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada [f]Department of Epidemiology and Biostatistics, University of California San Francisco, 50 Beale Street, Suite 1200, San Francisco, CA 94105, USA

Abstract

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People who inject drugs (PWID) are at high risk of HCV. Limited evidence of the effectiveness of prevention interventions and low uptake of treatment in this group highlight the need for increased investment in biomedical interventions, notably safe and efficacious vaccines. While several candidates are currently in development, field trials in PWID present challenges, including ethical issues associated with trial literacy, informed consent and standards of care. Significant biological and social factors and differences between HIV and HCV suggest that HCV warrants targeted vaccine preparedness research to lay the groundwork for successful implementation of future trials.

*Corresponding author. Tel.: +61 293850936; fax: +61 293850920.

Keywords

Hepatitis C virus; Vaccine; People who inject drugs

1. Introduction

Chronic hepatitis C virus (HCV) infection is a major cause of morbidity and mortality globally and a key factor driving increases in rates of liver cancer and demand for liver transplantation in high- and middle-income countries [1]. In comparison to hepatitis B virus, for which there is a safe and efficacious vaccine, and for which therapeutic agents for the treatment of chronic infection are available and reasonably well tolerated, there is no vaccine for HCV and current antiviral treatments are complex, costly, toxic, and of limited efficacy in the relatively small proportion able to access them [2]. The burden of HCV-related disease is associated with significant costs to the health system resulting from the need to manage chronic illness and the demand on services for treatment of advanced liver disease. As the incidence of advanced liver disease increases these costs will continue to escalate [3,4], highlighting the need for increased investment in effective prevention interventions, notably safe and efficacious vaccines [5].

As an RNA virus with significant mutability and resulting genetic diversity, HCV, like HIV, presents challenges for vaccine development [6,7]. However, HCV transmission events, acute infection, viral dynamics and infection outcomes are distinct from those that occur with HIV. HCV is significantly more infectious than HIV and parenteral transmission is more efficacious [8,9]. While HCV affects almost 3% of the world's population [1,10], unlike HIV, many people are not aware of their status. In the U.S., it is estimated that 75% of the estimated 2.7–3.9 million Americans living with chronic HCV infection are unaware that they are infected [11]. Despite this, international efforts to develop an effective HCV vaccine lag well behind HIV vaccine development.

People who inject drugs (PWID) are at high risk of HCV infection and are the key affected community globally. HCV prevalence and incidence of up to 95% and 45/100 person-years, respectively, have been reported in PWID [12–18]. Evidence of the effectiveness of stand-alone interventions to prevent HCV infection in this group is limited. Studies of the effects of exposure to preventive interventions, including drug treatment [19], needle and syringe distribution (reviewed in [20]), harm reduction and education programs [21], and bleach disinfection [22], have failed to provide conclusive evidence of efficacy. While a recent Dutch study showed significant protective effects of comprehensive harm reduction (needle and syringe distribution and methadone treatment) on HIV and HCV incidence [23], a peer education intervention RCT found reductions in risk behavior but no difference in HCV incidence (18.4/100 person-years) between the intervention and control groups [24]. These data suggest that further decreases in incidence are unlikely to be achieved without large-scale and effective biomedical interventions, notably preventive vaccines [25]. Despite improvements in, and the relative cost effectiveness of, antiviral treatments for HCV [3,26–28], barriers to screening and diagnosis [29] mean that treatment is unlikely to impact transmission in the short to medium-term. Low uptake among PWID [30], the likelihood of re-infection [17,31,32] and the prohibitive cost of medications suggest that treatment is implausible as a global prevention strategy for this population. By contrast, modeling studies have shown that HCV vaccine strategies targeting PWID can be both cost effective [33] and the most efficient approach to controlling the epidemic [25]. Canadian researchers showed that targeted immunization with an 80% effective HCV vaccine and 51% compliance would prevent more infections, including new infections, than a universal approach and reduce HCV-related deaths and overall costs [33].

Research in non-human primates suggests that the design of at least a partially effective vaccine against HCV is feasible [7,34,35]. First, the immunological responses associated with spontaneous eradication of the virus [36] are becoming more clearly understood and many researchers propose that duplication of such immune events through immunization is a realistic option [37]. Studies in both humans and chimpanzees demonstrating reduced susceptibility to re-infection following clearance and re-exposure also suggest effective immunological protective mechanisms [17,31,38–41]. However, results on protective immunity in drug users are inconsistent, which might be partially explained by differences in study design [17,31,32,42,43]. While some chimpanzee studies indicate that it is possible to impede the progression to chronic infection after both homologous and heterologous challenges, other studies have not been as successful in preventing infection or chronic persistent infection (reviewed in [34]).

Several candidate vaccines designed to prevent initial or chronic HCV infection in uninfected people, reduce viral persistence in infected individuals, or sustain virological response in individuals with chronic infection, are currently in preclinical development or early stage clinical trials (reviewed in [6,7,34]). The majority of reported trials are on therapeutic HCV vaccines, where results have been mixed. Wedemeyer et al. [44] examined the effect of the HCV peptide vaccine IC41 on HCV-specific T-cell responses and virological relapse rates in 60 patients with chronic HCV genotype 1 infection when added to pegylated interferon plus ribavirin standard therapy. In that trial, HCV-specific T-cell responses were associated with lower relapse rates, but the vaccine did not prevent HCV-RNA relapse [44,45]. In a recent Phase 1 trial of dendritic cell immunotherapy in HCV infected individuals who had failed conventional therapy, durable immune responses were not observed, nor effects on HCV viral load, antibody response or levels of circulating cytokines [46]. A third therapeutic candidate, the HCV Core ISCOMATRIX^{TM} vaccine, was recently evaluated in 30 healthy volunteers [47]. Antibody responses were detected in all but one participant and there was no indication of a dose response, suggesting it would be worth pursuing further work in HCV infected patients. Only one recent trial of a prophylactic vaccine has been reported on: a Phase 1 trial of a prophylactic vaccine (HCV E1E2) in healthy adults [48]. The vaccine was found to be safe, generally, well tolerated at the different dosage levels, and with measurable induced antibody and lymphoproliferative responses. All of these Phase 1 trials were conducted in healthy volunteers, and with one exception [47], explicitly excluded participants with a history of drug use in the past year.

This paper reviews challenges presented by field trials in human subjects of candidate prophylactic HCV vaccines in PWID, including ethical issues associated with trial literacy, informed consent, standards of care, recruitment and retention, and the need for high incidence of infection. While our review suggests that the challenges of ensuring the interest and participation of this population in candidate HCV vaccine trials should not be under-estimated, we also identify a number of opportunities, including the potential for formative research to better understand the social and cultural drivers of vaccination demand in this group and the possibility of developing models of best practice for conducting prevention trials with vulnerable populations.

2. Challenges

Clinical trials of candidate HCV vaccines raise significant biological, methodological and ethical challenges.

2.1. Biological

Important concerns include expectations regarding efficacy, viral heterogeneity, and immunology. HCV is an RNA-based virus with a variable genome and the capacity to

evolve over time to evade drug and immunologic pressure [49]. The seven major genotypes share less than 80% sequence homology with each other, in excess of 50 subtypes have been identified [50,51], and both the duration and success rate of current treatments for HCV are genotype dependent, presenting challenges for both vaccine and drug development [2].

First-generation HCV vaccines are expected to be of moderate efficacy (≤60%), a key issue encountered in HIV vaccine trial preparation (reviewed in [7]). A principal HCV candidate developed by Okairos and currently in Phase I trials, is based on novel replication defective Adenovirus vectors with low/no seroprevalence in humans: the chimpanzee Adenovirus AdCh3, and the human Adenovirus Ad6, encoding the HCV non-structural antigens, with genetically inactivated RNA-dependent RNA polymerase (NSmut) [52]. In various animal models, strong induction of HCV T- and B-cell responses have been shown. In chimpanzees, the vaccine induces potent, broad and long-lasting T-cell responses capable of protecting against acute and chronic infection after challenge with highly heterologous virus [53]. The NSmut sequence is from HCV genotype 1, subtype b, BK strain, which is conserved among different isolates and contains more than 90 CD4+ and 70 CD8+ epitopes. While protection is expected to be moderate or better (≥80%) for infection with type 1 virus, protection against other subtypes may be lower, and several studies indicate considerable diversity in circulating HCV virus among PWID [54–56]. Both efficacy and cross-clade protection have been identified as significant factors affecting HIV vaccine trial acceptability [57] and may be important determinants of HCV vaccine trial participation. A recent systematic review which found a moderate level of HIV vaccine acceptability (65.6 on a 100-point scale) across 20 studies involving 7,576 participants found significantly lower acceptability (40.4 vs. 73.8) for moderate (50%) versus highly (80–95%) efficacious hypothetical vaccines [58]. In addition, Phase I HCV vaccine trials are conducted in healthy volunteers, and not in PWID who may have various comorbidities and may demonstrate poorer immunological responses to viral infections and even vaccine challenge, as has been the case for hepatitis B vaccine [59]. Other concerns include side effects, durability of protection, and the potential for detectable vaccine-induced antibody seroconversion. Detection of antibody was an important issue for both participants and researchers in HIV vaccine trials [60], raising the potential for unblinding/unmasking. However, it is unknown how this factor will play out with HCV vaccines currently in development which are anticipated to prevent persistent, rather than primary, infection and thus how the antibody response or detection will develop.

2.2. Methodological

Trial design issues include trial literacy, standard of care, trial size and duration, protocol adherence and cohort retention. A recent study of trial-experienced and trial-naive PWID found low acceptability (55–60%) of key clinical trial concepts such as equipoise, placebo and double-blinding. Participants who demonstrated understanding of placebo and double-blinding were significantly more likely to perceive these concepts to be acceptable [61]. Challenges associated with the standard of care for PWID in prevention trials are not limited to low- and middle-income country settings. Despite the fact that sharing of contaminated syringes has been identified as a major risk factor for HCV infection, coverage of sterile injecting equipment is often suboptimal and gaps in coverage continue to sustain the epidemic [62]. Globally, only 8% of injectors have access to needle and syringe programs and less than half the countries with known injecting drug use populations provide access to opioid substitution treatment [63]. Moreover, in many settings, prevention interventions for PWID remain controversial, unsupported or banned [64], potentially making the provision of standard of care difficult, if not impossible.

Evidence is also mounting that treatment of acute HCV is highly efficacious [38,65]. Incorporating treatment for incident cases into vaccine trials will be challenging. In 2006

Chiron and NIDA began discussions and planning regarding the design and implementation of trial to test a prophylactic vaccine (E1/E2) vaccine. The scope of the planning was wide and included input from groups studying HCV among PWID. A significant amount of time was spent discussing the parameters of future trials and when and whether treatment for acute HCV infection could be offered. While this took place at the same time that Novartis was taking over Chiron, the trial idea was subsequently dropped and Dr. Frank Vocci, formerly with NIDA, noted that this decision was principally in association with the perceived challenges and costs associated with providing treatment for acute HCV infection (personal communication with KP, January 2008).

Estimates of the impact of existing prevention strategies on HCV incidence are necessary in order to determine appropriate standards of care in future vaccine trials [51]. In addition to concerns in relation to standards of care, inaccurate estimates of incidence, high attrition, suboptimal adherence and lack of community engagement have been identified as factors contributing to the premature termination of recent late-stage HIV prevention trials [66,67]. Efficacy trials are lengthy and expensive and the capacity to conduct them is limited. Effective evaluation of candidate HCV vaccines in Phase II/III studies will require the ability to recruit and follow-up HCV uninfected individuals in settings of relatively high HCV incidence. While several studies provide estimates of incidence, accurate and current estimates are necessary, as even small changes in incidence can significantly impact trial sample size and duration. Lower-than-expected rates of enrolment and higher than expected rates of loss-to-follow-up can also result in underpowered trials that fail to reveal effective interventions, or delay the public health impact of a positive trial.

While little work has been conducted on the feasibility of conducting HCV vaccine trials with PWID, rates of willingness to participate in HIV vaccine trials between 41 and 86% have been reported in this group [68]. Significantly, the AIDSVAX B/E efficacy trial in Thailand demonstrated that PWID could be successfully enrolled and retained in a preventive vaccine trial [69] and while studies indicate that recruitment and retention of uninfected PWID is feasible [13–17,19], long-term commitments to study participation and multi-dose vaccine schedules are required in proof of concept and efficacy trials. Retention is critical because loss-to-follow-up reduces study power and biases results. PWID can be a challenging population to track and retain in intervention studies due to factors including mobility, unstable living conditions and high rates of arrest and incarceration [70]. Higher risk individuals, particularly those not connected to mainstream public health programs, may be even more difficult to recruit and follow-up. Several studies have also shown that incidence is highest among new injectors who are often less engaged with the health system and may be hardest to reach [14,16,18,71]. Community engagement and ethnographic fieldwork provide mechanisms to increase recruitment and retention by identifying potential sites and populations and assessing community interest in future vaccine trials [72].

2.3. Ethical

PWID are often socially vulnerable due to factors including poverty, stigma, racism and gender inequality. These powerful social and cultural forces must be addressed when conducting HCV research or implementing prevention programs. Communities at risk of HCV may also distrust the government and biomedical research [73,74] and researchers must pay attention to how knowledge and participation are affected by poverty, culture and stigma in order to minimize potential ethical concerns [57]. In addition, where law enforcement and incarceration remain the dominant policy responses to injecting drug use, this can undermine public health programming and intervention studies by increasing risky behaviors and displacing drug users [75–77]. Anti-vaccine activism and government mistrust and attitudes may vary by social network, gender or ethnic affiliation [78]. Community groups are likely to be vigilant regarding ethical issues, especially perceived

exploitation of vulnerable populations. Our experience over two decades suggests that partnership approaches, combined with the provision of support and referral services, may increase trust and improve retention [14,16,17,23,32,72,79,80].

A frequent concern in prevention trials in high risk groups is the potential for risk inhibition or compensation following receipt of vaccine. Mathematical models have predicted that the potential benefits of an HIV vaccine may be completely lost if continued or increased risk behavior occurs following immunization [81]. However, behavioral disinhibition has not been observed in studies of HIV post-exposure prophylaxis and actual vaccine interventions [82,83]. Nevertheless, these issues will remain, and may potentially impact factors such as the provision of clean injecting equipment.

3. Opportunities

As Baral et al. [84] have observed, “A consistent and disturbing finding in reviewing the published work on vaccination in PWID is that they are at high risk for vaccine-preventable infections, but generally have among the lowest immunization coverage rates” (p. 672). Hepatitis B virus (HBV) vaccination programs that target behavioral risk groups have been successful in some settings. In the Netherlands, estimated HBV vaccine coverage following implementation of a targeted vaccination program via Public Health Services was 39% in PWID versus 6% in men who have sex with men [85]. While studies have shown that acceptance of HBV vaccination among PWID is high when convenience is maximized and remuneration offered [86–88], accelerated schedules have also been recommended for PWID in response to poor completion [59,89].

Little is known about the social and cultural dimensions of vaccine demand in PWID. Formative research can support vaccine trial design through improved understanding of the knowledge and attitudes of target groups, identifying barriers to trial participation and intervention uptake, and improving ethical informed consent [90]. A recent study designed to inform preparedness for candidate HCV vaccine trials identified the benefits of early and extended community engagement in informing site selection, identifying motivations and concerns and providing affected community input into the development of research protocols [72].

Better understanding of PWID attitudes and decision making around vaccination uptake is necessary to inform and facilitate vaccine trial readiness and trial operations [91]. Planning for clinical trials also needs to recognise the concerns of participants and to provide information in a format that is responsive to their needs. As the development of HCV vaccines progresses, methods need to be developed to maximize informed and committed involvement by PWID in vaccine trials. While clinical trial literacy is crucial because it speaks to the capacity to provide informed consent, investing time and resources in developing effective and sustained community engagement is also necessary to build the capacity of PWID to participate in clinical trials [92].

Many PWID face the possibility of HCV infection with a complex sense of inevitability, fostered by structural barriers to effective prevention [93]. This ‘sense of inevitability’, potentially a major barrier to effective behavioral interventions, may represent a constructive opportunity with respect to vaccine trials, as vaccines represent a ‘new’ way of engaging with one's sense of personal risk and ability to respond. For some atleast, vaccines may represent an ‘easy’ way of bypassing or rendering irrelevant the structural barriers to avoiding infection. Finally, HCV vaccine trials can benefit from lessons learned from HIV prevention trials [94]. In contrast to HIV prevention trials, which are often conducted ‘on’ vulnerable populations in resource poor settings, high HCV incidence in PWID in resource-

rich settings provides opportunities to develop models of best practice for conducting prevention trials 'with' the communities most likely to benefit.

4. Conclusions

Throughout this commentary we have drawn analogies between HCV and HIV vaccine research. While there is much to be learned from HIV vaccine research, we suggest that HCV also poses unique challenges and requires targeted efforts specific to this infection. Firstly, HCV is not HIV. Transmission events, acute infection, viral dynamics and infection outcomes are different from those that occur with HIV. People at risk for HCV and participating in HCV research, including vaccine-related research, must be informed and educated about a different virus, different testing and interpretations, as well as risk, transmission and infectivity patterns. HCV is significantly more infectious than HIV and sharing of injecting equipment is a highly efficacious route of transmission [8,95]. HCV infection is spontaneously cleared by 20–40% of infected individuals, and substantially more so among women than men [17]. While there are similarities in terms of vaccine design and evaluation of immune responses, there are important differences in other areas, including differences in the effect of the vaccine on infection outcome. These issues have been reviewed by Strickland et al. [7]. In brief, a successful prophylactic HCV vaccine will likely aim to protect against viremia, by inducing immune mediated clearance and preventing establishment of chronic infection, which is relatively easy to assess. By contrast, HIV vaccine candidates have shown limited promise in eliciting the immune responses that will prevent infection and research has shifted to include candidates designed to modify disease progression by altering viral set-point, an outcome that is more challenging to assess [7,96]. Efforts to develop and test HIV vaccines have also received a great deal more resources and effort than HCV vaccine research [7,34,96,97].

Secondly, PWID are a difficult to reach population and HCV vaccine trials with this group will present particular challenges. PWID at high risk of HCV are younger and may be newer to injecting than those at risk of HIV [18]. While the HIV vaccine trial conducted in Thailand involved participants recruited from methadone clinics in Bangkok, it is possible that this population may be more stable than injectors at risk of HCV [69]. Moreover, in developed country settings, populations in drug treatment, particularly those engaged in opioid substitution treatment, are not likely to be candidates for vaccine trials as a high proportion are anti-HCV positive [98,99]. There is a need for high quality data on the factors associated with recruitment and retention of out-of-treatment PWID, both in cohort studies and clinical trials. Thirdly, prevention trials must also provide standard of care prevention for participants. As noted previously, there remains considerable uncertainty around the appropriate dose and mix of interventions necessary to prevent HCV, as well as ongoing controversy around their implementation and scale up. Based on the evidence reviewed here, a minimum prevention package for PWID enrolled in candidate HCV vaccine trials includes access to risk reduction counseling, sterile injecting equipment, drug dependency treatment, and other medical care and treatment evaluation as needed.

HCV is associated with significant mortality and morbidity globally [1]. PWID are the population at greatest risk of HCV infection [12–18] and stand to benefit greatly from a vaccine. While current prevention approaches have been successful at reducing risk and harm, impact on HCV incidence has been minimal and the epidemic is unlikely to be contained without at least a partially effective vaccine. A safe and efficacious vaccine could significantly reduce HCV transmission among PWID, averting considerable morbidity and mortality and decreasing associated costs. Our review suggests that lessons learned from HIV, while helpful, will not completely inform HCV trial preparation or implementation. The challenges of ensuring interest and participation among PWID in field trials of

candidate HCV vaccines should not be under-estimated. In addition to distinct biological challenges in relation to HCV such as viral heterogeneity, and trial design issues including standards of care, PWID are often socially and economically marginalized, vulnerable to high rates of arrest and incarceration and may suspect and/or distrust the medical community. Little is known about attitudes towards immunization, barriers to uptake, and willingness to participate in vaccine trials in this group. However, in contrast to HIV and other infectious diseases such as tuberculosis, high HCV incidence in high- and middle-income settings provides opportunities to develop models of best practice for conducting prevention trials with this population. The significant biological and social factors and differences between HIV and HCV reviewed here suggest that hepatitis C warrants targeted vaccine preparedness research in order to lay the groundwork for successful implementation of future trials with PWID.

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