HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2015 July 21.

Published in final edited form as:

Vaccine. 2014 September 22; 32(42): 5460–5467. doi:10.1016/j.vaccine.2014.07.091.

Assessing the feasibility of hepatitis C virus vaccine trials: Results from the Hepatitis C Incidence and Transmission Study-community (HITS-c) vaccine preparedness study

Bethany White[1], **Annie Madden**[2], **Maria Prins**[3,4], **Margaret Hellard**[5], **Handan Wand**[1], **Gregory J Dore**[1], **Kimberly Page**[6], and **Lisa Maher**[1]

[1]The Kirby Institute, UNSW Australia, Sydney, NSW, 2052, Australia [2]Australian Injecting & Illicit Drug Users League (AIVL), Sydney Building, Level 2/112-116 Alinga Street, Canberra ACT 2600, Australia [3]Academic Medical Centre, Center for Infection and Immunity Amsterdam (CINIMA) University of Amsterdam, The Netherlands [4]Cluster of Infectious Diseases, Department of Research, Public Health Service, Amsterdam, The Netherlands [5]Centre for Population Health, The Macfarlane Burnet Institute for Medical Research, 85 Commercial Road, Melbourne Victoria 3004, Australia [6]Department of Epidemiology and Biostatistics, University of California San Francisco, 50 Beale Street, Suite 1200, San Francisco, CA 94105, USA

Abstract

Efficacy trials of preventive hepatitis C virus (HCV) vaccine candidates raise complex and challenging scientific and ethical issues. Based on data from the first three years of a community-based prospective observational study – the Hepatitis C Incidence and Transmission Study-community (HITS-c) – this paper examines the feasibility of conducting trials of candidate HCV vaccines with people who inject drugs (PWID). Of the 166 PWID confirmed HCV antibody negative and eligible for enrolment, 156 (94%) completed baseline procedures. Retention was high, with 89% of participants retained at 48 weeks and 76% of participants completing at least 75% of study visits within two weeks of schedule. The rate of primary HCV infection was 7.9/100 py (95% CI 4.9, 12.7). Of the 17 incident cases, 16 completed at least one follow-up assessment by 24 weeks and 12 (75%) had evidence of chronic viremia with progression to chronic HCV infection estimated to be 6/100 py. Power calculations suggest a chronic HCV infection rate of at least 12/100 py (primary HCV infection rate 16/100 py) will be required for stand-alone trials of highly efficacious candidates designed to prevent chronic infection. However, elevated primary HCV infection was observed among participants not receiving opioid substitution therapy who reported heroin as the main drug injected (26.9/100 py 95% CI 14.5, 50.0) and those who reported

Correspondence: Professor Lisa Maher, The Kirby Institute, UNSW Australia, Sydney, NSW, 2052, Australia. (T) +61 2 9385 0900 (F) +61 2 9385 0920 lmaher@kirby.unsw.edu.au.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Contributors

LM designed and led the Hepatitis C Vaccine Preparedness Study and LM and BW wrote the protocol for the HITS-c study. Statistical analysis was conducted by BW, supervised by HW and reviewed by LM and GD. BW reviewed the literature and wrote the first draft of the manuscript. All authors participated in interpretation of the data and revisions of the manuscript and contributed to and approved the final manuscript.

unstable housing (23.5/100 py 95% CI 7.6, 72.8), daily or more frequent injecting (22.7/100 py 95% CI 12.2, 42.2) and receptive syringe sharing (23.6/100 py 95% CI 9.8, 56.7) in the six months prior to baseline. These data suggest that it is possible to recruit and retain at-risk PWID who adhere to study protocols and that modification of eligibility criteria may identify populations with sufficiently high HCV incidence. Results support the feasibility of large multi-centre HCV vaccine trials, including in the Australian setting.

Keywords

hepatitis C virus; vaccine preparedness study; people who inject drugs

Introduction

Feasibility or vaccine preparedness studies (VPS) support Phase III vaccine trial design through increasing understanding of the mechanisms and effects of interventions, identifying barriers to trial participation, improving ethical informed consent procedures, and informing recruitment, retention and adherence strategies [1–3]. VPS lay the groundwork for future trials by answering key scientific questions, building community capacity, and establishing the necessary infrastructure for trial conduct [2]. A key aim of these studies is to demonstrate capacity to recruit and retain at-risk individuals with sufficient clinical trial literacy (CTL) and willingness to participate (WTP) in future trials [1, 4].

Identified over 20 years ago [5], the hepatitis C virus (HCV) is a major cause of morbidity and mortality worldwide with approximately 3% of the world's population infected [6]. Chimpanzee studies indicate that generation of protective immunity against HCV via vaccination is possible [7–10]. In two Phase I trials, preventive vaccines candidates were shown to be safe and immunogenic [11, 12]. An additional two trials in humans are currently in progress. The first is a Phase I trial of healthy volunteers and people with HCV (ClinicalTrials.gov identifier: NCT01296451) and the second is a staged Phase I/II trial of the same preventive candidate among people who inject drugs (PWID)(ClinicalTrials.gov identifier: NCT01436357).

As the key population at risk of HCV in developed countries [13], effective engagement and recruitment of large numbers of exposed but uninfected PWID will be required for successful Phase III vaccine trials. Trials of candidate HCV vaccines are likely to face particular challenges in attracting and retaining suitable participants and in developing appropriate protocols to assess safety, immunogenicity and efficacy [1]. The identification of populations with sufficiently high HCV incidence to demonstrate vaccine candidate efficacy will be of particular importance.

Previous Australian studies have documented high incidence of HCV among PWID [14, 15]. HCV incidence in community-based cohorts of PWID has ranged between 10.7/100 py (95% CI 6.8, 16.8) [1990–1995] in Victoria [16], 30.8/100 py (95% CI 24.3, 39.0) [1999–2002] in NSW and 44.1/100 py (95% CI 34.4–56.6) [1999–2002] in South West Sydney [17]. However, recent evidence suggests that HCV incidence may be declining among Australian PWID [18]. Temporal variations in HCV incidence highlight the importance of

current and accurate estimates of HCV incidence, which are crucial to power trials of candidates designed to prevent chronic HCV infection. Of note, the preventive vaccine candidate currently being assessed (ClinicalTrials.gov identifier: NCT01436357 & NCT01296451) aims to elicit a T-cell response associated with spontaneous clearance and therefore viral persistence estimates (progression to chronic HCV infection) are necessary for sample size projections for Phase III assessment.

While HIV VPS have included PWID, this population has typically comprised only a minority of study participants [19–21]. As part of the first HCV VPS, this paper reports key outcomes impacting HCV vaccine trial feasibility in PWID based on a community-based prospective observational study of HCV antibody negative PWID – the Hepatitis C Incidence and Transmission Study- community (HITS-c). The study aimed to identify 1) retention at 48 weeks; 2) adherence to study protocols; 3) HCV incidence by baseline characteristics and risk behaviour; 4) progression to chronic HCV infection; and 5) sample size estimates for future trials based on retention and chronic HCV infection observed in the HITS-c cohort.

Methods

Research methods have been previously described [22, 23]. Briefly, recruitment sites in three Sydney regions (South West, Inner and Western Sydney) were selected following ten months of ethnographic fieldwork [24]. Potentially eligible PWID were identified via targeted outreaching sampling [25] or incentivised peer referral. Those identified via targeted outreach sampling were approached directly by study staff and were not incentivised for referring peers to the study. The incentivised peer-referred sample were referred by their peers who received $30 AUD for each referral (up to three each), who were in turn incentivised $30 AUD for each peer they referred. Behavioural data and sera were collected by research assistants trained in venepuncture and pre- and post-test counselling.

Eligibility criteria for study screening were aged 16 years or older, self-reported HCV antibody (anti-HCV) negative or unknown status, injected drugs in the past 12 months and willingness to provide at least three forms of contact information. Enrolled participants received $50 AUD for the completion of baseline and follow-up risk behaviour and serological assessments every 24 weeks.

HCV antibody and RNA testing

Venous blood samples were screened for anti-HCV using standard ELISA (Abbott Architect™) and confirmed by Monlisa HCV Ultra Ag/Ab (BioRad™) and for HCV RNA by quantitative HCV detection assay COBAS Ampliprep/COBAS TaqMan HCV 2.0 (Roche™). Anti-HCV and RNA testing was conducted every 12 or 24 weeks depending on HCV infection status.

HCV incident case definitions

Incident cases included participants who tested anti-HCV negative at screening and were positive for anti-HCV and/or HCV RNA at their first or subsequent 24 week follow-up visit post-baseline. Two additional participants with acute infection (anti-HCV negative at

screening and HCV RNA positive at baseline one week later) were included as prevalent incident cases. For all cases, date of infection was estimated as the midpoint between the last negative and first positive anti-HCV test, with the two prevalent incident cases contributing minimal HCV negative follow-up time given the first positive anti-HCV test occurred within six weeks of last negative test for both. Spontaneous HCV viral clearance was defined as a minimum of two consecutive negative RNA tests following incident infection by 24 week follow-up. Participants who did not demonstrate spontaneous clearance by 24 weeks were considered chronically infected.

Measures

Factors assessed for association with retention, adherence and HCV incidence included recruitment method, recruitment region and demographic characteristics: age (< the median age of 27 vs. those aged ≥27), gender, ethnic background (Anglo-Australian vs. culturally and linguistically diverse [CALD]), education, housing and employment status. Incarceration history, recent needle and syringe program (NSP) access and injecting risk behaviour were also examined in relation to all three outcomes. A composite variable was created to examine the proportion of participants potentially eligible for, but not currently receiving, opioid substitution therapy (OST), by combining responses to questions about the main drug injected and OST uptake in the last six months. Participants who indicated mainly injecting an opioid (primarily heroin but also methadone, buprenorphine or other opiates) and having been prescribed OST (methadone, buprenorphine or Suboxone) were the reference group. Associations between HCV incidence and WTP in future HCV vaccine trials were also examined. Finally whether HCV vaccine CTL was associated with HCV incidence was assessed (those who scored < the median score of 5 vs. those scoring ≥5 out of ten true/false questions) [22].

Data analysis

Data were analysed using Stata 12.1 [26]. Retention at 48 weeks was defined as completion at least one follow-up visit by 48 weeks post-enrolment. Factors significantly associated with retention ($p \leq 0.05$) in bivariate logistic regression were entered into a multivariate model. Using backwards stepwise elimination, only variables remaining significant at $p \leq 0.05$ were retained in the final model given a lack of consistently reported risk factors in the literature (e.g.[17, 27–30]). Adherence was examined among participants who had completed four quarterly study visits, with participants completing at least three out of four visits (75%) within 14 days of schedule defined as adherent. Using a similar approach, factors significantly associated with adherence ($p \leq 0.1$) in unadjusted logistic regression were entered into a multivariate model with stepwise elimination used to identify variables remaining significant at $p \leq 0.1$ for retention in the final model. Cumulative HCV incidence was estimated by dividing the total number of incident infections observed during the first three years of the study by the total number of person years (py) of observation, calculated from the date of screening to the estimated date of infection (incident cases) or the date of last follow-up prior to 31 October 2011 (non-infected cases). The exact binomial method was used to calculate 95% confidence intervals (CI). Cox proportional hazards models were used to assess baseline factors bivariately associated with HCV infection, producing hazard ratios (HRs) and corresponding CIs.

Results

Between November 2008 and October 2011, 268 PWID were screened with 166 (62%) confirmed anti-HCV negative of whom 156 (94%) were enrolled. Slightly more participants were recruited via incentivised peer referral (n=91, 58%) than targeted outreach sampling (n=65, 42%). A majority were recruited in South West Sydney (n=97, 62%), with similar proportions recruited in Inner (n=30, 19%) and Western (n=29, 19%) Sydney.

Retention at 48 weeks

Eighty nine percent (106/119) of participants who had been enrolled for a minimum of 48 weeks completed at least two follow-up visits by their 48 week anniversary. Factors independently associated with 48 week retention were recruitment in South West Sydney (adjusted odds ratio [AOR] 4.79; CI 1.00, 22.88), no incarceration in the past year (AOR 6.09; CI 1.56, 23.75) and stable housing (AOR 4.79; CI 0.98, 23.28) (Table 1). Retention at 72 weeks (89%) and 96 weeks (83%) remained high.

Adherence to study protocols

Virtually all (105/106) participants retained at 48 weeks completed all four quarterly study visits by their 48 week anniversary, of whom 80 (76%) completed at least three out of four (75%) visits within two weeks of schedule. Factors associated with adherence in unadjusted analyses at $p \leq 0.1$ included longer time since first injection (OR 2.25; CI 0.90, 5.63), recruitment via targeted outreach sampling (OR 0.43; CI 0.15, 1.18) and recruitment in South West Sydney (OR 3.13; CI 1.05, 9.34) which were entered into multivariate logistic regression. Only recruitment in South West Sydney remained independently associated with adherence (AOR 3.73; CI 1.17, 11.97).

Hepatitis C virus incidence by baseline characteristics and risk behaviour

Seventeen HCV incident infections were observed over 215 py of follow-up, yielding an incidence rate of 7.90/100 py (CI 4.9, 12.7). While higher HCV incidence was observed among female participants (12.9/100 py CI 6.7, 27.2), those from CALD backgrounds (13.6/100 py CI 7.1, 26.2) and those aged less than 27 years (12.8/100 py CI 0.74, 21.9) (Table 2), only age remained independently associated with incidence in multivariate analysis (adjusted HR 5.10; CI 1.54, 16.81) [31].

To examine whether modified eligibility criteria could identify populations at highest HCV risk, HCV incidence was calculated by baseline characteristics and risk behaviour (Table 3). Participants not on OST who reported heroin as the main drug injected in the past six months had an elevated rate of HCV infection (26.9/100 py CI 14.5, 50.0), as did those who reported unstable housing (23.5/100 py CI 7.6, 72.8), daily or more frequent injecting (22.7/100 py CI 12.2, 42.2), receptive syringe sharing (23.6/100 py CI 9.8, 56.7) and ancillary equipment sharing (17.6/100 py CI 5.7, 54.5) (Table 3). However, as previously reported, incident HCV infection was only independently associated with daily or more frequent injecting in the six months prior to baseline and not being on OST while mainly injecting heroin [31]. HCV incidence did not vary by stated WTP in future HCV vaccine trials or by CTL score (Table 4).

Chronic HCV infection

Among the 16/17 incident cases who completed at least one follow-up assessment by 24 weeks post-infection, four (25%) spontaneously cleared primary infection. The incidence of HCV with progression to chronic infection was estimated to be 0.75*7.9/100 py= 5.9/100 py (CI 3.7, 9.5).

Sample size estimates

Sample size estimates were informed by retention at 48 weeks and the observed incidence of chronic HCV infection at 24 weeks. Double the primary HCV infection incidence was also assessed as a comparison (16/100 py), guided by optimisation of eligibility criteria. Candidate vaccine efficacies (60%, 70% and 80%) were informed by prior HCV vaccine modelling [32] and consultation with investigators involved in a current Phase I/II HCV preventive vaccine trial among PWID in the US (ClinicalTrials.gov identifier: NCT01436357).

Sample size projections for the estimates of chronic HCV infection stratified by candidate efficacy were calculated (Tables 5 and 6). Based on the incidence of chronic HCV infection (6/100 py), an initial sample of n=912 anti-HCV negative PWID would be required for a trial of a candidate of 60% efficacy (Table 5). Alternatively, a candidate with 80% efficacy would reduce the required sample to n=344. Only when the rate of chronic infection was twice the observed rate (i.e. 12/100 py), and the efficacy of the candidate high (80%), did the required sample size required fall to n=176, a sample of comparable size to the HITS-c cohort (n=156).

Discussion

Primary HCV incidence in our study was ~8/100 py and the incidence of chronic infection was ~6/100 py. Sample size projections suggest that a primary infection rate double that observed in HITS-c would be required to evaluate a highly efficacious (80%) preventive candidate aiming to elicit a T-cell response associated with spontaneous clearance with a similar sample size. However, rates of primary HCV infection higher than 16/100 py were observed in several subgroups of HITS-c participants, including those who reported mainly injecting heroin while not receiving OST, those with unstable housing, and those who reported daily or more frequent injecting, receptive syringe and ancillary equipment sharing. These results suggest that by optimising eligibility criteria, sub-populations with sufficient HCV incidence can be identified, supporting future HCV vaccine field trial feasibility. Our data also suggest that the provision of OST and NSP in the context of future vaccine trials will be a necessary component of the standard of care.

The observed HCV incidence of 7.9/100 py in the current study is markedly lower than the 30.8/100 py observed in PWID in NSW a decade earlier and substantially lower than the rate of 44.1/100 py observed in the Sydney arm of the same study [17]. Temporal variations in incidence underline the potential impact of this crucial element on trial planning. Indeed, lower than expected incidence rates have resulted in the premature termination of late-stage HIV prevention trials [4]. Further, sample size estimates for a Phase III Tenofovir trial

among PWID in Thailand, initially based on the earlier AIDSVAX B/E Vaccine Trial [33], had to be revised and the sample substantially increased due to an observed decrease in risk behaviour among participants [34].

A recent meta-analysis of HCV infection among PWID concluded that the acquisition of HCV in this group appears to vary both over time and between settings [35]. The authors suggested that the interval between injection initiation and HCV seroconversion may be widening, possibly as a result of the scaling-up of harm reduction interventions. Further, the cyclical nature of drug markets [36, 37] impact the natural history of injecting drug use, and interact with prevention coverage and HCV transmission. Epidemic stage and saturation of infection within at risk populations are also likely to impact observed incidence rates [19], as are changes in demographics, including mortality [38]. Consequently, continued monitoring of incident HCV infection among PWID is critical to ensure that trial designs are informed by contemporary data in order to reduce the risk of premature termination and null findings.

Retention in HITS-c at 48 weeks was 89% and remained high (83%) at 96 weeks, demonstrating that it is possible to retain anti-HCV negative active PWID in long-term follow-up. HITS-c retention was comparable to a previous HIV VPS (comprising only 23% PWID) which reported 88% retention at 18 months [19]. Importantly, we documented adherence to study visit protocols, an outcome rarely reported in HIV VPS. Adherence to at least three out of four study visits within two weeks of schedule was 76% suggesting the feasibility of future HCV vaccine field trials from this perspective. Both retention and adherence were independently associated with recruitment in South West Sydney, the region visited by the study team three times each week (compared to one day/week in the other regions) providing participants enrolled in these sites with greater opportunity to complete follow-up assessments.

Retention at 48 weeks was also independently associated with not having been incarcerated in the past year and stable housing at baseline. Unstable housing and recent criminal justice system involvement could be considered potential exclusion in future trials, given neither was associated with HCV infection and both factors reduced the odds of retention. However, incarceration [39, 40] and unstable housing [41–43] have been associated with HCV incidence in other settings, and HCV incidence was notably higher (23.5/100 py) among unstably housed participants in the current study. The optimisation of eligibility criteria should be considered in the context of the local epidemiology of HCV infection among PWID, with the identification of sub-populations at increased risk of both loss-to-follow-up and HCV infection likely to require specific consideration and additional resources to minimise attrition and maximise trial completion.

HCV incidence was unrelated to WTP and CTL in the current study. However, as previously reported, our participants indicated a strong desire to participate in future HCV vaccine trials with 88% expressing WTP [44]. Further, CTL increased significantly following a brief intervention designed to improve understanding of key HCV vaccine trial concepts [22], suggesting this group has the capacity to provide truly informed consent and that the ethical implementation of HCV vaccine trials will be possible in Australia.

With promising Phase I trials of preventive candidates recently completed [11, 12] and ongoing assessment Phase I/II trials in the US (ClinicalTrials.gov identifier: NCT01436357) and UK (ClinicalTrials.gov identifier: NCT01296451), our findings are particularly apposite and timely. Despite recent advances in direct acting anti-viral therapies for HCV infection and the potential impact of these new agents on trends in HCV incidence [45], barriers to access and prohibitive costs mean that uptake by PWID is likely to remain low [46], and the development of a safe and effective vaccine remains an important public health goal. This study has identified key elements for successful recruitment and retention of PWID eligible for future HCV vaccine trials. While sample size estimates suggest that a primary HCV infection rate of at least 16/100 py will be required for stand-alone trials of preventive candidates with chronic HCV infection as the primary endpoint, results support the feasibility of large multi-centre HCV vaccine trials, including in the Australian setting.

Acknowledgments

We would like to thank study participants and their communities for their time and commitment to the study. For the recruitment and interviewing of participants the authors are grateful to Ms Anna Bates, Ms Jarliene Enriquez, Mr Sammy Chow, Ms Ju Park, Ms Len Liao, Ms Alyza Donald and Mr Steve Pham. For the logistic support for specimen handling Dr Suzy Teutsch, Ms Hui Li, Mr Brendan Jacka and Ms Alicia Steller are gratefully acknowledged. This study was initially funded by the University of New South Wales (The UNSW Hepatitis C Vaccine Initiative) and subsequently by the National Health and Medical Research Council (Grant #630483, Hepatitis C Vaccine Preparedness Study). Bethany White was supported by National Health and Medical Research Council (NHMRC) Dora Lush Postgraduate Scholarship. Professors Lisa Maher and Margaret Hellard are supported by NHMRC Senior Research Fellowships and Gregory Dore by a NHMRC Practitioner Fellowship. Kimberly Page received support from the U.S. National Institutes of Health award numbers R01DA016017, R01DA031056 and HHSN2662040074C (NIAID STI/CTG). The Kirby Institute is affiliated with the Faculty of Medicine, UNSW and is funded by the Australian Government Department of Health and The Burnet Institute receives funding from the Victorian Operational Infrastructure Support Program (Department of Health, Victoria, Australia). The content is solely the responsibility of the authors and does not necessarily represent the position of the Australian Government or the official views of the National Institute on Drug Abuse, National Institute of Allergy and Infectious Diseases, or the National Institutes of Health.

References

1. Maher L, White B, Hellard M, Madden A, Prins M, Kerr T, et al. Candidate hepatitis C vaccine trials and people who inject drugs: Challenges and opportunities. Vaccine. 2010; 28:7273–8. [PubMed: 20831914]
2. Suligoi B, Wagner T, Ciccozzi M, Rezza G. The epidemiological contribution to the preparation of field trials for HIV and STI vaccines: Objectives and methods of feasibility studies. Vaccine. 2005; 23:1437–45. [PubMed: 15670878]
3. Tolley E, Severy L. Integrating behavioural and social science research into microbicide clinical trials: Challenges and opportunities. Am J Public Health. 2006; 96:79–83. [PubMed: 16317214]
4. Institute of Medicine. Methodological challenges in biomedical HIV prevention trials. Washington, DC: The National Academies Press; 2008.
5. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989; 244:359–62. [PubMed: 2523562]
6. Lavanchy D. The global burden of hepatitis C. Liver International. 2009; 29:74–81. [PubMed: 19207969]
7. Houghton M. Prospects for prophylactic and therapeutic vaccines against the hepatitis C viruses. Immunol Rev. 2011; 239:99–108. [PubMed: 21198667]
8. Halliday J, Klenerman P, Barnes E. Vaccination for hepatitis C virus: closing in on an evasive target. Expert Review of Vaccines. 2011; 10:659–72. [PubMed: 21604986]

9. Folgori A, Capone S, Ruggeri L, Meola A, Sporeno E, Ercole B, et al. A T-cell HCV vaccine eliciting effective immunity against heterologous virus challenge in chimpanzees. Nature Medicine. 2006; 12:190–7.
10. Dahari H, Feinstone SM, Major ME. Meta-analysis of hepatitis C virus vaccine efficacy in chimpanzees indicates an importance for structural proteins. Gastroenterology. 2010; 139:965–74. [PubMed: 20621699]
11. Frey SE, Houghton M, Coates S, Abrignani S, Chien D, Rosa D, et al. Safety and immunogenicity of HCV E1E2 vaccine adjuvanted with MF59 administered to healthy adults. Vaccine. 2010; 28:6367–73. [PubMed: 20619382]
12. Barnes E, Folgori A, Capone S, Swadling L, Aston S, Kurioka A, et al. Novel Adenovirus-Based Vaccines Induce Broad and Sustained T Cell Responses to HCV in Man. Sci Transl Med. 2012; 4:115ra1.
13. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005; 5:558–67. [PubMed: 16122679]
14. Iversen, J.; Topp, L.; Maher, L. Prevalence of HIV, HCV and Injecting and Sexual Behaviour Among NSP Attendees 1995–2010. Sydney: The Kirby Institute, University of New South Wales; 2011.
15. Maher L, Li J, Jalaludin B, Chant K, Kaldor J. High hepatitis C incidence in new injecting drug users: a policy failure? Aust N Z J Public Health. 2007; 31:30–5. [PubMed: 17333606]
16. Crofts N, Aitken CK. Incidence of bloodborne virus infection and risk behaviours in a cohort of injecting drug users in Victoria, 1990–1995. Med J Aust. 1997; 167:17–20. [PubMed: 9236754]
17. Maher L, Jalaludin B, Chant K, Jayasuriya R, Sladden T, Kaldor J. Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia. Addiction. 2006; 101:1499–508. [PubMed: 16968352]
18. Iversen J, Wand H, Topp L, Kaldor J, Maher L. Reduction in HCV Incidence Among Injection Drug Users Attending Needle and Syringe Programs in Australia: A Linkage Study. Am J Public Health. 2013; 103:1436–44. [PubMed: 23763399]
19. Seage GR III, Holte SE, Metzger D, Koblin BA, Gross M, Celum C, et al. Are US populations appropriate for trials of human immunodeficiency virus vaccine? Am J Epidemiol. 2001; 153:619–27. [PubMed: 11282787]
20. Koblin BA, Heagerty P, Sheon A, Buchbinder S, Celum C, Douglas JM, et al. Readiness of high-risk populations in the HIV Network for Prevention Trials to participate in HIV vaccine efficacy trials in the United States. AIDS. 1998; 12:785–93. [PubMed: 9619811]
21. Koblin B, Holte S, Lenderking B, Heagerty P. Readiness for HIV vaccine trials: changes in willingness and knowledge among high-risk populations in the HIV network for prevention trials. The HIVNET Vaccine Preparedness Study Protocol Team. J Acquir Immune Defic Syndr. 2000; 24:451–7. [PubMed: 11035616]
22. White B, Madden A, Hellard M, Kerr T, Prins M, Page K, et al. Increased hepatitis C virus vaccine trial literacy following a brief intervention among people who inject drugs. Drug Alcohol Rev. 2013; 32:419–25. [PubMed: 23113829]
23. White B, Dore GJ, Lloyd A, Rawlinson W, Maher L. Ongoing susceptibility to hepatitis B virus infection among people who inject drugs in Sydney. Aust N Z J Public Health. 2012; 36:351–7.
24. Maher L, White B, Donald A, Bates A, Enriquez J, Pham S, et al. Using ethnographic fieldwork to inform hepatitis C vaccine preparedness studies with people who inject drugs. Int J Drug Policy. 2010; 21:194–201. [PubMed: 19482463]
25. Watters J, Biernacki P. Targeted sampling-options for the study of hidden populations. Soc Probl. 1989; 36:416–30.
26. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011.
27. Aitken C, Lewis J, Tracy S, Spelman T, Bowden D, Bharadwaj M, et al. High incidence of hepatitis C virus reinfection in a cohort of injecting drug users. Hepatology. 2008; 48:1746–52. [PubMed: 18844233]
28. Page K, Hahn J, Evans J, Shiboski S, Lum P, Delwart E, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. J Infect Dis. 2009; 200:1216–26. [PubMed: 19764883]

29. Shannon K, Kerr T, Marshall B, Li K, Zhang R, Strathdee SA, et al. Survival sex work involvement as a primary risk factor for hepatitis C virus acquisition in drug-using youths in a Canadian setting. Arch Pediatr Adolesc Med. 2010; 164:61–5. [PubMed: 20048243]

30. Wood E, Kerr T, Marshall BDL, Li K, Zhang R, Hogg RS, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. Br Med J. 2009; 338

31. White B, Dore GJ, Lloyd A, Rawlinson W, Maher L. Declining hepatitis C virus incidence among people who inject drugs in Sydney, Australia. submitted.

32. Hahn JA, Wylie D, Dill J, Sanchez M, Lloydsmith J, Page-Shafer K, et al. Potential impact of vaccination on the hepatitis C virus epidemic in injecting drug users. Epidemics. 2009; 1:47–57. [PubMed: 20445816]

33. Pitisuttithum P, Gilbert P, Gurwith M, Heyward W, Martin M, van Griensven F, et al. Randomized, double blind, placebo controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV1 vaccine among injection drug users in Bangkok, Thailand. J Infect Dis. 2006; 194:1661–71. [PubMed: 17109337]

34. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Chuachoowong R, Mock PA, et al. Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok tenofovir study, Thailand. PLoS ONE. 2011; 6:e25127. [PubMed: 21969870]

35. Hagan H, Pouget E, Des Jarlais D, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. Am J Epidemiol. 2008; 168:1099–109. [PubMed: 18849303]

36. Maher, L.; Curtis, R. Women on the edge of crime: Crack cocaine and the changing contexts of street-level sex work in New York City. New York, USA: Oxford University Press; 1998.

37. Maher, L.; Dixon, D.; Hall, W.; Lynskey, M. Running the risks: Heroin, health and harm in South West Sydney. Sydney: National Drug and Alcohol Research Centre; 1998.

38. de Vos AS, van der Helm JJ, Matser A, Prins M, Kretzschmar ME. Decline in incidence of HIV and hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction? Addiction. 2013; 108:1070–81. [PubMed: 23347124]

39. Bruneau J, Roy É, Arruda N, Zang G, Jutras-Aswad D. The rising prevalence of prescription opioid injection and its association with hepatitis C incidence among street-drug users. Addiction. 2012; 107:1318–27. [PubMed: 22248184]

40. van Beek I, Dwyer R, Dore G, Luo K, Kaldor J. Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. Br Med J. 1998; 317:433–7. [PubMed: 9703523]

41. Miller CL, Johnston C, Spittal PM, Li K, LaLiberté N, Montaner JSG, et al. Opportunities for prevention: Hepatitis C prevalence and incidence in a cohort of young injection drug users. Hepatology. 2002; 36:737–42. [PubMed: 12198668]

42. Kim C, Kerr T, Li K, Zhang R, Tyndall M, Montaner J, et al. Unstable housing and hepatitis C incidence among injection drug users in a Canadian setting. BMC Public Health. 2009; 9:270. [PubMed: 19640297]

43. Craine N, Hickman M, Parry JV, Smith J, Walker AM, Russell D, et al. Incidence of hepatitis C in drug injectors: the role of homelessness, opiate substitution treatment, equipment sharing, and community size. Epidemiol Infect. 2009; 137:1255–65. [PubMed: 19224654]

44. Park JN, White B, Bates A, Enriquez J, Liao L, Maher L. Motivators and barriers influencing willingness to participate in candidate HCV vaccine trials: Perspectives of people who inject drugs. Drug Alcohol Depend. 2012; 123:35–40. [PubMed: 22071117]

45. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatology. 2013; 58:1598–609. [PubMed: 23553643]

46. Walsh N, Maher L. HIV and viral hepatitis C coinfection in people who inject drugs: implications of new direct acting antivirals for hepatitis C virus treatment. Current Opinion in HIV and AIDS. 2012; 7:339–44. [PubMed: 22498482]

Table 1

Overall 48 week retention by recruitment site and factors associated with retention among PWID enrolled in HITS-c HCV VPS 2008–2011

	n=119	Retained (n)	Retained (%)	OR	95% CI[a]	p	AOR	95% CI[a]	p
Total		**106**	**89**						
Recruitment region									
Inner Sydney	26	20	**76**	1.00			1.00		
South West Sydney	72	69	**96**	6.90	1.58, 30.09	0.010	4.79	1.00, 22.88	0.050
Western Sydney	21	17	**81**	1.28	0.31, 5.28	0.738	0.80	0.16, 4.01	0.789
Recruitment method									
Targeted outreach sampling	47	41	**87**	1.00					
Incentivised peer referral	72	65	**90**	1.36	0.43, 4.33	0.604			
Gender									
Male	89	78	**88**	1.00					
Female	30	28	**93**	1.98	0.41, 9.46	0.395			
Age									
<27 years	58	48	**83**	1.00					
≥27 years	61	58	**95**	4.03	1.05, 15.47	0.042			
Ethnicity									
Caucasian Australian	83	73	**88**	1.00					
Culturally and linguistically diverse	36	33	**92**	1.51	0.39, 5.84	0.553			
Education, years									
≤10 years	75	65	**87**	1.00					
≥11 years	44	41	**93**	2.10	0.55, 8.10	0.280			
Unstable housing, current									
Yes (boarding house, refuge, homeless)	11	7	**64**	1.00			1.00		
No	108	99	**92**	6.29	1.54, 25.62	0.010	4.79	0.98, 23.28	0.052
Moved twice or more, last 12 months									
Yes (lived ≥ 3 places)	43	35	**81**	1.00					
No (lived ≤ 2 places)	76	71	**93**	3.25	0.99, 10.65	0.052			
Full-time employment, last 6 months									
No	102	90	**88**	1.00					

	n=119	Retained (n)	Retained (%)	OR	95% CI[a]	p	AOR	95% CI[a]	p
Yes	17	16	**94**	2.13	0.26, 17.56	0.481			
Incarcerated, last 12 months									
Yes	26	19	**73**	1.00			1.00		
No	93	87	**93**	5.34	1.61, 17.70	0.007	6.09	1.56, 23.75	0.009
Accessed NSP, last 6 months									
No	47	43	**91**	1.00					
Yes	52	46	**88**	0.71	0.19, 2.70	0.619			
OST, last 6 months									
Yes	46	42	**91**	1.00					
No OST, mainly injected heroin	32	27	**84**	0.51	0.13, 2.09	0.352			
No OST, mainly injected another drug	41	37	**90**	0.88	0.21, 3.77	0.864			
Time since first injection									
≥5 years	57	48	**84**	1.00					
< 5 years	62	58	**94**	2.72	0.79, 9.34	0.113			
Injecting frequency, last 6 months									
<Daily	92	80	**87**	1.00					
≥Daily	24	23	**96**	3.45	0.43, 27.95	0.246			
Receptive syringe sharing, last 6 months									
No	103	93	**90**	1.00					
Yes	13	10	**78**	0.36	0.08, 1.52	0.164			
Receptive ancillary equipment sharing, last 6 months (spoon, water, filter)									
No	102	95	**93**	1.00					
Yes	14	8	**57**	0.10	0.03, 0.36	0.001			

[a] Confidence interval

Vaccine. Author manuscript; available in PMC 2015 July 21.

Table 2

HCV incidence rates by recruitment method, recruitment site, socio-demographic characteristics and follow-up, HITS-c HCV VPS 2008–2011

	n=129	Cases (n)	Cases (%)	Person years	Incidence (per 100py)	95% CI[a]	Unadjusted p value
Total		**17**	**14**	**215.15**	**7.9**	**4.9, 12.7**	
Recruitment region							
South West Sydney	83	12	15	138.9	8.6	4.9, 15.2	
Inner Sydney	23	2	9	39.9	5.0	1.3, 20.1	
Western Sydney	23	3	13	36.4	8.2	2.7, 25.6	0.929
Recruitment method							
Targeted outreach sampling	52	7	13	86.3	8.1	3.9, 17.0	
Incentivised peer referral	77	10	12	128.3	7.8	4.2, 14.4	0.923
Gender							
Male	96	10	10	161.09	6.2	3.3, 11.5	
Female	33	7	21	54.06	12.9	6.7, 27.2	0.159
Age							
≥27 years	66	4	6	113.31	3.5	1.3, 9.4	
<27 years	63	13	21	101.84	12.8	0.74, 21.9	0.020
Ethnic background							
Anglo-Australian	89	8	9	149.01	5.4	2.7, 10.7	
Culturally and linguistically diverse	40	9	23	66.14	13.6	7.1, 26.2	0.060
Education, years							
≤10 years	78	10	13	133.93	7.5	4.0, 13.9	
≥11 years	51	7	14	81.22	8.6	4.1, 18.1	0.888

[a] Confidence interval

Vaccine. Author manuscript; available in PMC 2015 July 21.

Table 3

HCV incidence rates by modifications in baseline eligibility criteria among participants enrolled in HITS-c HCV VPS 2008–2011

	n=129	Cases (n)	Cases (%)	Person years	Incidence (per 100py)	95% CI[a]
Unstable housing, current						
Yes (boarding house, refuge, homeless)	118	14	12	202.38	6.92	4.1, 11.7
No	11	3	27	12.77	23.5	7.6, 72.8
Moved twice or more, last 12 months						
No	86	11	13	145.31	7.6	4.2, 13.7
Yes	42	6	14	67.14	8.9	4.0, 19.9
Full-time employment, last 6 months						
No	110	14	13	182.06	7.8	4.6, 13.0
Yes	19	3	16	33.09	9.1	2.9, 28.1
Incarcerated last, 12 months						
No	105	15	14	175.67	8.5	5.1, 14.2
Yes	24	2	8	39.48	5.1	1.3, 20.3
Accessed NSP, last 6 months						
No	38	5	13	61.4	8.1	3.3, 19.6
Yes	88	12	14	147.3	8.1	4.6, 14.3
OST, last 6 months						
Yes	50	3	18	91.25	3.3	1.1, 10.2
No OST, mainly injected heroin	30	10	59	37.15	26.9	14.5, 50.0
No OST, mainly injected another drug	47	4	24	82.01	4.9	1.8, 13.0
Time since first injection						
≥5 years	67	6	9	118.99	5.0	2.3, 11.2
< 5 years	62	11	18	96.16	11.4	6.3, 20.7
Injecting frequency, last 6 months						
<Daily	94	7	7	164.66	4.3	2.0, 8.9
≥Daily	32	10	31	44.02	22.7	12.2, 42.2
Receptive syringe sharing, last 6 months						
No	109	12	11	187.49	6.4	3.6, 11.3
Yes	17	5	29	21.19	23.6	9.8, 56.7

	n=129	Cases (n)	Cases (%)	Person years	Incidence (per 100py)	95% CI[a]
Receptive ancillary equipment sharing, last 6 months (spoon, water, filter)						
No	112	14	13	191.6	7.3	4.3, 12.3
Yes	14	3	21	17.1	17.6	5.7, 54.5

[a] Confidence interval

Table 4

HCV incidence rates by stated willingness to participate in future HCV preventive vaccine trials and median clinical trial literacy score, HITS-c HCV VPS 2008–2011

	n=127[a]	Cases (n)	Cases (%)	Person years	Incidence (per 100py)	95% CI[b]
Willing to participate in future HCV vaccine trials[c]						
No (not very likely/not likely at all)	25	2	8	46	4.3	1.1, 17.3
Yes (very likely/somewhat likely)	102	13	13	169.05	7.7	4.4, 13.2
Clinical trial literacy[c]						
Score < median 5	66	9	14	106.36	8.5	4.4, 16.3
Score ≥ median 5	61	6	10	108.69	5.5	2.5, 12.3

[a] These outcomes were assessed at 12 week follow-up and therefore excluded 2 cases of anti-HCV negative at screening/HCV RNA positive at baseline who did not complete this visit

[b] Confidence interval

[c] Assessed by the question *"How likely would you be to enrol in a trial of a vaccine to prevent hepatitis C infection if it started this week?"*

Table 5

Estimated sample sizes for trials of candidate vaccines of various efficacies designed to prevent chronic HCV infection[a]

	Incidence of chronic HCV infection (number of participants required)	
Vaccine efficacy	**6/100py**	**12/100py**
60% (HR=0.40)	912	466
70% (HR=0.30)	568	290
80% (HR=0.20)	344	176

[a]Estimates assumed 80% power ($p<0.05$), 90% retention

Table 6

Impact of expected rates of HCV chronic infection, vaccine efficacy and retention on sample size*

	Chronic infections expected		6/100py		12/100py	
	12 months post vaccination (n)	**18 months post vaccination (n)**	**Annual incidence of chronic HCV infection**	**Total followed with 90% retention (n)**	**Annual incidence of chronic HCV infection**	**Total followed with 90% retention (n)**
60% efficacy (HR=0.40)						
Placebo	**26**	**39**	6%	410	12%	210
Vaccine	**10**	**15**	2.4%	410	4.8%	210
Total	**36**	**54**	–	820	–	420
70% efficacy (HR=0.30)						
Placebo	**16**	**24**	6%	256	12%	131
Vaccine	**5**	**8**	1.8%	256	3.6%	131
Total	**21**	**32**	–	512	–	262
80% efficacy (HR=0.20)						
Placebo	**10**	**15**	6%	155	12%	79
Vaccine	**2**	**3**	1.2%	155	2.4%	79
Total	**12**	**18**	–	310	–	158

*Estimates assumed 80% power ($p<0.05$)