JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000002685

Low incidence of hepatitis C among a cohort of HIV-negative gay and bisexual men using HIV pre-exposure prophylaxis (PrEP) in Melbourne, Australia, and the contribution of sexual transmission.

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Declaration of Interests: Gilead Sciences funded this analysis of Hepatitis C within the PrEPX study, however, Gilead did not have input into the study design or the analysis. VJC has received speaker's fees and conference assistance from Gilead Sciences and advisory board fees from ViiV Healthcare. MWT received speaker's fees from Gilead Sciences. EJW reports receipt of grants from the Victorian, Tasmanian and the South Australian governments for PrEPX; other from Gilead Sciences (free study drug for VicPrEP, compensation to her institution for chairing a nursing education session and for attending an advisory board meeting, and uncompensated attendance for attending 2 Gilead meetings regarding listing of Truvada on the Australian pharmaceutical benefits scheme); grants from, Gilead Science and Merck Sharp & Dohme outside the submitted work; and financial support from, Gilead Sciences, Abbott Laboratories, Janssen-Cilag, Boehringer Ingelheim, ViiV Healthcare, and Merck Sharp & Dohme. DM received grants from Alfred Health. MS received a research fellowship from the National Health and Medical Research Council, and investigator-initiated grants from Gilead Sciences and Bristol-Myers-Squibb. MH received grants from the Australian Department of Health, Gilead Sciences, Abbvie and Bristol-Myers-Squibb. JA received grants from the Australian Government's Department of Health. JS has grant research funding from Gilead, Abbvie and Merck. He has also received speaker fees from Gilead Sciences. All other authors declare no potential conflicts of interest. Gilead Sciences donated study drug to the VicPrEP study (precursor to the PrEPX study).

Short title: Hepatitis C infections in PrEP users

Data sharing

The raw data underpinning this analysis contains potentially highly sensitive information that cannot be adequately de-identified by nature of its highly personal content. As such, the authors have not deposited this raw data in a publically-accessible data repository.

ABSTRACT

Background: PrEPX was an Australian HIV pre-exposure prophylaxis (PrEP) study conducted between 2016 and 2018. This analysis aimed to estimate hepatitis C (HCV) incidence and explore likely modes of transmission.

Setting: Cohort study of PrEP users in Victoria, Australia.

Methods: HCV tests were conducted at enrolment and every 12 months thereafter. HCV incident cases were identified from laboratory data. Likely modes of transmission were inferred from computer-assisted self-interviews (CASI), medical records, and interviews.

Results: Among 3,202 PrEPX participants tested for HCV at baseline, HCV RNA-positive prevalence was 0.22% (95% CI 0.09–0.45). Among participants testing HCV antibody- or RNA-negative at baseline, 2,058 had at least one follow-up HCV test. Eight incident HCV cases were identified during 2,111 person-years of follow-up (incidence 0.38/100 person-years); all were primary infections in men who had sex with men (MSM). Clinical, laboratory and CASI data were available for all, and six cases were interviewed. Three cases were attributable to injecting drug use (IDU). A fourth case reported IDU, but his HCV was attributable to sexual transmission. Four other cases reported no IDU and probably acquired HCV sexually. Most cases reported anal trauma in the context of condomless receptive anal intercourse during group sex at sex-on-premises venues (SOPV).

Conclusion: Incident HCV was uncommon in PrEPX compared to international PrEP studies, and most cases were transmitted sexually. Our findings highlight the need for HCV

prevention messaging by clinicians, in SOPV and on digital platforms utilised to arrange group sex, and for HCV screening among some PrEP-using MSM.

Key words (MeSH Descriptors): Hepatitis C, Pre-Exposure Prophylaxis, HIV, Homosexuality, male, Disease Transmission, Infectious, Sexually Transmitted Diseases, Viral, Substance Abuse

INTRODUCTION

HIV pre-exposure prophylaxis (PrEP) using once-daily co-formulated tenofovir disoproxil* and emtricitabine (TD*/FTC) is highly efficacious at preventing HIV among cis-gender men who have sex with men (MSM).[1,2] However, MSM who use PrEP are at high risk of other sexually transmissible infections (STIs),[3-5] and this risk may include Hepatitis C Virus (HCV) infection. Sexual transmission of HCV has been observed among HIV-positive MSM,[6-10] and observational cohort data suggest that HCV may also be transmitted sexually among HIV-negative MSM using PrEP.[11-15]

Health promotion messaging on HCV prevention and HCV testing recommendations for MSM using PrEP need to be informed by context-specific HCV incidence data that include the risk of sexual transmission.

The PrEPX study was an Australian population-level PrEP study conducted in Victoria, South Australia and Tasmania that enrolled over 5,000 participants between 2016 and 2018. Enrolment was open to any persons who were at risk of HIV, regardless of gender, but as previously described, the vast majority (99%) were men who have sex with men.[4] We aimed to determine the incidence of HCV among PrEPX participants, and to describe each incident case in detail to determine the likely mode of HCV transmission.

METHODS

We analysed HCV diagnoses among PrEPX participants in Victoria who enrolled at Melbourne Sexual Health Centre (MSHC) or at general practice (GP) clinics that participated in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) network. The PrEPX protocol has been published previously.[16] Baseline visits were conducted between 29th June 2016 and 29th March 2018. For this analysis, participants were censored at their last HCV test before 1st April 2018.

HCV testing

The PrEPX enrolment assessment included an HCV test, usually HCV antibody (Ab), or for participants with a known history of HCV, an HCV ribonucleic acid (RNA) test. Any positive HCV Ab tests were followed by a HCV RNA test. In this paper, "HCV test" refers to either a HCV Ab test, HCV RNA test, or both, depending on the participant's HCV history. Liver enzyme testing was not routinely required by the PrEPX protocol, but permitted at clinicians' discretion. Participants were routinely followed-up every three months for clinical and laboratory monitoring, and for repeat prescriptions for TD*/FTC. Clinicians were asked to perform a repeat HCV test every 12 months, but had discretion to test more frequently if clinically indicated.

Calculation of HCV prevalence and incidence

To calculate HCV prevalence at baseline, we defined the denominator as the number of PrEPX participants who had an HCV test at enrolment, and the numerator as the number of PrEPX participants who had a positive HCV RNA test at enrolment. To calculate HCV incidence during the study, we defined the denominator as person-time accrued during the study, which was the sum of individual participants' person-time starting at their first

recorded negative HCV test through to their last recorded negative HCV test or until HCV diagnosis. We defined incident HCV cases as participants who were HCV Ab-negative at baseline and subsequently tested positive for HCV Ab and RNA during follow-up, or participants who had a positive HCV Ab test and negative RNA test at baseline and subsequently tested RNA-positive during follow-up. Participants who tested HCV RNA positive at baseline were excluded from the incidence calculation, as including them would have been difficult, given different RNA clearance rates among these participants. Confidence intervals were calculated in STATA® using the quadratic approximation to the Poisson log likelihood for the log-rate parameter.

Behavioural data

Behavioural data were collected at enrolment and follow-up visits by computer-assisted self-interview (CASI). For every incident HCV case we reviewed CASI data and medical records, and sought to conduct interviews using a pre-defined set of questions (see online supplement,http://links.lww.com/QAI/B646). Interviews were conducted in-person for four participants, and by telephone for two participants. Our results denote these data sources as CASI surveys$^{(S)}$, medical records$^{(M)}$, and interviews$^{(I)}$.

RESULTS

Demographics and behavioural data at baseline

Of the total PrEPX cohort, 3,464 participants enrolled at MSHC or ACCESS GP clinics, of whom 3,202 (92.4%) had a valid HCV test result at baseline (Supplementary Box 1,http://links.lww.com/QAI/B645). Their median age was 35 years (IQR 28 to 42).

According to clinician-completed enrolment surveys, 99.1% had a male gender identity, 98.7% identified as gay or bisexual, 4.9% currently injected drugs, 13.5% had used methamphetamines in the preceding three months, and 48.2% had condomless receptive anal sex with casual partners in the preceding three months. At enrolment, 2669 participants (83.4%) completed CASI, among whom 61.5% reported recent condomless anal intercourse with casual partners, 5.7% reported recent IDU, and 9.9% reported ever IDU. Reported recent use of substances in the context of sex (chemsex) included use of methamphetamine (13.2%), gamma-hydroxybutyrate (GHB, 9.9%), amyl nitrite (36.8%), and alcohol (42.0%) (Table 1).

HCV prevalence at baseline

Among 3,202 participants with a valid HCV test at baseline, 14 participants were HCV Ab positive, of whom 7 were HCV RNA positive, producing an HCV RNA prevalence of 0.22% (95% CI 0.09 – 0.45) (Supplementary Box 1,http://links.lww.com/QAI/B645). All of these participants were successfully treated during the study period, and none had evidence of re-infection during the study.

HCV incidence during follow-up

Among 3,188 PrEPX participants who had a negative HCV Ab or RNA test at baseline, 2,058 participants had at least one follow-up test during the study, with a median follow-up period of 1.03 years (IQR 0.84 – 1.33 years), accumulating 2,111 person years (PY) of follow-up. Eight HCV incident cases (RNA positive) were identified, producing an incidence rate of 0.38/100PY (95% CI 0.19-0.76). All HCV incident cases were primary infections (no previous HCV) (Supplementary Box 2,http://links.lww.com/QAI/B645).

Potential contributors to HCV transmission for incident cases

All participants with incident HCV infections were MSM. Clinical, laboratory and survey data were available for all cases, and six cases were available for interview. For each of these cases, clinical data relating to HCV are listed in Table 2, alongside data on potential contributors to HCV transmission. Each case is described in more detail in the online supplementary results,http://links.lww.com/QAI/B645.

DISCUSSION

Incident cases of HCV were uncommon among PrEPX participants, with an incidence rate of 0.38/100PY, in a study population with low baseline HCV RNA-positive prevalence of 0.22%. All incident HCV infections occurred in people without previous HCV. Of eight HCV incident cases, three (37.5%) were attributable to IDU, and five (62.5%) were attributable to condomless receptive anal intercourse, often in a context of anal trauma, chemsex and group sex at SOPV. One of the participants with sexually-acquired HCV was simultaneously diagnosed with HIV, which has been shown epidemiologically to increase the risk of sexually-acquired HCV.

Our findings represent the lowest incidence of HCV infection reported in a cohort of MSM using PrEP. The AmPrEP study in Amsterdam reported an HCV incidence of 2.30/100PY, among 350 PrEP-using MSM,[17] on a baseline HCV prevalence of 4.8%,[18] six times higher than our HCV incidence. AmPrEP participants diagnosed with incident HCV had higher numbers of receptive condomless anal sex acts with casual partners (median 10 *vs* 3, in three months), were more likely to have been diagnosed with anal STIs (36% *vs* 13%), and more commonly injected drugs (40% *vs* 5%) or shared straws during intranasal drug use (60% *vs* 29%), compared to HCV-negative participants.[17]

The PROUD study in London reported an incidence of 1.9/100PY among 409 PrEP-using MSM, on a baseline prevalence of 2.1%, five times higher than our HCV incidence. Among 25 participants with incident HCV, injecting drug use was reported by 11, denied by 12, and unknown for two participants.[19] Risk factors for incident HCV were otherwise not described in detail.

A French hospital-based cohort of 1,049 PrEP-using MSM found an HCV incidence of 1.44/100PY, on a baseline prevalence of 0.86%, 4-fold higher than our HCV incidence.[12] Their seven incident cases included five that were attributed to sexual transmission, and two related to intranasal rather than injecting drug use. The authors did not comment on IDU among these HCV incident cases.

The ANRS Prevenir study in Paris reported an HCV incidence of 0.67/100PY and 0.60/100PY among participants who used PrEP daily and on-demand, respectively,[20] but they did not describe HCV risk factors in detail.

The French ANRS IPERGAY PrEP trial reported an HCV incidence of 1.40/100PY on a low baseline HCV prevalence of 0.23%. Participants with incident HCV infections reported a greater number of sexual partners and were more likely to have ingested drugs (not IDU), compared to HCV-negative participants.[21]

One possible explanation for the low incidence of HCV in PrEPX is that government-subsidised DAA treatment for HCV became available four months prior to commencement of the PrEPX study, followed by rapid uptake of HCV treatment.[22] This resulted in micro-elimination of HCV among MSM, particularly in Victoria, where DAA treatment was targeted towards HIV-HCV co-infected individuals.[23] Such micro-elimination is particularly relevant if HIV-negative men on PrEP and HIV-positive men are involved in the same HCV transmission networks, as indicated by phylogenetic analyses from the UK, France and Amsterdam.[17,24,25]

Of our five cases classified as sexually-transmitted HCV, all reported receptive condomless anal intercourse with casual sexual partners and participation in group sex, and all who were interviewed reported attending a SOPV around the time of their HCV acquisition. Four participants reported non-injecting drug use during sex, two reported receptive brachioproctic sex (i.e. fisting), four reported anal trauma around the time of their HCV acquisition, and one experienced an initial outbreak of anal HSV2 after which he attended a group sex event at a SOPV. The role of anal trauma and sex at SOPV in the acquisition of HCV was also highlighted in a 2010 survey involving 13,111 European MSM, among whom 70% were HIV-negative, which found that a recent diagnosis of HCV was independently associated with visiting a SOPV and practicing receptive fisting.[26]

Some limitations need to be considered when interpreting our findings. Firstly, although ACCESS captures participant movement between participating clinics, some PrEPX participants may have been diagnosed with HCV elsewhere. However, such diagnoses would have been detected at subsequent study visits when participants returned for their PrEP prescriptions. Secondly, the PrEPX protocol stipulated annual HCV screening, but some participants enrolled less than 12 months before termination of the PrEPX study, and hence some of them did not have a follow-up HCV test. Of the 3,202 participants included in the baseline analysis, 916 enrolled less than 12 months before study closure. However, 335 of them nonetheless had an HCV test (sooner than the protocol-stipulated 12 month mark), leaving 518 participants who did not have a follow-up HCV test after enrolment, and hence were not included in the incidence calculation. Also, by testing for HCV annually rather than 3- or 6-monthly, we may have slightly underestimated HCV incidence by overestimating person-time at risk. Another limitation of our HCV testing protocol is the use of HCV antibody screening (rather than HCV RNA) in participants who had no known history of HCV, and hence we may have missed early HCV infections due to possible delays in HCV

Ab seroconversion. Thirdly, we included only participants who attended ACCESS clinics; we did not include participants at clinics that did not collect the same level of behavioural data. This may have introduced a degree of selection bias. Fourthly, observational studies have suggested that sharing of non-injecting drug use equipment, such as straws for intranasally-administered drugs, may be a risk factor for HCV transmission,[9] and this is a possible alternative mechanism for some of our cases of sexually-acquired HCV. Finally, we were not able to interview two incident cases, but we did have multiple data sources for all cases.

Our study indicates that incident HCV among Australian PrEP-using MSM is less common than seen in Amsterdam, the UK and France. Available data on behavioural risk factors for HCV were broadly similar between these studies, suggesting that the observed difference in HCV incidence is likely the result of differences in HCV prevalence among MSM populations in different parts of the world, rather than due to behavioural differences. Most of the incident HCV cases in PrEPX appear to have resulted from sexual transmission, in the context condomless receptive anal intercourse at SOPV or other group sex settings, anal trauma, and chemsex. This presents a health promotion opportunity for clinicians and for HCV awareness campaigns, which should be promoted to MSM who attend SOPV and on digital platforms used to arrange group sex. Such campaigns should discuss the HCV risk associated with anal trauma, discuss the importance of HCV testing, and provide information on HCV treatment availability.

Author Contributions

VJC designed this analysis, conducted interviews, analysed the data and wrote the first draft, subsequent draft and the final version of this manuscript. MWT analysed data from the ACCESS network to calculate HCV incidence. EJW is the principal investigator of the PrEPX study, and contributed to each draft and the final version of this manuscript. DM assisted with interpretation of qualitative data, and contributed to each draft and final version of this manuscript. MS, MH, RS-D, JA, CKF and JD all contributed to each draft and the final version of this manuscript. JS conceptualised this analysis, secured funding to conduct this analysis, and contributed to each draft and the final version of this manuscript.

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Table 1: Behavioural data at baseline for PrEPX participants enrolled at GP clinics and Melbourne Sexual Health Centre (MSHC).

	GP Clinics		MSHC	
Total	2230		439	
Condom use with casual partners[1]				
No anal sex	133	(6.0%)	239	(54.4%)
Always used a condom	550	(24.7%)	42	(9.6%)
Did not always use a condom	1485	(66.6%)	155	(35.3%)
Unanswered	62	(2.8%)	3	(0.7%)
Recreational injecting drug use				
No	1987	(89.1%)	400	(91.1%)
Yes, ever[2]	225	(10.1%)	39	(8.9%)
Yes, within the last 12 months	146	(6.6%)	6	(1.4%)
Missing	18	(0.8%)	0	(0.0%)
Methamphetamine use in the context of condomless anal intercourse.[3]				
Yes	294	(13.2%)		
No	1931	(86.8%)		
GHB use in the context of condomless anal intercourse.[4]				
Yes	221	(9.9%)		
No	2004	(90.1%)		
Amyl nitrite use in the context of condomless anal intercourse.				
Yes	818	(36.8%)		
No	1407	(63.2%)		
Alcohol use in the context of condomless anal intercourse.				
Yes	935	(42.0%)		
No	1290	(58.0%)		

Notes:

1. Condom use with casual partners references the last six months at GP clinics, or the last 3 months at MSHC.
2. "Ever" includes participants who reported injecting drugs within the last 12 months.
3. Only participants who attended GP clinics were asked about the use of drugs or alcohol in the context of anal intercourse. These questions all relate to the previous six months.
4. Five participants declined to answer the question on GHB use in the context of condomless anal intercourse.

Table 2: Hepatitis C-related clinical data, potential contributors to transmission, and transmission classification.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Interviewed	Yes	Yes	No	Yes	Yes	No	Yes	Yes
ALT result	590	1140	1548	445	3249	612	454	103
HCV genotype	1a	1a	1a	1a	3	3	3	3
Drug use during sex	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Injecting drug use	No	No	No	Yes	Yes	Yes	No	Yes
Condomless RAI[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Group sex	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
SOPV attendance[2]	Yes	Yes	Not known	Yes	No	Not known	Yes	Yes
Receptive fisting	Yes	No	Not known	Yes	No	Not known	No	No
HIV[3]	No	No	Yes	No	No	No	No	No
Syphilis	No	No	No	No	No	No	No	No
Anal chlamydia	No	No	No	Yes	No	No	No	No
Anal gonorrhoea	No	No	Yes	Yes	No	No	No	No
Previous anal HSV	Yes, HSV2	Yes, HSV1	Not known	No	No	Not known	Yes	No
Current anal HSV	No	No	No	Yes, HSV2	No	No	No	No
Anal trauma	Yes	Yes	Not known	Yes	No	Not known	Yes	No
Inferred HCV mechanism of transmission	Sexual	Sexual	Sexual	Likely sexual	Injecting	Injecting	Sexual	Shared injecting

Abbreviations:

- HCV: Hepatitis C virus
- Ab: Antibody
- RNA: Ribonucleic acid
- ALT: Alanine aminotransferase. Upper limit of normal: 55
- RAI: Receptive anal intercourse
- HIV: Human immunodeficiency virus
- HSV: Herpes simplex virus
- SOPV: Sex-on-premises venue

Notes:

1. Condomless anal intercourse refers to intercourse with casual partners.
2. SOPV attendance refers to attendance at a sex-on-premises venue at the likely time of HCV acquisition.
3. Case 3 was initially HIV-negative, and was diagnosed with HIV at the same time as his HCV diagnosis.
4. Behavioural descriptors (e.g. “group sex”) and STI data relate to the period of likely HCV acquisition, as determined by cases’ HCV testing pattern.