Title

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Journal

Journal of Viral Hepatitis, 29(7)

ISSN

1352-0504

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Publication Date

2022-07-01

DOI

10.1111/jvh.13678

Peer reviewed

Received: 10 June 2021 | Revised: 3 March 2022 | Accepted: 8 March 2022

DOI: 10.1111/jvh.13678

JOURNAL OF VIRAL HEPATITIS JVH WILEY

ORIGINAL ARTICLE

Low incidence and prevalence of hepatitis C in two cohorts of HIV pre-exposure prophylaxis adherence interventions in men who have sex with men in Southern California

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Funding information
Data for this analysis were collected as part of the California Collaborative Treatment Group 595 study supported by the California HIV/AIDS Research Program EI-11-SD-005. PATH-PrEP demonstration study was funded by the California HIV Research Program EI11-LA-002 with additional support from the Center for HIV Identification, Prevention, and Treatment (CHIPTS) NIMH grant MH58107; the UCLA Center for AIDS Research (CFAR) grant 5P30AI028697; and the National Center for Advancing Translational Sciences through UCLA CSTI Grant UL1TR000124. Gilead Sciences provided drug supply and additional support for some drug-assay testing. RJL received honoraria and travel support from Gilead Sciences.

Abstract

HIV pre-exposure prophylaxis (PrEP) has been associated with incident hepatitis C virus (HCV) infection in men who have sex with men (MSM) due to decreased condom use. We examined rates of HCV among MSM and transgender women at high-risk of HIV on PrEP in Southern California using data from two trials (NCT01761643 and NCT01781806). Five of 599 participants (0.84%, 95% CI, 0.27–1.93) had HCV antibodies detected at entry. Factors associated with HCV seropositivity included being older ($p = .002$) and lower education level ($p < .001$). HCV-positive participants had no reported cases of sexually transmitted infection (rectal, urethral or pharyngeal gonorrhoea and/or chlamydia) at entry while HCV-negative participants had a prevalence of 18% (95% CI, 15%–21%). There were no significant differences in substance use and sexual risk behaviour between HCV-positive and HCV-negative participants 1–3 months prior to entry. Among early PrEP adopters, incident HCV did not occur despite ongoing condomless intercourse. Screening intervals for HCV in MSM on PrEP should be led by a risk behaviour assessment.

KEYWORDS
hepatitis C, MSM (men who have sex with men), PrEP

Abbreviations: ARS/AIS, anal receptive sex/anal insertive sex; GHB/GBL, gamma-hydroxybutyrate/gamma-butyrolactone; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; RPR, rapid plasma regain; STI, sexually transmitted infection; TDF-FTC, tenofovir disoproxil fumarate-emtricitabine; TGW, transgender Women; UK, United Kingdom.

The manuscript was written at the University of California, San Diego. The data was collected from four academic medical centers including University of California, San Diego; University of Southern California; Harbor–University of California Los Angeles; and Long Beach Health Department.

1 | INTRODUCTION

HIV pre-exposure prophylaxis (PrEP) uptake, adherence and persistence is critical to ending the HIV epidemic in the US.[1,2] However, there is concern that HIV PrEP use may also promote elevated risk for incident hepatitis C (HCV) via increase in condomless intercourse or similar behaviors.[3] HCV infection in North America, Europe, Australia and Asia has been on an upward trend beginning in 1995 and since 2000 has been associated with sexually transmitted infection (STI) among HIV-positive men who have sex with men (MSM).[4,5]

HIV and HCV are spread through injecting and sexual networks[6] commonly associated with condomless anal sex, higher number of sexual partners, recent STIs, and recreational drug use prior to or during sex.[7–9] Most data on HCV-HIV co-infection have been among HIV-positive MSM[8,10] who have a higher prevalence of co-infection than HIV-negative MSM.[11–13] However, sexual transmission of HCV has been reported in HIV-negative MSM[14,15] and HIV-negative MSM on PrEP may be at increased risk of HCV infection due to shared transmission networks between HIV-negative and HIV-positive MSM[3,13,16] and condomless anogenital contact.[17] This overlap in sexual networks between HIV-positive and HIV-negative MSM[3,18] can facilitate the introduction of HCV into the HIV-negative population of MSM. In this brief report, we specifically examine the prevalence and incidence of HCV in cohorts of sexually active HIV-negative MSM and transgender women (TGW) in PrEP trials.

2 | METHODS

2.1 | Population

Data from two parallel 48-week prospective trials in Southern California were combined to include adult MSM and TGW at increased risk of acquiring HIV infection who received daily PrEP with tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) and had available paired specimens. These were a randomized clinical trial of text messaging for PrEP adherence (CCTG 595-NCT01761643)[19] with 398 participants enrolled from February 2013 to February 2016, and a strategy study of real-time plasma tenofovir concentration measurement and feedback to support PrEP adherence (PATH-PrEP-NCT01781806)[17] with 301 participants enrolled from April 2014 to July 2016. A total of 599 participants with at least one follow-up visit with paired HCV testing samples were included in this analysis (Figure 1), 86 participants were excluded from the analysis due to missing baseline HCV samples (Table S3).

2.2 | Data

The primary outcome for this analysis was HCV-status at last study visit. HCV serology was routinely collected in PATH-PrEP study, while paired banked specimens were obtained at entry and last study visit in CCTG 595. CCTG 595 participants with reactive HCV antibodies at last study visit had their entry specimen assayed to determine if seroconversion had occurred since study inception. Participants were also routinely screened for syphilis (rectal, urethral and pharyngeal) gonorrhoea and chlamydia at regular intervals by NAAT (Hologic Aptima, Long Beach Public Health Lab). Participants with new STI diagnoses were notified and referred for treatment. Screening assessments for syphilis were conducted using serum rapid plasma regain (RPR) and confirmatory treponemal test, but only results for gonorrhoea and chlamydia were used for STI measures in this study as incident syphilis could not be differentiated from pre-existing syphilis. PrEP adherence was measured using dried blood spot concentrations for intra-erythrocytic TFV-DP at Weeks 12 and 48 using a liquid chromatography–tandem mass spectrometry assay and included as the mean adherence level measured at Week 12 and last study visit.[20] Concentrations of >719 fmol/

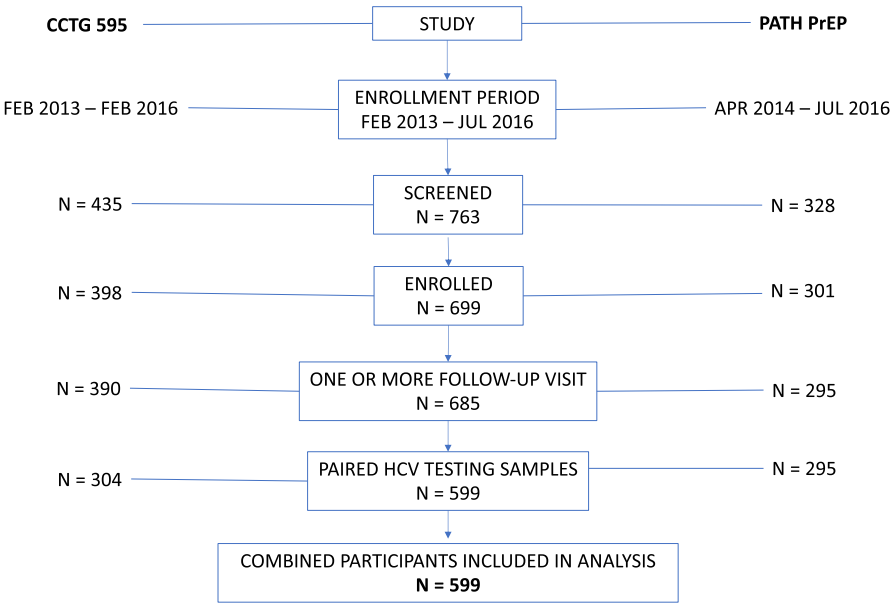

FIGURE 1 Flow chart of study participants

punch were considered adequate adherence, and >1246 fmol/punch was near-perfect adherence for participants in CCTG 595. While concentrations of >700 fmol/punch were considered protective in PATH-PrEP, we used the cut-off of >719 fmol/punch for this analysis. Sexual risk behaviour and substance use for the past 1–3 months prior to enrolment were collected using a computer assisted self-report survey (Table S1).

2.3 | Statistical analysis

Prevalence and incidence of HCV and STI were calculated at baseline and last study visit with binomial exact method to calculate 95% confidence interval. Cumulative incidence is defined as the proportion of participants who were HCV positive over 48 weeks of follow-up time between 2013 and 2016 and calculated as the number of new cases of HCV over number of individuals in the study population at risk. Baseline differences by HCV-status were assessed using Fisher's exact for categorical data and Wilcoxon rank sum and *T*-test for continuous data. A *p*-value <.05 was considered statistically significant. Data management and statistical analysis were conducted using Stata/SE 15.1 (StataCorp, College Station, Texas, USA).

3 | RESULTS

A total of 599 participants with paired HCV serology samples were included in this analysis. Five participants had HCV antibodies detected at entry (prevalence 0.84%, 95% CI 0.27–1.93), there were no new positives by the end of study; thus, zero incident HCV cases (upper limit of 1-sided 95% CI, 0.49%) were detected during the study period. Factors associated with HCV seropositivity at entry included being older in age (median 51 years HCV-positive vs. median 38 years HCV-negative, $p = .002$) and having a lower education level (60% high-school or less HCV-positive vs. 9% high-school or less HCV-negative, $p < .001$). HCV-positive individuals were less likely to maintain PrEP adherence over the course of the study (40% not adequate HCV-positive vs. 13% not adequate HCV-negative, $p = .029$) (Table 1).

HCV-positive participants had no reported cases of STIs (positive for rectal, urethral or pharyngeal gonorrhoea and/or chlamydia) at entry; thus, zero prevalence (upper limit of 1-sided 95% CI, 45%) of STI among HCV-positive participants and no incident cases through Week 48. Among HCV-negative participants, there were more chlamydia than gonorrhoea cases (Figure 1A) and prevalence of STIs at entry was 18% (106 of 594; 95% CI, 15%–21%), increasing to 20% (97 of 485; 95% CI, 17%–24%) by Week 48 (Figure 1B).

There were no significant differences in substance use and sexual risk behaviour between HCV-positive and HCV-negative participants 1–3 months days prior to entry (Figure 2). Among HCV-negative participants, methamphetamines (40%) and poppers (20%) were the only drugs reported by participants. Poppers, an inhalant form of amyl nitrite, were the most common drug among HCV-negative participants of whom 51% reported use in the past 1–3 months prior to entry. Majority of participants (95% of HCV-negative and 60% of HCV-positive) engaged in anal sex in the past 1–3 months prior to entry (Table 1).

4 | DISCUSSION

HCV infection was not common among HIV-negative MSM and TGW on PrEP trials in Southern California. Among early PrEP adopters, the prevalence of HCV antibodies was <1% and no incident HCV was detected during the study period despite ongoing risk behaviour and high prevalence of STIs. PrEP use has been linked to high rates of STI due to the decreased condom use. There is little research available on HCV and HIV co-infection in Southern California, and with the increased benefits of PrEP in prevention of HIV, it was of interest to see how PrEP would be associated with HCV in the HIV-negative population. Our results show participants who were undergoing daily PrEP had low adherence level among HCV positive participants which may be an indication of increased risk of acquiring HIV infection and possible transmission route between HIV-negative and HIV-positive MSM.

A study by Milam et al. reported an estimated one additional condomless receptive anal intercourse act per month after PrEP initiation in a demonstration study[21] and a cohort of PrEP users in San Francisco also had high rates of STI with 41% of participants reporting decreased condom use over study period.[22] STI rates among PrEP users in both studies included in this secondary analysis were high,[17,23] with a prevalence ranging from 4% to 20% among HCV-negative participants.

HCV prevalence in this study is similar to studies among MSM cohorts in the United States, United Kingdom (UK), Canada and Australia. Among 485 HIV-uninfected MSM receiving PrEP in a medical centre in San Francisco from 2011 to 2014, only two incident HCV infections were reported for patients older than 35 years.[24] Similarly to our cohort of HCV positive participants, the only reported risk factor for the two patients for HCV infection was condomless sexual intercourse. A survey of 2030 MSM in Manchester, UK, had 0.9% of new HCV diagnosis, among which 1.8% were HIV-positive MSM and 0.2% HIV-negative MSM. The authors found HCV positivity was significantly associated with HIV status, with HIV-positive MSM reporting lower rates of sexual partners and insertive unprotected anal intercourse ($p < .05$) compared with HIV-negative MSM.[25] A study in Canada of 442 MSM from primary care settings reported 1.4% prevalence among HIV-negative MSM without the history of injection drug use (IDU)[12] and a study in Australia with HCV prevalence of 1.07% among HIV-negative MSM.[13] While only the San Francisco study included MSM on PrEP, the findings are consistent with low HCV prevalence among HIV-negative MSM reporting higher numbers sexual partners and condomless anal insertive sex. To get a sense of the prevalence and incidence of HCV infection in HIV-positive MSM in San Diego, CA, Chaillon A et al.[26] reported a stable incidence of HCV between 2000 and 2014 (0.83/100 person

TABLE 1 Characteristic and risk factor by hepatitis C (HCV) status at baseline

	HCV negative	HCV positive			HCV negative	HCV positive	
	N = 594	*N* = 5	*p*-value		*N* = 594	*N* = 5	*p*-value
Demographic				*Substance use (past 30 days)*			
Gender			1.00	Ecstasy			1.00
Male to female	2 (<1%)	0 (0%)		No	450 (76%)	3 (60%)	
Male	592 (100%)	5 (100%)		Yes	122 (21%)	0 (0%)	
Race and ethnicity			.38	Missing	22 (4%)	2 (40%)	
White	306 (52%)	2 (40%)		Heroin			1.00
African American	65 (11%)	2 (40%)		No	555 (93%)	3 (60%)	
Hispanic/Latino	164 (28%)	1 (20%)		Yes	15 (3%)	0 (0%)	
Asian	23 (4%)	0 (0%)		Missing	24 (4%)	2 (40%)	
Other	36 (6%)	0 (0%)		Marijuana			.25
Education Level			.008	No	290 (49%)	3 (60%)	
Highschool or less	56 (9%)	3 (60%)		Yes	282 (47%)	0 (0%)	
Some college or more	538 (91%)	2 (40%)		Missing	22 (4%)	2 (40%)	
Age at enrolment, mean (SD)	38 (10)	51 (5)	.002	Methamphetamines			.071
Sexually transmitted infections				No	480 (81%)	1 (20%)	
Hepatitis B			1.00	Yes	92 (15%)	2 (40%)	
Negative	534 (90%)	5 (100%)		Missing	22 (4%)	2 (40%)	
Positive	2 (<1%)	0 (0%)		Hallucinogens			1.00
Missing	58 (10%)	0 (0%)		No	532 (90%)	3 (60%)	
Any gonorrhoea			1.00	Yes	39 (7%)	0 (0%)	
Negative	267 (45%)	3 (60%)		Missing	23 (4%)	2 (40%)	
Positive	58 (10%)	0 (0%)		Dissociative			1.00
Missing	269 (45%)	2 (40%)		No	541 (91%)	3 (60%)	
Any chlamydia			1.00	Yes	32 (5%)	0 (0%)	
Negative	269 (45%)	3 (60%)		Missing	21 (4%)	2 (40%)	
Positive	58 (10%)	0 (0%)		Popper			.61
Missing	267 (45%)	2 (40%)		No	273 (46%)	2 (40%)	
Syphilis			.78	Yes	300 (51%)	1 (20%)	
Negative	269 (45%)	3 (60%)		Missing	21 (4%)	2 (40%)	
Positive	43 (97%)	0 (0%)		Cocaine			1.00
Missing	282 (48%)	2 (40%)		No	464 (78%)	3 (60%)	
				Yes	109 (18%)	0 (0%)	
				Missing	21 (4%)	2 (40%)	
Sexual risk behaviour (past 30 days)				*PrEP adherence*			
Anal sex in past 30 days			1.00	Mean PrEP adherence			.029
No	11 (2%)	0 (0%)		Not adequate/below quantification	80 (13%)	2 (40%)	
Yes	563 (95%)	3 (60%)		Adequate/protective	267 (45%)	0 (0%)	
Missing	20 (3%)	2 (40%)		Perfect	223 (38%)	2 (40%)	

TABLE 1 (Continued)

	HCV negative	HCV positive			HCV negative	HCV positive	
	N = 594	*N* = 5	*p*-value		*N* = 594	*N* = 5	*p*-value
No. male partners for anal sex, median (IQR)	5 (3, 10)	3.5 (3, 4)	.39	Missing	24 (4%)	1 (20%)	
No. unprotected ARS, median (IQR)	1 (0, 3.5)	4.5 (1, 8)	.34				
No. unprotected AIS, median (IQR)	2 (0, 4)	1 (1, 1)	.60				
No. HIV negative partners, median (IQR)	1 (0, 3)	1 (0, 2)	.68				

Notes: Percentages are column totals. *p*-value is for Fisher's exact test and Wilcoxon rank sum/*T*-test. Mean PrEP adherence is mean value measured at week 12 and last study visit.

Abbreviations: any chlamydia, any of rectal and/or urine cases; any gonorrhoea, any of rectal, urine and/or pharyngeal cases; ARS/AIS, anal receptive sex/anal insertive sex.

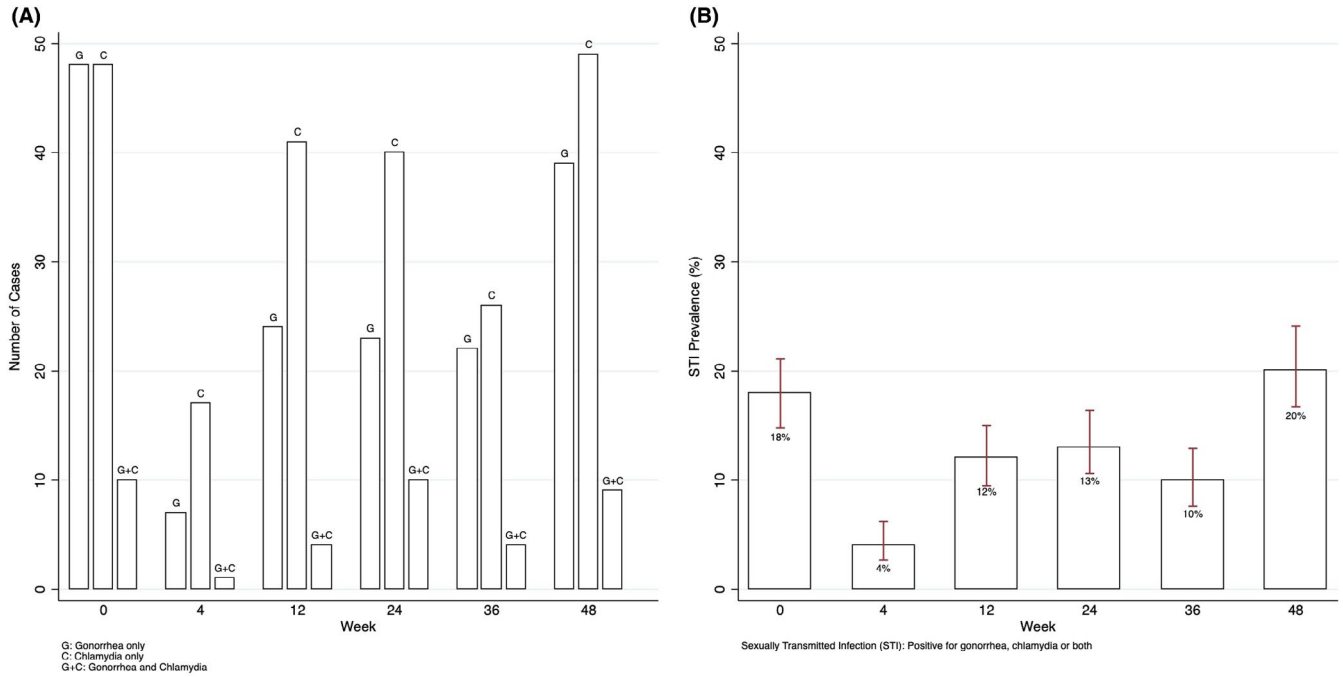

FIGURE 2 (A) Number of cases of gonorrhoea and chlamydia among Hepatitis C negative participants by visit week, and (B) Prevalence and 95% confidence intervals of sexually transmitted infections (positive for gonorrhoea, chlamydia or both) among Hepatitis C negative participants by visit week

year; 95% CI 0.41–1.48) from two primary HIV clinics, and an increase to 3.01/100 person year (95% CI 1.97–4.42) in 2015. Our cohort enrolled patients between 2013 and 2016 out of which only eight patients were enrolled in 2015 from San Diego. It is likely that our cohort enrolment in San Diego was near complete prior to the peak in HCV incidence. In addition, a study by Chew et al.[27] shows low HCV prevalence among newly HIV-diagnosed MSM in Los Angeles.

The low HCV prevalence in our study differs from a cohort in Amsterdam[3] suggesting high incidence of HCV among HIV-negative MSM on PrEP. Hoornenborg et al. had 18 of 375 HIV-negative MSM (4.8%, 95% CI 2.9–7.5) positive for HCV at baseline, with median age of 33 years (IQR 28–42) compared with 40 years of age for HCV-negative MSM. They also reported significant differences in sexual risk behaviours at baseline between HCV-positive and HCV-negative MSM on PrEP including self-reported STI, number of receptive condomless anal sex in past 3 months, injection drug use in past 3 months and use of gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL), methamphetamine or mephedrone during sex in the past 3 months. There were no significant differences in drug use between HCV-positive

and HCV-negative participants at baseline in our study, possibly due to low power to detect a difference. The MSM/TGW in our cohort was older and had lower baseline HCV prevalence compared with the Amsterdam cohort. It is possible that the HCV positive participants in our cohort are cases from other sources as these individuals were comparatively older and did not have any STI, fitting more in line with CDC recommendations for screening individuals born between 1945 and 1965.

Global prevalence of HCV in HIV negative MSM was estimated to be 1.5% by Jin et al.[6] with notably higher rates in current or past IDU. In MSM taking PrEP, global incidence was found to be 14.8 per 1000 person years. However, global incidence was determined by only four studies, none of which took place in the United States. Wynn et al.[28] estimated that HCV seroprevalence in San Diego was 2.1% in 2018, with a majority of infections found in IDU and those aged 55–74. Although this study did not examine rates specific to those taking PrEP, HCV seroprevalence was no different in HIV negative MSM aged 18–54 compared with men aged 18–54.

This report is limited by having to combine datasets from two separate studies without exact mirroring of the questionnaires; thus, limited data are combined. However, laboratory results of STI and HCV were not subjected to data collection differences. We did not have information on mode of drug administration (i.e., snorting and injection drug use) in the questionnaire which would be informative towards understanding the mechanism of infection. The low prevalence rate of HCV in this group limit the power to conduct further analysis of factors related to HCV. We were unable to determine if the five anti-HCV antibody positive MSM had active HCV infection, conducting a phylogenetic analysis on background sequences of HCV infections in HIV-positive MSM from Southern California to determine potential transmission between HIV-positive and HIV-negative individuals would be very informative. Finally, as only two TGW enrolled in the study, our results are driven by MSM at elevated risk for HIV seeking PrEP shortly after regulatory approvals by the US Food and Drug Administration of TDF-FTC.

5 | CONCLUSION

Among early PrEP adopters engaged in Southern California PrEP demonstration projects, the seroprevalence of HCV was low. Incident HCV did not occur during the study period, despite ongoing risk behaviour and a high prevalence of bacterial STIs. While routine testing of HCV among sexually active MSM may be most reasonable among those with additional risk factors for HCV acquisition, our findings do not support a need for frequent screening of HCV for all MSM on PrEP and should be guided by risk behaviour assessment.

ACKNOWLEDGMENTS

We gratefully acknowledge and thank all participants who contributed to the study and the CCTG clinical site staff for the implementation and data collection.

CONFLICT OF INTEREST

No competing financial interests exist.

ETHICS APPROVAL

The studies were approved by the Institutional Review Boards at UC San Diego and UC Los Angeles.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Hassan A, Agustin HGS, Burke L, et al. Low incidence and prevalence of hepatitis C in two cohorts of HIV pre-exposure prophylaxis adherence interventions in men who have sex with men in Southern California. *J Viral Hepat*. 2022;00:1–7. doi:10.1111/jvh.13678