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Hepatitis C Infection In Men Who Have Sex With Men

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HEPATITIS C INFECTION IN MEN WHO HAVE SEX WITH MEN

by

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Jing Zhao, MS MPH, PHD
2019

DEDICATION

To MSM at risk for HCV

HEPATITIS C INFECTION IN MEN WHO HAVE SEX WITH MEN

by

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MS, CHINA CDC, 2009
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Presented to the Faculty of The University of Texas

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of the Requirements

for the Degree of

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HEPATITIS C INFECTION IN MEN WHO HAVE SEX WITH MEN

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Hepatitis C virus (HCV) infection is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation. Current treatment rates and efficacy are inadequate to manage the disease burden caused by HCV; thus, efforts are needed to control HCV transmission. Besides the well-known transmission routes, which are health-care-associated transmission and transmission through injecting drugs, HCV could also be transmitted by sexual contact, especially among men having sex with men (MSM). MSM also have higher drug use prevalence than the general population, which may contribute to HCV infection by sexual disinhibition and other risky behavior. Since 2000, there have been emerging reports indicating HCV epidemics or outbreaks among HIV positive MSM in Europe, Australia and North America. However, previous studies often focused on HIV positive and/or injection drug using MSM, and there is still a need for study targeting on non-injection drug using MSM. The overall objective of this study is to investigate characteristics associated with HCV infection in MSM who used drugs but not injected drugs (NIDU MSM).

This study used data from two projects, DASH project and YMAP project, and applied latent class analysis and dyadic data analysis to analyze the data. The main finding of this study included: (1) overall HCV prevalence in NIDU MSM was higher than the rest of general population; (2) NIDU MSM ≥ 42 years old had a higher risk of HCV infection than NIDU MSM < 42 years old; (3) NIDU MSM ≥ 42 years old who used > 6 drugs were associated with increased probability of HCV infection among all NIDU MSM; (4) among NIDU YMSM, syphilis mono-infection, HIV mono-infection, and syphilis/HIV co-infection were associated with increased risk of HCV infection.

This study may provide a better understanding of HCV transmission among NIDU MSM. These results may provide a profile of subgroups with a higher HCV transmission possibility among NIDU MSM. In the long term, the results of the study may guide the development of healthcare and behavioral intervention programs related to HCV transmission, and may also guide tailored screening or treatment strategies for HCV infection.

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BACKGROUND

Background and literature Review

Hepatitis C Virus infection

Hepatitis C virus (HCV) infection affects primarily the liver and causes acute and chronic hepatitis in humans with a high propensity for chronicity. [1] It has become a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation. [2]

Worldwide, three to four million people are newly infected each year and 170 million people are chronically infected accounting for 3% of the global population. [3] In the United States, it is estimated that 3.5 million people are living with HCV infection, which accounts for about 1% of the population. [4] The number of estimated new annual HCV infections increased from 16,500 in 2011 to 41,200 in 2016 [5], tripling in six years.

Young people ages 20-29 years who inject drugs account for the greatest increases, and the highest overall number of cases. [5]

Among infected individuals, about 25% could spontaneously eliminate the virus, and the remaining 75% are chronically infected. Of those with chronic HCV infection, the risk of cirrhosis of the liver is between 15–30% within 20 years. [6] Worldwide, about 399,000 people die each year due to all HCV-related causes, mainly from HCV-related cirrhosis and hepatocellular carcinoma. [7]

The current treatment paradigm can achieve 95% cure rates. [8] However, these medicines are very expensive in many high- and middle-income countries, which creates a major barrier for people with HCV infection to obtain access to proper treatment. Meanwhile, the rate of access to diagnosis and treatment is low. In 2015, of

the people living with HCV globally, 20% knew their diagnosis, and only 7.4% of those diagnosed were started on treatment in 2015 [7]. A study modeling current and future disease burden of HCV indicates that the current treatment rate and efficacy are inadequate to reduce the disease burden of HCV; thus, more efforts are needed to control HCV transmission. [9]

HCV can be transmitted from one individual to another through bodily fluids. The first transmission route has proven to be health-care-associated transmission, such as unsafe injection practices and procedures. [10] Approximately half of the chronic infection happened through this transmission route in developing countries. [9] The second transmission route is well considered to be transmission among people who inject drugs through unsterile injection equipment and contaminated drug solutions. According to a systematic review, this route primary contributed to the infection, especially incident infection, in middle- and high-income countries [11]. The third transmission route could be sexual transmission. Since 2000, there has been increasing reports of HCV epidemic among HIV positive MSM in Northern Europe, North America, and Australia [12-15], linked to high-risk sex behaviors and potentially underreported non-injection drug use [16, 17].

HCV among people who use drugs

There is a high prevalence of illicit drug use in the United States and the prevalence has been increasing in recent decades. Approximately 29.5 million aged 12 years or older (0.6% of the population) are suffering from drug use disorders [18]. In 2014, in North America, the drug-related death rate is 164.5 /per million among 15-64 years, 3.5 times than the global average number.

Among people who use drugs, about one third are injection drug users (IDU) [19] constituting the “core” population of HCV infection. Among IDU 40%-90% are infected by HCV, and IDU accounted for more than 50% of all cases of HCV. [20] For non-injection drug users (NIDU), less attention was paid to their HCV infection. One systematic review, however, reported that the HCV prevalence ranged from 2.3% to 35.3% in NIDU and is much higher than the prevalence in the non-drug using population. [21]

HCV among MSM

There are an estimated 8.4 million MSM in the US [22], of whom 16% are infected with HIV [23]. During the last decade, there have been increasing reports of acute HCV epidemic among MSM in Western countries. [13, 14, 24-26] One recently published systematic review and meta-analysis, which quantitatively synthesized 28 studies since 2000, reported that the pooled estimated incidence rate was 6.4 per 1000 person-year (95%CI: 5.0-7.5), and the incident rate of HCV among HIV positive MSM was 19 times than that of HCV among HIV negative MSM. [27] Another recently published systematic review and meta-analysis, which quantitatively synthesized 42 studies from 1990 to 2015, studied HCV prevalence among HIV positive MSM and reported that the pooled hepatitis C virus prevalence was 8.1%. [28]

It is believed that HCV was first introduced in this population by parenteral transmission through injection drug use [14, 29, 30], then researchers proved HCV transmission network among MSM by using phylogenetic approaches [17] and sexual transmission was thought to be the most possible transmission mechanism [12].

In this population, researchers revealed that the HCV epidemics have been associated with behavioral factors (such as group sex, recreational drug use, sex with drug use, sex practices disrupting the anal mucosal), and biological characteristics (such as HIV co-infection, and recent history of syphilis). [27, 31]

HCV among MSM who use drugs

Research suggests that MSM are more likely to use drugs compared to adults in the general population. According to a National Household Survey on Drug Abuse, the prevalence of drug use in the past month is 16.3% among MSM, while 9.9% among men only having female partners. [32] A national MSM sample found a 42% previous year prevalence for any non-injection substance use. [33] This higher rate of drug use can be a reaction to homophobia, discrimination, or violence that MSM experience because of their sexuality. [34] One systematic review and meta-analysis, targeted only HIV positive MSM, reported that the pooled HCV prevalence was 40% among IDU and was 6.7% among NIDU, and the prevalence was increasing over time among both subgroups. [28]

Summarizing various studies, there are three distinct characteristics of drug use behavior among MSM. First, most drug use MSM are not drug-dependent, but rather use episodically (i.e., using substances less than weekly). National HIV Behavioral Surveillance (NHBS) data show that 69%–86% of drug use MSM report less than weekly substance use [32–35]. This pattern perhaps less concerning from a drug-dependence perspective, however, is associated with high-risk sexual behaviors [24, 38]. Second, drug use MSM are more likely to use drugs related to sex (meth, EDDs, poppers), or club drugs (Ketamine, MDMA, GHB, etc.), which are related to high-risk

sexual behaviors and contribute substantially to HIV transmission rates. Third, multiple drug use (i.e. taking more than one substance at the same time or periodically over a period of time) is very common among drug using MSM. For example, in the San Francisco NHBS sample, more than 90% of Methamphetamine, cocaine or popper using MSM reported using other substances. In a sample of MSM from San Diego, who were HIV positive and used methamphetamine, 95% used multiple drugs. Two studies in New York targeting club drug using MSM, reported similar findings. Among various drug using MSM samples, 11%-44% of respondents reported recent use of more than three substances.

It is biologically plausible that mucosally administered drug use may directly be associated with HCV infection by sharing insertion equipment, mucosal trauma and mucosal hyperemia. [35] Drug using may also alter mental status, decrease pain, improve sexual function or desire, therefore drug-using MSM may get involved in riskier sexual behaviors, such as multiple sex partners, marathon sex, anonymous sex, low condom use, and other risk behaviors, such as exchange sex for drugs and money, and sharing needles when injecting drugs. Those risk behaviors substantially contribute to the transmission of HIV, Hepatitis, and other STDs. However, it is difficult to disentangle the extent to which non-injecting drug use directly facilitates HCV infection versus the effect of disinhibiting riskier sexual behaviors.

There are case-control studies of HIV positive MSM from UK and German, showing higher levels of nasally administered drug use in HCV cases than in controls. [15, 36] One study in the US indicated that methamphetamine use during sex was the most

significant risk factor for HCV transmission in non-injection drug use, HIV-positive MSM. [37]

There is a need for more understanding the practice associated with HCV infection in NIDU MSM, which could lead to better informed and more effective prevention. This proposed study intended to use traditional epidemiology method and latent class analysis to explore risk factors associated with HCV infection in NIDU MSM, and to use a social network analysis approach to evaluate risk factors associated with HCV infection in NIDU MSM.

Latent class analysis

Latent class analysis (LCA) is a statistical model, in which several items are used to determine the class of individuals. [38, 39] The hypothesis of LCA is the similarity of the response for the individuals within a class. [40] LCA assumes homogeneity within a class, heterogeneity among classes, and that the difference in response to items within a class is only due to random error. [39, 40] Different from cluster analysis, which is not a statistical model, LCA can provide not only the results of classification but also the probability that one individual belongs to a certain class. In addition, LCA can provide the probability that one individual belongs to a certain class given a “yes” response to a certain item.

People who use drugs often use different kinds of drugs, by multiple routes of administrations (for example smoking, chewing, swallowing, snorting, inhaling or taking in pill form), and patterns of substance use vary among different populations [41]. Drug-using MSM are also not a homogeneous population. Only focusing on certain kinds of

drugs may result in lack of generalizability. LCA is a well-established methodology to identify subgroups with distinct behavior in a population. This technique has been applied to explore classes of drug use [42-48] and then to explore associations of each class with specific risk factors.

Researchers using LCA analysis among MSM who use drugs have focused primarily on HIV infection and related risk factors. In these studies, classes of MSM who use drugs are between 2 to 6, such as low-risk (limited or negligible) drug use, recreational/club drug use, conventional drug use, street drug use, multiple drug use, etc. In one US internet-based MSM sample, a using sex-drugs group was more likely to engage in particular potentially high-risk sexual behaviors, and a distinct polydrug use group was identified. [49] Another US internet-based MSM sample showed that MSM who used polydrug were more likely to report unprotected anal intercourse, and sexual transmitted infection. [50] One US internet-based African American MSM sample identified 3 classes: persons who used polydrug were more likely to report sex exchange, recent sexually transmitted infection compared to other classes, and persons who used alcohol and polydrug were more likely to report sex under the influence [51]. A young MSM sample from Chicago reporting high substance use rates were classified into 3 distinct groups (persons who used alcohol and marijuana, polydrug, and less marijuana) [52]. In a Malaysia Asia internet-based MSM sample, an ATS (amphetamine-type stimulant) class was more likely to have more than 6 male sex partners, have group sex, report inconsistent condom use, be HIV infected, and have a sexually transmitted infection compared to a low-risk drug use group [53]. Very few published literatures can be found, which applied LCA for classifying NIUD MSM and explored the association with

HCV infection and other risk factors. This study used LCA to identify subgroups of NIDU MSM and evaluate the relationship between drug use patterns and HCV infection.

Social network analysis

The science and techniques of network analysis have a great impact on the research on the dynamics of interacting elements. [54] The concept of “social network” was first introduced by J.A. Barnes in 1954 in the context of anthropology, representing social contact between individuals. [55] In 1985, this concept was first applied in Epidemiology on an HIV study to show the usefulness of a network approach to evaluate an infectious agent with unknown etiology and to develop strategies to reduce the transmission through personal contact. [56]

The spread of an infectious disease naturally forms a transmission network, and this network underlies the person to person contact network. Especially for sexually transmitted disease, people are usually infected by their close network, not by a random person at large. By observing and analyzing the structure of contact network, we may get an insight into the epidemiological dynamics (understand and predict the spread of infection), and the knowledge of transmission route defined by network structure can be used as part of intervention and prevention.

Social network models incorporate both individual attributes (socioeconomic status, age, race, weight, etc) and relationship between elements (kinship, friendship, sexual relationship, affiliated organizations, etc.), which may lead to or influence the infection of disease, whereas traditional infectious disease models are only based on individual

attributes and uniform-mixing assumption (assume the probability of person-to-person contacts are the same for each individual).

Inspired by the first application of social network analysis on HIV/AIDS [56], more research has been conducted in the field of STDs by using sexual network or social network information, such as HIV [57-61], syphilis [62-64], gonorrhea [65], and chlamydia [66]. Very few published studies have used a social network approach to study sexually transmitted HCV. One study incorporated epidemiological and phylogeographical approaches indicating that some subtype of HCV was associated with younger people, possibly with higher rates of sexual transmission, suggesting social factors may play a key role in determining the rate and pattern of HCV transmission. [67] However, further study is needed in this field to further understand sexual transmission by using social network approach.

This study explored HCV transmission factors by using a simple network structure -- dyads within egocentric networks. This study analyzed the relationships between the character of dyadic links in a subset of egocentric networks of MSM and the likelihood that subjects are infected with HCV. According to Neaigus, dyads data may also yield useful results and is feasible among hidden populations such as MSM [68].

Knowledge gap

Very few published studies have examined HCV infection among NIDU MSM, which could be a neglected subpopulation at risk of HCV infection. In addition, research on sexual transmission of HCV among heterosexual and homosexual couples has yielded mixed results. This proposed study would infer, although cannot confirm, sexual transmission evidence among the study populations. Furthermore, latent class analysis and social network analysis methods have been used for HIV related study among MSM, but seldom used for HCV study among MSM. This proposed study is attempting to use these approaches to evaluate and discuss HCV infection by using the subset of data from two NIH funded projects: Drugs, AIDS, STDs, and Hepatitis project (DASH, PI: Lu-Yu Hwang), and Young Men's Affiliation Project (YMAP, PI: Kayo Fujimoto).

Public Health Significance

This study may provide a better understanding of HCV transmission among NIDU MSM. We will obtain the characteristics of the study populations associated with HCV infection. These results may provide a profile of subgroups with a higher HCV transmission possibility among NIDU MSM. In the long term, the results of the proposed study may guide the development of healthcare and behavior intervention programs related to HCV transmission, and may also guide tailored screening or treatment strategy on HCV infection. Therefore, the results of the study may help to reduce the subsequent burden of advanced liver diseases attributed to HCV in NIDU MSM, by slowing the incidence and decreasing the prevalence of HCV infection in this marginalized and underrepresented population.

Specific Aims and Hypothesis

This proposed study will explore the risk factors of HCV infection in two study populations of NIDU MSM. The results will provide a profile of sub-population in MSM that susceptible to HCV infection, and provide some evidence of sexual transmission of HCV among NIDU MSM.

Specific aim 1

To determine risk factors associated with HCV infection among NIDU MSM in Houston, using a subset of data from Drugs, AIDS, STDs, and Hepatitis (DASH) project.

Hypothesis: NIDU MSM who engage in risky sexual behaviors (unprotected anal intercourse, multiple sexual partners, trading sex, etc.) will be more likely to have HCV infection, compared to those who do not engage in these risk sexual behaviors.

Specific aim 2

To investigate subgroups of non-injection drug use among MSM using latent class analysis, and to evaluate the effect of these subgroups on HCV infection, using a subset of data from Drugs, AIDS, STDs, and Hepatitis (DASH) project.

Hypothesis: NIDU MSM have distinct drug use subgroups, and these subgroups are different in the risk of HCV infection. Sex-related drug use will be associated with HCV infection.

Specific aim 3

To examine relationships between dyadic links in a subset of egocentric networks of NIDU MSM, engagement in high-risk sex behaviors, and the likelihood that subjects are infected with HCV, using a subset of data from Young Men's Affiliation Project (YMAP).

Hypothesis: dyadic links and ego attributes related to high-risk sex behaviors, HIV infection and syphilis infection will be associated with HCV infection among young NIDU MSM.

PARENT STUDY: DASH PROJECT

The data of the first and second studies came from the data of Drugs, AIDS, STDs, and Hepatitis (DASH) project.

The DASH project was a community-based intervention study among non-treatment drug using population for HIV, HBV, and HCV prevention. The project screened 2800 individuals who injection and non-injection drugs from February 2004 to October 2007 in two inner city neighborhood communities in Houston, Texas. Participants were recruited by using outreach and chain referral method. [20] Chain referral method is a sampling technique where a small pool of initial study subjects is used to recruit future subjects through their social networks. This sampling method is often used to reach hidden populations. This study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center.

The eligibility criteria for individuals included in the screening process were: 1) 18 years old or above, 2) self-reported living in Houston, 3) self-reported use of illegal and non-medical prescribed drugs including cocaine or heroin in the last 48 hours and confirmed presence of drug metabolites by urinalysis (OnTrak Varian Testik, Palo Alto, CA.), 4) willing to sign the informed consent form for HIV, HBV, and HCV testing. Individuals with negative drug metabolites test were excluded from the study.

Data collection

Every individual completed an initial screening interview, which comprised a verbally administered questionnaire via computer-assisted personal interview (CAPI, QDS,

Bethesda, MD) to obtain the demographic information, history of drug use for drugs, sexual behaviors, history of sexually transmitted diseases, and blood transfusion and occupational exposure to blood.

Separate from the screening interview, the baseline enrollment interview collected additional information on drug use, including frequency of drug use in past 30 days, a detailed history of bingeing for each of these drugs, experience in injection drug use.

Laboratory methods

All serum specimens obtained from screened individuals were tested for HIV1/2 antibodies, HBsAg and HCV antibody infection using Core Combo HIV-HBsAg-HCV (Core Diagnostics, United Kingdom). Verification of HIV was conducted by enzyme immunoassay (EIA), using Abbott PPC Commander system, third generation HIV antibody test (Abbott Laboratories, Chicago, IL). Verification of HCV, anti-HBs, and anti-HBc was conducted by Abbott AxSYM system, using microparticle enzyme immunoassay (MEIA) (Abbott Laboratories, Chicago, IL).

Definition of HCV infection was the presence of antibody to HCV. HIV infection was defined as repeatedly reactive results by EIA. Case definition of HBV was the detection of anti-HBs or anti-HBc.

PARENT STUDY: YMAP PROJECT

The material of the third study obtained from Young Men's Affiliation Project (YMAP) in Houston, TX.

YMAP is a longitudinal network study conducted from 2014 to 2017 to investigate social networks and attendance history at social venues and health-promoting venues among young MSM, and to determine how these networks affect HIV and sexually transmitted disease risk and prevention in Houston, TX and Chicago, IL. [62, 70-72] Respondents were included in this study if they identified as male sex assigned at birth and current male identification, were aged between 16-29 years old, reported oral or anal sex with another male in the past 12 months, were residing in and planning to remain in Houston for the following year, and were English-speaking. The study was approved by the institutional review boards at each location (HSC-SPH-12-0830).

Data collection

The sampling method in the YMAP study was Respondent Driven Sampling (RDS). [73] This method has been applied to recruit hard-to-reach populations such as MSM. The "seeds" were defined as respondents enrolled via representatives at health service providing facilities or at social venues. "Sprouts" were defined as respondents who were referred by "seeds". Four vouchers were given to each participant to recruit other YMSM (sprouts) to produce chained samples.

Interviews were conducted using a computer-based personal-interview combined with a computer-assisted self-interview delivered via Qualtrics (Qualtrics LLC, Provo, Utah). In the computer-assisted personal interviews, the trained data collector read questions

from the computer and entered data. Information were collected on demographic characteristics, drug use, social and sexual networks, and behavior with peers, and participants' affiliation with community organizations and businesses.

Laboratory methods

After the interview, each participant provided biological blood specimen for HIV, HCV, and syphilis. HIV tests included fourth generation rapid test, using Alere Determine HIV-1/2 Ab/Ag combo (Abbott Laboratories, Chicago, IL), viral load quantitative test, using Cobas AmpliPrep/Cobas TaqMan HIV-1 test kit, version 2.0 (Roche Molecular Diagnostics, Pleasanton, CA), and confirmatory test, using Geenius HIV -1/2 Confirmatory test (Bio-rad, Marnes-la-Coquette, France). Tests for syphilis infection included rapid plasma regain (RPR) test, using Macro-Vue RPR Card test Kit (BD Diagnostics, Franklin Lakes, NJ), and fluorescent treponemal antibody FTA test, using Immunofluorescence Assay FTA-Absorption Test System (Zeus Scientific, Branchburg, NJ). The test for HCV was HCV antibody rapid test (Boson Biotech, Xiamen, CN).

METHODS FOR SPECIFIC AIM 1

Study design and study population

This study was a cross-sectional study using a subset of screening data from DASH project, restricting to individuals who reported never having injected drugs and ever having male-to-male sex. Among 2800 individuals who were screened, 273 NIDU MSM were selected in this proposed study (Figure 1).

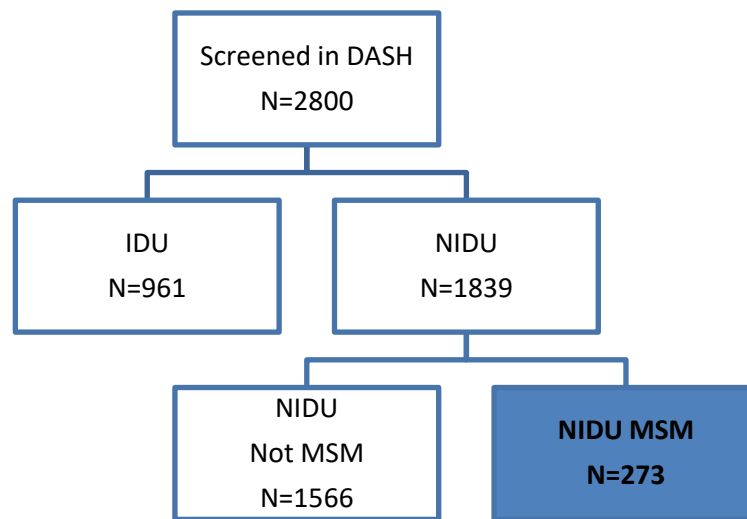


Figure 1. Study population for specific aim 1

Ascertainment of dependent and independent variables

Dependent variable was HCV status, which is defined as the existence of HCV antibody or not. Independent variables were demographic measures such as age, race, living arrangement, jail history of more than 24 hours, and behavior measures such as number of sexual partners, frequency of condom use, trade sex for money or drugs, drug or alcohol use in past 7 days, number of drugs used in past 7 days, and biological measures such as HIV status, HBV status, history of sexually transmitted diseases.

Power estimation

Assuming a sample size of 284 participants and a two-sided test with 0.05 significant level, a minimal odds ratio was 1.7 to obtain a power of at least 80%, for overall HCV prevalence is 15.5% and assuming 5%-15% in unexposed group and 10%-30% in exposed group (Table 1). This power estimation was calculated by using OpenEpi software. [69]

Table 1 Study power ($1-\beta$) estimation given sample size of 273, significant level of 0.05 and different HCV prevalence in exposed/unexposed groups for specific aim 1

HCV prevalence in unexposed	HCV prevalence in exposed				
	10%	15%	20%	25%	30%
	$1-\beta$ (OR)	$1-\beta$ (OR)	$1-\beta$ (OR)	$1-\beta$ (OR)	$1-\beta$ (OR)
5%	0.6 (2.1)	0.9 (3.3)	0.9 (4.7)	1.0 (6.3)	1.0 (8.1)
10%	0.1 (1.0)	0.4 (1.6)	0.9 (2.2)	1.0 (3.0)	1.0 (3.8)
15%	0.4 (0.6)	0.1 (1.0)	0.4 (1.4)	0.8 (1.7)	1.0 (2.4)

Statistical analysis

Univariable analysis was conducted for each demographic characteristic, behavioral and biological variable. Number and percentage were calculated for categorical variables, while median and interquartile range (IQR) was computed for continuous variables. Then, Exact Logistic Regression was conducted for bivariable analysis to statistically test the association between the independent variables and HCV infections, and crude odds ratio (cOR) and 95% confidence interval with p-values were obtained. A final multivariable model was constructed by first using all variables significant at $p < 0.25$ in bivariable analysis as full model, then backward elimination was used to reach the final model. The statistical significance level was 5%. SAS 9.4 was used to manage and

analyze the data (Cary, NC). Hosmer-Lemeshow goodness of fit test was used to test the fit of the final model.

METHODS FOR SPECIFIC AIM 2

Study design and study population

This study was a cross-sectional study using a subset of baseline data from the DASH project, restricted to participants who reported male-to-male sex and never injected drugs. Among 2800 individuals who were screened, 1260 who were negative for HIV and HBV were enrolled for intervention to improve HBV vaccination adherence, and within the enrolled participants, 118 NIDU MSM were selected in this proposed study.

(Figure 2)

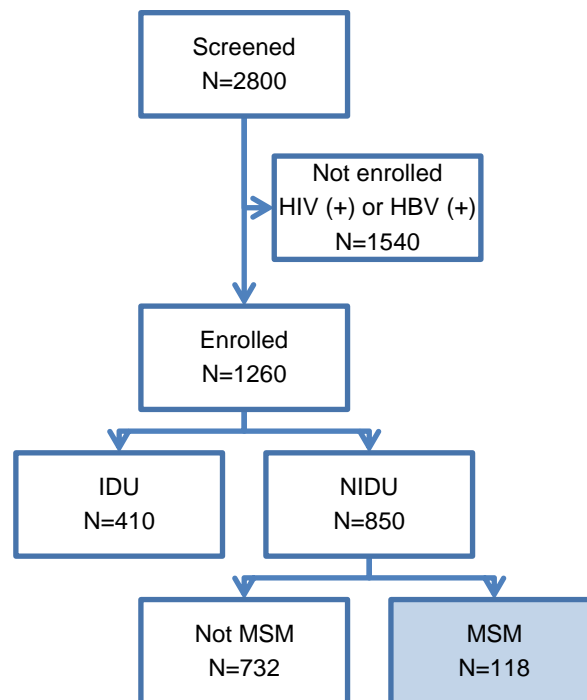


Figure 2. Study population for specific aim 2

Measures

For latent class analysis, indicators used for class identification included the use of the following drugs: crack cocaine, powder cocaine, methamphetamine, marijuana, alcohol, and heroin.

For multi-nominal logistic regression, the dependent variable was the class of persons who used drugs classified by latent class analysis (e.g. class 1 vs 2, class 2 vs 3 and class 1 vs 3) (see statistical analysis below). The independent variable comprised demographic measures (such as age, race/ethnicity, education level, living arrangement, jail history of more than 24 hours), risk behavior variables (such as number of sexual partners in the past 30 days, sexual orientation, condom use, trading sex for money or drugs in past 30 days), HCV status, sexually transmitted diseases histories.

For multivariable logistic regression, the dependent variable was HCV status. Independent variables were demographic measures (such as age, race/ethnicity, education level, living arrangement, jail history of more than 24 hours), risk behavior variables (such as number of sexual partners in the past 30 days, sexual orientation, condom use, trading sex for money or drugs in past 30 days), sexually transmitted diseases history, and classes of drug use (drug use subgroups defined by latent class analysis).

Power estimation

For latent class analysis no formal approach has been taken so far; however, several useful statistics were used to evaluate the fitting of the model.

For logistic regression, assuming a sample size of 110 participants and a two-sided test with 0.05 significant level, a minimal detectable odds ratio was 3.8 to obtain a power of at least 80%, for overall HCV prevalence is 17% and assuming 5%-15% in unexposed group and 20%-35% in exposed group (Table 2). This power estimation was calculated by using OpenEpi software. [69]

Table 2 Study power ($1-\beta$) estimation given sample size of 118, significant level of 0.05 and different HCV prevalence in exposed/unexposed groups for specific aim 2.

HCV prevalence in unexposed	HCV prevalence in exposed			
	20%	25%	30%	35%
	$1-\beta$ (OR)	$1-\beta$ (OR)	$1-\beta$ (OR)	$1-\beta$ (OR)
5%	0.7 (4.7)	0.8 (6.3)	0.9 (8.1)	1.0 (10.2)
10%	0.3 (2.2)	0.5 (3.0)	0.8 (3.8)	0.9 (4.8)
15%	0.1 (1.4)	0.3 (1.8)	0.5 (2.4)	0.7 (3.0)

Statistical analysis

Descriptive statistics was used to demonstrate the characteristics of the study sample. Latent class analysis was used to examine the subgroups of drug use (Figure 3). Drug use indicator variables were used in the LCA model. Starting with a one class model and increasing the number of classes, a series maxima were reached. Multiple model fit statistics were used to determine the best-fitting, most parsimonious model, including the chi-square value, Bayesian information criteria (BIC), LMR and so on.

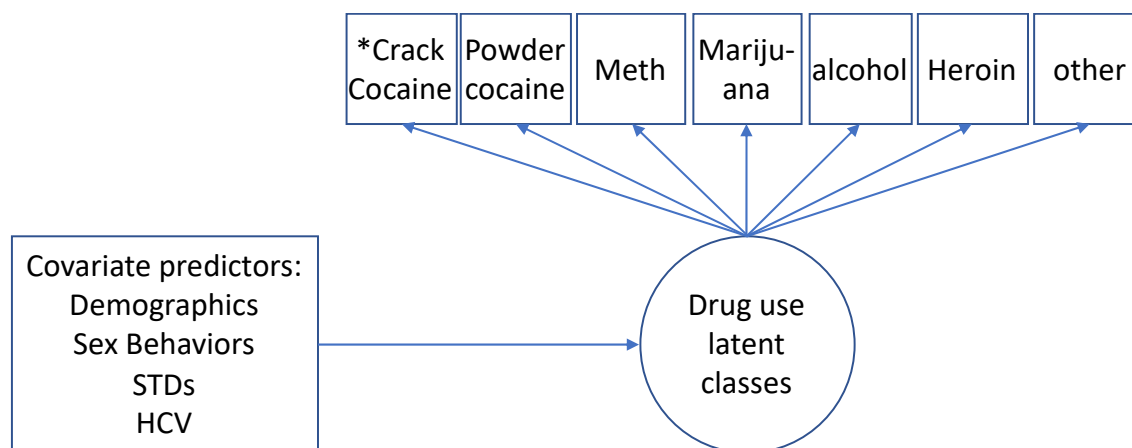


Figure 3. Latent class model of drug use among MSM with covariate predictors

* The reply for the question: “Have you ever used this drug?”

After deciding on the appropriate number of classes that best fit the data, multi-nominal logistic regression was used to explore the characteristics of drug use subgroups and the association between classes (different subgroups of drug use) and demographical, behavioral, HCV status variables. A final multivariable model was constructed by first using all variables significant at $p < 0.25$ in bivariable analysis as full model, then backward elimination was used to reach the final model. In addition, multivariable logistic regression was used to examine characteristics of individual associated with HCV infection, controlling for drug use subgroups. A final multivariable model was constructed by first using all variables significant at $p < 0.25$ in bivariable analysis as full model, then backward elimination was used to reach the final model.

The statistical significance level was 5%. Mplus 6.1 (Muthén & Muthén, CA) was used to conduct the LCA model building. SAS 9.4 (Cary, NC) was used to manage the data and build multi-nominal and multivariable logistic regression.

METHODS FOR SPECIFIC AIM 3

Study design and study population

This study was a cross-sectional network study. The study sample was a subset of YMAP baseline data restricted to participants who report never having injected drugs, collected from December 2014 to December 2015 in Houston. A total of 366 participants in YMAP were selected into this study.

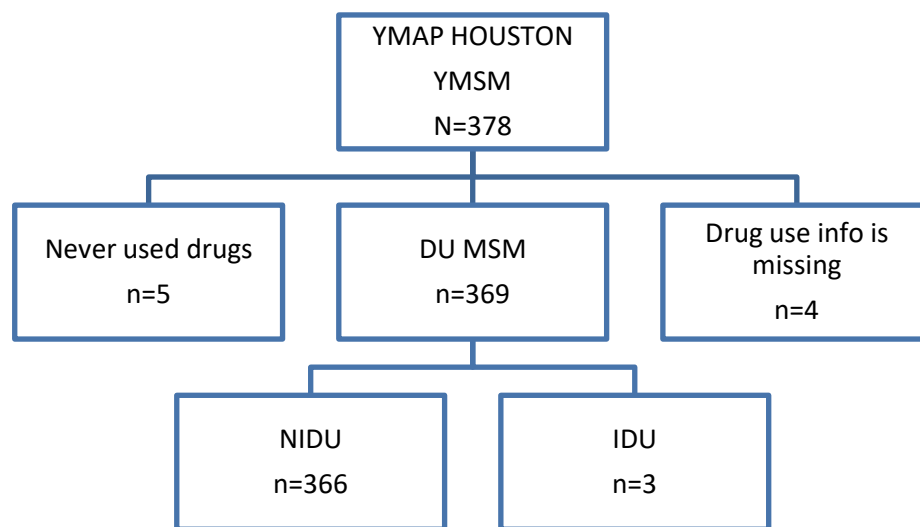


Figure 4. Study population for specific aim 3

Measures

Dependent variable was HCV status, which was defined as the existence of HCV antibody or not.

Independent variables included two sets, respondent's measures and sexual network dyad measures. For respondent's measures, demographic information (such as age,

race, education level, living arrangement, and jail history for more than 24 hours) was used. For sexual network dyad measures, all these data were treated as clustered data on respondent, including sexual ties (determined by asking respondents to nominate up to five people with whom they had sex within the past six months), and their behavioral measures (such as main/casual relationship, frequency of condom use, whether used drugs before sex, HIV status of both respondent and sex partner, and syphilis status of both respondent and sex partner).

Statistical analysis

The unit of analysis was the dyad, which was the pair of respondent and his nominated sexual partner.

Chi-square test was used to assess the relationship between baseline respondents' and their sexual partners' characteristics, such as age, race/ethnicity, sexual orientation, and HIV status.

Homophily was defined of the following variable, age homophily (evaluated by the absolute value of age difference between a respondent and his nominated sex partner), race/ethnicity homophily (evaluated by dichotomy scale: same/discordant), HIV serostatus homophily (evaluated as 1= respondent HIV seropositivity and respondent's perception about sex partner's positivity, 2=respondent HIV seropositive and respondent's perception about sex partner negative, 3=respondent HIV seropositivity and respondent's perception about sex partner's unknown, 4=respondent HIV seronegative and respondent's perception about sex partner positive, 5=respondent HIV seronegative and respondent's perception about sex partner negative, 6=respondent

HIV seronegative and respondent's perception about sex partner unknown).

Generalized Estimating Equations model (GEE) model, which can justify cluster observation of respondents [74] was used to conduct bivariate and multivariable analysis. Bivariate analyses were conducted between HCV status and each independent variable using crude odds ratio (cOR) and 95% confidence intervals. Multivariable GEE model was conducted to statistically test if there is an association between HCV infection status and the dyadic network measures. The statistical significance level was 5%. SAS 9.4 (Cary, NC) was used to manage the data and conduct the GEE analysis.

JOURNAL ARTICLE

Article I: Hepatitis C infection and its associated risk factors in men who have sex with men who reported non-injection use of drugs

This article has been formatted for the *Journal of Viral Hepatitis*

ABSTRACT

Background: Hepatitis C virus infection is more prevalent among high risk populations in the U.S. We assessed risk factors for HCV infection among men who have sex with men (MSM) who acknowledged drug use but not injection drug use. **Methods:** The DASH project, a community-based study in Houston, Texas, collected data from people who reported injection or non-injection use of drugs (drug use was defined as self-reported use of marijuana, alcohol, methamphetamines, cocaine, heroin, uppers, downers in the past 7 days and confirmed by urine test) collected in 2004-2007. Our analysis focused on the MSM who reported drug use but no injection drug use. Exact logistic regression was used to determine demographic characteristics, sexual risk behaviors and sexually transmitted disease history associated with HCV infection.

Results: Among 273 MSM, the HCV prevalence was 14.7%. Only age was significantly associated with HCV infection. Compared to participants aged 19-41, those aged 42-74 had 2.1 times the odds of having HCV infection (95%CI: 1.4-3.0). HIV status and sexual risk behaviors such as unprotected intercourse, multiple sex partners, and trading sex for money or drugs were not significantly associated with increased HCV infection.

Conclusion: MSM ages 42 years old and above were at greater risk for HCV infection than other age groups among MSM who reported drug use but no injection drug use.

Sexual risk behaviors were not identified as a risk factor of HCV infection. We call for health education about HCV infection to increase awareness of HCV testing and treatment in this subpopulation of MSM who reported drug use but no injection drug use.

INTRODUCTION

Hepatitis C virus (HCV) infection affects primarily the liver and causes acute and chronic hepatitis with a high propensity for chronicity[1]. It is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation in the United States[2]. In the United States, it is estimated that 3.5 million people are living with HCV infection, which accounts for about 1% of the population[3]. Studies shows the HCV prevalence is higher in some risk populations such as people who use drugs [4, 5] and HIV-positive men who have sex with men (MSM) [6]. HCV prevalence among IDU is reported as 70% and among NIDU 17.9%. [7] HCV prevalence among IDU is reported as 70% and among NIDU 17.9%. [7] However, the rate of access to diagnosis and treatment is low; of the people living with HCV globally, 20% knew their diagnosis, and only 7.4% of the diagnosed were started on treatment [8]. In addition, current treatment rates and efficacy are inadequate to manage the disease burden caused by HCV [9]; thus, efforts are needed to reduce HCV transmission.

Besides health-care-associated transmission and transmission through injecting drugs, other transmission routes, such as sexual transmission, sharing equipment of non-injection drug use, are not conclusive. HCV was found to be transmitted by sexual contact, especially among HIV-positive MSM [10-14], but for HIV-negative MSM, sexual contact might not increase the risk of HCV infection [15, 16]. Transmission by sharing

drug use equipment for non-injection drug use has also been reported but with mixed results [17-22]. One systematic review, however, reported that the HCV prevalence ranged from 2.3% to 35.3% in the population who reported drug use but no injection drug use and was higher than the prevalence in the population who did not use drugs[5].

For MSM and drug-using behavior, MSM were found to have a higher drug use prevalence than in the general population [23, 24], which might contribute to HCV infection by sexual disinhibition and other risky behaviors. One systematic review and meta-analysis, which targeted only HIV-positive MSM, reported that the pooled HCV prevalence was 6.7% among NIDU, and the prevalence was increasing over time [6].

Previous studies on risk factors associated with HCV infection focused mainly on HIV-positive MSM and/or MSM who reported injection drug use, so studies are needed that target MSM who reported drug use but no injection drug use. This study estimated HCV prevalence and examined risk factors associated with HCV infection among MSM who reported drug use but no injection drug use in Houston, TX. The hypothesis of this study was that sexual risk behaviors were significantly associated with HCV infection in MSM who reported drug use but no injection drug use. These results may provide a profile of subgroups with a higher HCV transmission possibility among MSM who reported drug use but no injection drug use. In the long term, the results of the study may guide the development of healthcare and behavior intervention programs related to HCV infection, providing better informed and more effective HCV prevention.

METHODS

Study set and participant sampling

Data were obtained from the Drugs, AIDS, STDs and Hepatitis (DASH) project, which was a community-based intervention study for HIV, HBV, and HCV prevention among a drug-using population [25]. The project screened 2,800 individuals with injection and non-injection use of drugs from February 2004 to October 2007 in two inner-city neighborhood communities in Houston, TX. Participants were recruited by using outreach and chain referral method. The eligibility criteria included in the screening process were: (1) 18 years old or above; (2) self-reported living in Houston; (3) self-reported use of illegal and non-medical prescribed drugs, including cocaine or heroin in the last 48 hours and confirmed presence of drug metabolites by urinalysis (OnTrak Varian Testik, Palo Alto, CA.); (4) willingness to sign the informed consent form for HIV, HBV, and HCV testing.

Data collection

Every individual completed an initial screening interview, which constituted a verbally administered questionnaire via computer-assisted personal interview (CAPI, QDS, Bethesda, MD) to obtain socio-demographic information (such as age, gender, race/ethnicity, sexual orientation, living arrangement, and jail history of more than 24 hours); history of drug use for drugs including marijuana, alcohol, methamphetamine, heroin, cocaine, uppers and downers (such as types and frequency of drugs used in the past 48 hours and 7 days, and lifetime injection drug use); sexual behaviors (such as number of sexual partners in the past 30 days, frequency of condom use, and trading sex for money or drugs in past 30 days); history of sexually transmitted diseases (such

as gonorrhea, herpes, chlamydia, and trichomoniasis); blood transfusion and occupational exposure to blood.

All serum specimens obtained from screened individuals were tested for HIV1/2 antibodies, HBsAg and HCV antibody infection using Core Combo HIV-HBsAg-HCV (Core Diagnostics, United Kingdom). Verification of HIV was conducted by enzyme immunoassay (EIA), using Abbott PPC Commander system, third generation HIV antibody test (Abbott Laboratories, Chicago, IL). Verification of HCV, anti-HBs, and anti-HBc was conducted by Abbott AxSYM system, using microparticle enzyme immunoassay (MEIA) (Abbott Laboratories, Chicago, IL).

Definition of HCV infection was the presence of antibody to HCV. HIV infection was defined as repeatedly reactive results by EIA. Case definition of HBV was the detection of anti-HBs or HBsAg or anti-HBc.

Statistical analysis

Univariable analyses were conducted for each socio-demographic characteristic, sexual risk behavioral and biological variable. Numbers and percentages were calculated for categorical variables, while medians and interquartile ranges (IQR) were computed for continuous variables. Chi-square or Fisher exact tests were used to test the difference of HCV status among different categories of each independent variable. Then, exact logistic regression analyses were performed for bivariable analysis to statistically test the association between each independent variable and HCV status, and odds ratio (cOR) and 95% confidence interval with p-values were obtained. Interaction terms were evaluated in the model. The statistical significance level was set at 5%. Hosmer-

Lemeshow goodness of fit test was used to test the fit of the final model. SAS 9.4 was used to manage and analyze the data (Cary, NC).

RESULTS

There were 273 MSM who reported drug use but no injection drug use in this study; of these, 14.7% were infected with HCV (Table 1). Age of the sample ranged from 19 to 74 years old, with the mean age of 39.6 years old (IQR: 35-46), 85% were African American, 61% were homeless at least once, 25% were currently living on the street, and 66% reported their sexual orientation as bisexual. About one third of the participants had traded sex for money, half had traded sex for drugs, and one third never used condoms while having sex. A total of 77% had been in jail, 49% had been diagnosed with a sexual transmitted disease, and 19% were HIV positive. The majority of the study participants had used crack cocaine (98%), alcohol (83%) and marijuana (58%) in the last 7 days. The demographic, socio-behavioral, and 7-day drug use profiles stratified by HCV status are presented in table 1.

Of the demographic, socio-behavioral, and drug use variables, only age was observed to have significant association with HCV status. Compared to the 19-41 year age group (HCV prevalence 7.1%), and the 42-74 year age group (24.6%) had more than 2 times the odds of having HCV infection (OR = 2.1, 95%CI: 1.4-3.0) (Table 2).

Being Caucasian, currently homeless, of straight sexual orientation, having a blood transfusion history, occupational blood exposure history, or being HIV positive was associated with increased HCV infection, but none of these associations were

statistically significant at the 5% level. No significant difference in HCV infection was discovered in any kind of drug use in the last 7 days.

Interaction terms were examined in the multivariable model, but none of them were significant at the 5% level. Only age was retained in the multivariable logistic regression model after backward selection. Also, the association between age and HCV infection did not change more than or equal to 15% when any other variables were entered in the model. The final model included only age as a predictor of HCV infection.

DISCUSSION

We found that the overall HCV prevalence in MSM who reported drug use but no injection drug use was relatively high, and only age was significantly associated with HCV infection, specifically among MSM ages 42 years old and above, who had the highest risk of HCV infection compared with the younger age group. In addition, sexual risk behavior and HIV infection were not significantly associated with HCV infection.

Overall, the HCV prevalence was 14.7% in these MSM who reported drug use but no injection drug use. The result was comparable to an average of 14.0% HCV infection in the general population who reported non-injection drug use, reported in a systematic review of 28 studies [5], but higher than the HCV prevalence in the general MSM population (2.8%), reported in a large community-based study in New York [27]. The prevalence was also higher than that among HIV-positive MSM (8.1%), described in a systematic review and meta-analysis of 42 studies [28]. These comparisons may suggest that, although it could not be explicitly determined, the behavior of non-injection

drug use outweighed the behavior of MSM with regard to HCV infection among these MSM who reported drug use but no injection drug use.

Age was the only factor that was significantly associated with HCV infection. Among MSM ages 45 years and older, the HCV prevalence was 27%, 8 times more likely to have HCV infection than the youngest age group (19-35 years old). This result was consistent with previous studies which demonstrated people born during 1945-1965, known as baby boomers, had the highest possibility of HCV infection compared with other generations [29]. Moreover, the baby boomers in our study had much higher HCV prevalence than general baby boomers, whose HCV prevalence was estimated to be 3.3% [30], indicating a high HCV disease burden in the subpopulation of the baby boomer generation who are MSM and report drug use but no injection drug use.

For the possible transmission route of HCV, our study findings did not support our hypothesis that sexual risk behaviors, including unprotected intercourse, multiple sex partners, and trading sex for money or drugs, significantly increased the risk of HCV infection. This result was consistent with that Joy et al. [31] who suggest the reuse of glass and metal syringes in medical practice dating back to 1940 to 1960 was associated with the highest expansion of HCV infection in the generation of baby boomer. Importantly, Joy et al. used molecular-clock approaches and reconstructed the epidemiology of HCV in North America, destigmatizing the baby boomers with nosocomial activity as the main contributor to HCV epidemic in North America, rather than risky sex and injection drug use behavior [31].

It is worth noting that HIV infection did not significantly increase the risk of HCV infection, which contrasts with the increasing reports of an HCV epidemic or outbreak in HIV-positive MSM in Europe, Australia, and North America since 2000 [10-14]. The possible reason was that the HCV infection rate was also high in HIV-negative participants in the present study, which raised the bar that detected the effect of HIV co-infection on promoting HCV transmission in this study. Another possible reason was that the HIV and HCV epidemics have unrelated transmission dynamics in this population, which was also reported in one study in Hong Kong [32]. To confirm the transmission dynamics, investigation of social and sexual networks combined with phylogenetic approaches may help unveil the transmission pattern of the two viruses.

Regarding types of drug use, none of them showed association with HCV infection. The reason was likely that only the last 7-day drug use information was collected in this screening investigation, which may not relate to chronic HCV infection. Information on detailed drug use history may help explain the relationship between drug use types and HCV infection. In addition, increased risk of HCV infection related to sharing implements for smoking or snorting drugs, as well as sharing non-injection drugs, should be evaluated, although some studies show no association between sharing implements or non-injection drugs with HCV infection [17-20], other studies have reported opposite results [21, 22].

Strengths of the study, besides the relatively large sample size, include that HCV and HIV status were confirmed by laboratory test in this project, not self-report, which greatly reduced misclassification. In addition, the use of drugs was confirmed by urine test, not self-report, which reduced information bias. However, there were several limitations in

this study. First, information collected in these screening data did not include some specific kinds of drug preferred by MSM in recent years, for example, sex/club drugs (ketamine, MDMA, LSD, and erectile dysfunction drugs). In addition, several sexual risk behaviors specific to MSM were not examined, such as frequency of receptive anal intercourse, or experience of mucosal trauma during sex. Furthermore, as mentioned above, sharing equipment for non-injection drug use was not investigated in this study, which might also be a transmission path of HCV infection. Last but not least, most of the participants were African American, which limited the generalizability of the results in this study to other racial/ethnic populations. Further study is warranted specifically among MSM who report drug use but no injection drug use, with greater racial/ethnic diversity, to more fully examine risk factors related to HCV infection.

In conclusion, individuals aged 45 years old and above had the highest risk of HCV infection among MSM who reported drug use but no injection drug use; sexual risk behaviors were not identified as a risk factor of HCV infection. For the baby boomer generation, the HCV testing rate was very low (<14%) [33]. Two factors, non-injection drug use and male-to-male sexual behavior, may marginalize this subpopulation in the baby boomer generation, possibly leading to an even lower testing rate. Health education should be promoted in this subgroup to enhance the awareness of HCV infection and increase HCV testing rates. We also call for regulating HCV testing in medical systems that care for this subpopulation, and for the promotion of treatment in HCV infected individuals to attenuate the disease burden.

Funding

This study was funded by The National Institute of Drug Abuse (NIDA# 1R01DA017505).

Table 1 Characteristics and HCV infection among MSM who reported drug use but no injection drug use in two inner city communities in Houston, TX (N=273)

Characteristics	Total	HCV+	HCV-	Chi-square P-value
Age (year)				<0.001
19-41	155 (56.8)	11 (7.1)	144 (92.9)	
42-74	118 (43.2)	29 (24.6)	89 (75.4)	
Race				0.478*
Caucasian	34 (12.5)	7 (20.6)	27 (79.4)	
Hispanic	8 (2.9)	1 (12.5)	7 (87.5)	
African American	231 (84.6)	32 (13.9)	199 (86.1)	
Homeless				0.643
Yes	107 (39.2)	17 (15.9)	90 (84.1)	
No	166 (60.8)	23 (13.9)	143 (86.1)	
Homeless (currently live on street)				0.229
Yes	68 (24.9)	13 (19.1)	55 (80.9)	
No	205 (75.1)	27 (13.2)	178 (86.8)	
Frequency of using condom				0.433
None	97 (35.5)	15 (15.5)	82 (84.5)	
Some	143 (52.4)	18 (12.6)	125 (87.4)	
All	33 (12.1)	7 (21.2)	26 (78.8)	
Self-considered sex orientation				0.125
Gay	49 (17.9)	3 (6.1)	46 (93.9)	
Straight	44 (16.1)	9 (20.5)	35 (79.5)	
Bisexual	180 (65.9)	28 (15.6)	152 (84.4)	
No. of sex partners in past 4 weeks				0.139
0	57 (20.9)	11 (19.3)	46 (80.7)	
1-4	109 (40.0)	19 (17.4)	90 (82.6)	
>5	106 (38.8)	10 (9.4)	96 (90.6)	
Trade sex for money				0.133
Yes	99 (36.3)	9 (9.1)	90 (90.9)	
No	56 (20.5)	9 (16.1)	47 (83.9)	
Unknown	118 (43.2)	22 (18.6)	96 (81.4)	
Trade sex for drug				0.217

Characteristics	Total	HCV+	HCV-	Chi-square P-value
Yes	137 (50.2)	15 (10.9)	122 (89.1)	
No	107 (39.2)	20 (18.7)	87 (81.3)	
Unknown	29 (10.6)	5 (17.2)	24 (82.8)	
Blood transfusion				0.462*
Yes	14 (5.1)	3 (21.4)	11 (78.6)	
No	259 (94.9)	37 (14.3)	222 (85.7)	
Occupational exposure				0.285*
Yes	17 (6.2)	4 (23.5)	13 (76.5)	
No	256 (93.8)	36 (14.1)	220 (85.9)	
Ever in jail for 24 hours or more				0.973
Yes	211 (77.3)	31 (14.7)	180 (85.3)	
No	62 (22.7)	9 (14.5)	53 (85.5)	
Diagnosed sexual transmitted diseases				0.541
Yes	86 (31.5)	12 (14.0)	74 (86.0)	
No	91 (33.3)	11 (12.1)	80 (87.9)	
Unknown	96 (35.2)	17 (17.7)	79 (82.3)	
Diagnosed syphilis ever				0.877
Yes	32 (18.1)	5 (15.6)	27 (84.4)	
No	54 (30.5)	7 (13.0)	47 (87.0)	
Unknown	91 (51.4)	11 (12.1)	80 (87.9)	
HIV status**				0.565
Yes	52 (19.2)	9 (17.3)	43 (82.7)	
No	219 (80.8)	31 (14.2)	188 (85.8)	
Alcohol				0.614
Yes	226 (82.8)	32 (14.2)	194 (85.8)	
No	47 (17.2)	8 (17.0)	39 (83.0)	
Marijuana				0.958
Yes	158 (57.9)	23 (14.6)	135 (85.4)	
No	115 (42.1)	17 (14.8)	98 (85.2)	
Methamphetamines				0.594*
Yes	11 (4.0)	1 (9.1)	10 (90.9)	

Characteristics	Total	HCV+	HCV-	Chi-square P-value
No	262 (96.0)	39 (14.9)	223 (85.1)	
Cocaine				0.733*
Yes	268 (98.2)	39 (14.6)	229 (85.4)	
No	5 (1.8)	1 (20.0)	4 (80.0)	
Heroin				0.182*
Yes	10 (3.7)	0	10 (100.0)	
No	263 (96.3)	40 (15.2)	223 (84.8)	
Uppers				NA
No	273 (100.0)	40 (14.7)	233 (85.3)	
Downers**				0.471*
Yes	3 (1.1)	1 (33.3)	2 (66.7)	
No	269 (98.5)	39 (14.5)	230 (85.5)	

* Fisher exact test P-value

** Missing value: HIV status n=2, Downers n=1

Table 2 Results of univariable exact logistic regression of factors associated with HCV infection among MSM who reported drug use but no injection drug use in two inner-city communities in Houston, TX (n=273)

Characteristics	OR (95% CI)	P-value
Age (year)		
42-74	2.1 (1.4-3.0)	<0.001
19-41	Reference	
Race		
Caucasian	1.4 (0.6-3.3)	0.930
Hispanic	1.5 (NA)	0.776
African American	Reference	
Homeless		
Yes	1.1 (0.8-1.5)	0.767
No	Reference	
Homeless (currently live on street)		
Yes	1.2 (0.9-1.8)	0.315
No	Reference	
Frequency of using condom		
None	0.9 (0.6-1.5)	1.000
Some	0.7 (0.5-1.2)	0.355
All	Reference	
Self-considered sex orientation		
Gay	0.4 (0.2-1.0)	0.094
Straight	1.7 (0.9-3.2)	0.215
Bisexual	Reference	
No. of sex partners in past 4 weeks		
1-4	1.2 (0.8-1.9)	0.649
>5	0.6 (0.4-1.0)	0.085
0	Reference	
Trade sex for money		
Yes	0.6 (0.4-1.0)	0.124
Unknown	1.4 (0.9-2.2)	0.280
No	Reference	
Trade sex for drug		

Characteristics	OR (95% CI)	P-value
Yes	0.7 (0.4-1.1)	0.238
Unknown	1.1 (0.6-2.3)	1.000
No	Reference	
Blood transfusion		
Yes	1.3 (0.7-2.5)	0.674
No	Reference	
Occupational exposure		
Yes	1.4 (0.8-2.5)	0.452
No	Reference	
Ever in jail for 24 hours or more		
Yes	1.0 (0.7-1.5)	1.000
No	Reference	
Diagnosed sexual transmitted diseases		
Yes	1.0 (0.6-1.6)	1.000
Unknown	1.3 (0.8-2.0)	0.507
No	Reference	
Diagnosed syphilis ever		
Yes	1.2 (0.6-2.4)	1.000
Unknown	0.9 (0.5-1.5)	0.953
No	Reference	
HIV status		
Yes	1.1 (0.8-1.7)	0.700
No	Reference	
Alcohol		
Yes	0.9 (0.6-1.4)	0.756
No	Reference	
Marijuana		
Yes	1.0 (0.7-1.4)	1.000
No	Reference	
Methamphetamines		
Yes	0.8 (0.3-2.1)	1.000
No	Reference	

Characteristics	OR (95% CI)	P-value
Cocaine		
Yes	0.8 (0.3-2.5)	1.000
No	Reference	
Heroin		
Yes	0.6 (NA)	0.199
No	Reference	
Uppers		
No	0.6 (NA)	0.199
Downers		
Yes	1.7 (0.5-5.7)	0.761
No	Reference	

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Article II: The association between non-injection drug use and hepatitis C infection among HIV-negative men who have sex with men

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ABSTRACT

Objectives: This study investigated the association between drug use latent class and Hepatitis C Virus (HCV) infection in HIV-negative men who have sex with men (MSM) who reported drug use but not injection drug use. **Methods:** This cross-sectional study analyzed the data of 118 HIV-negative MSM who reported drug use but not injection drug use recruited from two inner-city communities between 2004 and 2007. Latent class analysis (LCA) was used to identify drug use latent classes. Multinomial logistic regression analysis was used to evaluate the association between drug use latent class and HCV infection. **Results:** Four distinct latent classes of drug use were identified: (1) persons ≥ 42 years old who used only crack cocaine, (2) persons about 42 years old who used >2 drugs, (3) persons <42 years old who used >5 drugs, and (4) persons ≥ 42 years old who used >6 drugs. Class 4, persons ≥ 42 years old who used >6 drugs were significantly associated with HCV infection. Compared with persons about 42 years old who used >2 drugs, persons ≥ 42 years old who used >6 drugs had more than 16 times the odds of having HCV infection (adjusted OR = 16.9, 95%CI: 1.4-205.4), and compared with persons <42 years old who used >5 drugs, persons ≥ 42 years old who used >6 drugs were about 22 times as likely to have HCV infection (adjusted OR=21.8, 95%CI: 1.5-322.8). **Conclusions:** The subgroup of MSM ≥ 42 years old with non-injection but multiple use of heroin, speedball, and

methamphetamine, in addition to crack cocaine and marijuana, had high probability of HCV infection. Public health and education programs, as well as drug treatment and rehabilitation programs, should be developed for this high-risk subgroup to prevent HCV acquisition and transmission.

INTRODUCTION

Compared with the general population, men who have sex with men (MSM) are disproportionately affected by infectious diseases, such as HIV, syphilis and other sexually transmitted infections (STI) (CDC, 2017). MSM may also be disproportionately affected by HCV. HCV infection, which is a leading cause of liver failure and transplantation in the United States (Razavi et al., 2013), has been relatively understudied in MSM until 2000, when reports of an HCV epidemic or outbreaks in MSM began to emerge (Bottieau, Apers, Van Esbroeck, Vandenbruaene, & Florence, 2010; Giraudon et al., 2008; Urbanus, van de Laar, et al., 2009; Urbanus, van Houdt, van de Laar, & Coutinho, 2009; van de Laar et al., 2007; Wandeler et al., 2012). Most of these studies focused on MSM who are HIV positive, MSM who inject drugs, or both. Studies targeting HIV-negative and non-injection drug using MSM are needed.

Although HCV prevalence rates are comparable in HIV-negative MSM and in the general U.S. population (Blaxhult, Samuelson, Ask, & Hökeberg, 2014; Price et al., 2013), people who use drugs but do not inject drugs have been found to have a higher HCV infection rate (2.3% to 35.3%) than in the general population (1%) (Scheinmann et al., 2007). Furthermore, MSM have been reported with a higher rate of drug use than in

heterosexual men (past month prevalence 16.3% vs 9.9%) (Cochran, Ackerman, Mays, & Ross, 2004). These results showed a higher HCV infection rate in HIV-negative MSM with non-injection drug use than in the general population.

People who use drugs are usually heterogeneous with regard to drug types, because drug types are various and one individual may choose multiple drug types at the same time or different times. Analyzing types of drug use independently may overlook the complexity of multiple drug use or result in lack of generalizability. To analyze the drug use variables simultaneously, we applied latent class analysis to identify subgroups of drug use (Carlson, Wang, Falck, & Siegal, 2005; Kuramoto, Bohnert, & Latkin, 2011; Monga et al., 2007; Sherman et al., 2009; Wittchen et al., 2009), and further explored the association between drug use subgroups and disease. In one US internet-based MSM sample, a distinct multiple drug use group was identified (McCarty-Caplan, Jantz, & Swartz, 2014). Another study recruited a similar sample of MSM and found that high multiple drug using MSM were more likely to report unprotected anal intercourse, and STIs (Yu, Wall, Chiasson, & Hirshfield, 2015). In a Malaysia Asia internet-based MSM sample, an amphetamine-type stimulant class was associated with sexual risk behavior and the infection of HIV and STIs, compared to a low-risk drug use group (Lim et al., 2015).

To the best of our knowledge, there are no studies of HCV infection targeting HIV-negative MSM with non-injection drug use. To fill this knowledge gap, this study applied LCA to identify latent classes among MSM who reported drug use not no injection drug use, and examined the association between latent classes and HCV infection in HIV-negative MSM. It was hypothesized that, first, there are distinct latent classes in the

target population, and, second, one or more latent classes are associated with HCV infection. The results of this study may provide insight for HCV prevention and health education programs targeted at HIV-negative MSM with non-injection drug use.

METHODS

Samples from DASH project

Data for the present study were collected from a cohort of people who used drugs enrolled in the Drugs, AIDS, STDs, and Hepatitis (DASH) project, a community-based intervention study among a non-treatment drug-using population for HIV, HBV, and HCV prevention (Hwang et al., 2010). The DASH project recruited individuals from two highly endemic drug-using urban neighborhoods in Houston, TX, from February 2004 to October 2007. Participants were recruited by outreach workers using a chain referral approach. People were eligible for the study if they were: 18 years old or above, had local residence, self-reported use of illegal and non-medical prescribed drugs including cocaine or heroin in the last 48 hours and confirmed presence of drug metabolites by urinalysis (OnTrak Varian Testik, Palo Alto, CA.), and willingness to sign the informed consent form for HIV, HBV, and HCV testing.

Individuals with negative HIV and HBV screening tests were enrolled into the baseline study. Enrollment interviews were conducted using verbally administered questionnaires via computer-assisted personal interview method (CAPI, QDS, Bethesda, MD). Baseline data were from the enrollment interview. All data collection procedures and laboratory protocols were approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston.

Data for this study were restricted to 118 participants who reported male-to-male sex and did not report any injection drug use. (See DASH study population flow chart figure 1)

Measures

For sociodemographic characteristics, information was collected on age, race/ethnicity, sexual orientation, education level, marital status, working status, income level, living arrangement, jail history of more than 24 hours, and drug treatment history. Sexual behavior variables included number of male sexual partners in the past 30 days, frequency of condom use, trading sex for money or drugs in the past 30 days, and trading money or drugs for sex in the past 30 days. Disease status comprised self-reported STI history for gonorrhea, herpes, chlamydia, and trichomoniasis, as well as HCV infection status, screened by HIV1/2 antibodies, HBsAg and HCV antibody Combo test (Core Diagnostics, United Kingdom), confirmed by Microparticle enzyme immunoassay test (Abbott Laboratories, Chicago, IL). HCV infection was defined as HCV antibody positive. Also, history of blood transfusion, and occupational exposure to blood was collected during the enrollment interview.

Drug use variables and age were used as latent class indicators. Drug use variables included the participants' response to the question, "Have you ever used the following drugs: crack cocaine, methamphetamine, marijuana, alcohol, fry¹, powder cocaine, heroin, speedball (a mixture of heroin and cocaine) and codeine syrup?" Drug use indicators were denoted as: "never use" (0) or "have ever used" (1). Also, age was

¹ Fry: embalming fluid and phencyclidine (PCP)-laced cigarettes or marijuana sticks

considered as an indicator variable because age has been associated with drug use types. (Bluthenthal, Wenger, Chu, Bourgois, & Kral, 2017; Golub, Johnson, & Dunlap, 2005) Based on a median age of 42, participants were categorized as “< 42 years old” (0) or “≥ 42 years old”.

Statistical analysis

We applied LCA to identify drug use latent classes among our MSM sample. An LCA model uses a maximum likelihood approach to identify subgroups or classes of individuals with similar patterns of responses to a set of indicator variables (A. L. McCutcheon, 1987; Whitesell et al., 2006). Based on indicator variables, LCA assigns each individual a probability of membership in the postulated multilevel latent variable (Allan L McCutcheon, 2002). LCA assumes homogeneity within a class, heterogeneity among classes, and that the difference in response to items within a class is only due to random error (A. L. McCutcheon, 1987; Whitesell et al., 2006).

We started with a 1-class model and increased the number of classes through 6-class models. To obtain the global not local maxima for each model, we used 5,000 random starts. We used BIC (the Bayesian Information Criteria), BLRT (the parametric bootstrap likelihood ratio test), and LMR (the Lo-Mendell-Rubin adjusted likelihood ratio test) to select the model. In addition, we used entropy, a standardized summary measure of the classification accuracy, to evaluate the precision of individual assignment based on their model-based posterior probabilities. Entropy ranges from 0 to 1, and the higher entropy value reflects the better classification (Ramaswamy, DeSarbo, Reibstein, & Robinson,

1993). We based our final latent class solution on not only statistical significance, but also substantive criteria, e.g., the epidemiological explanation of drug use.

After latent class identification, we conducted logistic regression models to examine the association between class membership and HCV status, sociodemographic characteristics, sexual behaviors, and sexual transmitted disease history. We used the AUXILIARY (r) option (Muthén & Muthén, 2012) for the multinomial logistic regression estimation. This technique incorporates the posterior-probabilities of membership into the estimation procedure, and helps examine the fidelity and utility of the specific latent class profiles (Petrus & Masyn, 2010). We conducted bivariate associations of latent class of drug use with each independent variable. Independent variables with a P-value less than 0.25 were entered into the joint model, which allowed us to evaluate the adjusted relationships between membership in a particular drug use class and HCV infection. We used Mplus 6.1 (Muthén & Muthén, CA) to conduct the LCA model building and multi-nominal and multivariable logistic regression and SAS 9.4 (Cary, NC) to manage the data.

RESULTS

In the DASH parental project study, the prevalence of HCV was 36.1% among 2,800 who used drugs and were contacted for HIV/HBV/HCV screening. The predominant risk characteristic associated with HCV infection was injection drug use (70% prevalence). (Hwang & Grimes, 2012). Among 273 MSM who reported drug use not including injection drug use, the HCV prevalence was 14.7%. Only age was significantly associated with HCV infection. Compared to participants who were less than 42 years

old, those age 42 or older had 2.1 times the odds of having HCV infection (95%CI: 1.4-3.0).

Among 273 MSM who reported drug use not including injection drug use, we analyzed 118 MSM who participated in the baseline interview, among whom 21 (17.8%) were infected with HCV. Table 1 presents the sociodemographic characteristics and behavioral variables for the analytical sample. For sociodemographic characteristics, the age of the participants ranged from 19 to 61 years old with the mean of 39.6 years old (IQR: 35-46), 83% were African American, 83% reported sexual orientation as bisexual or homosexual, 76% had less than a high school education or completed high school only, 65% were single, 50% worked less than 14 days in the past month, 50% had an income less than 400 dollars in the past month, 46% had been homeless at least once, 76% had been arrested and spent more than 24 hours in jail, and 35% never received drug treatment. For sexual risk behaviors, 41% of the participants had 0 or 1 male sexual partners in the past month, about two thirds of them used condoms less than half of the time while having sex, about two thirds of the participants had traded sex for money or drugs in the past month, more than half had traded money for drugs or sex in the past month. Regarding disease history, 45% had been diagnosed with STIs. Regarding drug use behavior, the majority of participants had used multiple drugs (defined as had ever used more than 2 drugs), and the most prevalent drug types were crack cocaine (98%), marijuana (89%), and alcohol (86%). The prevalence of other types of drug use were 57% for powder cocaine, 22% for codeine, 21% for fry, 14% for methamphetamine, 6.8% for heroin, and 3.4% for speedball.

For LCA, Table 2 presents the results of statistics and entropy for 1- through 6- latent classes. Although the BIC value was the lowest at the 2-class model solution, LMR supported for all 2- through 5- class model (p-value <0.05) and BLRT supported for 2- through 4- class model. Entropy showed that all 3- through 6- class models had satisfied precision (entropy >0.8). Therefore, both 3- and 4- class models were preferable. Based on statistical significance and practical utility, we selected the 4-class model as the best fit model.

Figure 2 shows the estimated probability of the 4-class model. Participants in class 1, accounted for 6.5% of the sample, had high probability (>95%) of using only crack cocaine and the lowest probability of using all other types of drugs, with 75% probability of being 42 years old or above. We referred to class 1 as *“persons ≥42 years old who used only cocaine”*. Class 2 members accounted for 70.3% of the sample, had high probability (>90%) of using crack cocaine, marijuana, and had moderate probability (50%) of using powder cocaine, with a half of the probability of being 42 years old or above. We referred to class 2 as *“persons about 42 years old who used >2 drugs”*. Class 3 members accounted for 20.1% of the participants, had high probability (>90%) of using crack cocaine, marijuana, powder cocaine, and especially compared with all other classes, class 3 members had the highest probability of using fry and codeine; the probability of being 42 years old or above was only 35%. We referred to class 3 as *“persons <42 years old who used >5 drugs”*. Individuals in class 4 accounted for 3.2% of the sample, had high probability of using all types of drugs except for fry and codeine, specifically, the probability of using methamphetamine, heroin, and speedball were the highest among individuals in class 4 compared to all other classes, and the probability

of being 42 years old or above were very high (>99%). We referred to class 4 as *“persons ≥ 42 years old who used >6 drugs”*.

Table 3 presents the results of our bivariate multinomial logistic regression. We found that only HCV status was significantly associated with drug use latent classes.

Compared with the members in other classes, class 4 members had the highest possibility of having HCV infection. The odds of having HCV infection among class 4 members was 14 times (OR=14.2, 95%CI: 1.3-157.4) the odds of having HCV infection among those who in class 2, and was 20 times (crude OR=20.5, 95%CI: 1.4-291.7) the odds of having HCV infection among those who in class 3. The probability of having HCV also showed higher in class 4 members than class 1 members, but the results was not statistically significant (crude OR=7.8, 95%CI: 0.5-134.7). For the associations between drug use classes with other variables, such as sociodemographic characteristics, sexual behaviors, self-reported STI history, blood transfusion history, and occupational blood exposure history, all the results were not statistically significant.

Table 4 presents the results of our multivariable regression model. We entered drug treatment history, self-reported STI history and trading money or drugs for sex in the past month in the model (these variables had p-values<0.25 in the bivariate analysis) to adjust for the association between drug use class and HCV infection. The results showed that HCV infection status was significantly associated with drug use classes. Compared with class 2 members, class 4 members had close to 17 times the odds of having HCV infection (adjusted OR = 16.9, 95%CI: 1.4-205.4), and compared with class 3 members, class 4 members had close to 22 times the odds of having HCV infection

(adjusted OR=21.8, 95%CI: 1.5-322.8), controlling for drug treatment history, self-reported STI history and trading money or drugs for sex in the past month.

DISCUSSION

In this study, we applied LCA to identify latent classes among MSM who reported drug use but did not report injection use of drugs. We found four distinct latent classes, which were class 1, persons ≥ 42 years old who used only crack cocaine; class 2, persons about 42 years old who used >2 drugs; class 3, persons <42 years old who used >5 drugs; and class 4, persons ≥ 42 years old who used >6 drugs. We also found associations between certain latent classes of drug use and HCV infection. After adjusting for drug treatment history, self-reported STI history, and behavior of trading money or drugs for sex in the past month, we found that persons ≥ 42 years old who used >6 drugs had close to 17 times the odds of having HCV infection, compared with persons about 42 years old who used >2 drugs, and close to 22 times the odds of having HCV infection, compared with persons <42 years old who used >5 drugs.

Among participants who were 42 years old or above, the membership of drug use latent class was polarized. Members in one class (class 1) only used crack cocaine, whereas members in the other class (class 4) used multiple drugs, including crack cocaine, marijuana, powder cocaine, methamphetamine, heroin, and speedball. The members in class 4 had a higher HCV infection probability than those who were in class 1, but the difference was not statistically significant. However, we need to interpret this non-significant result cautiously, because the sample sizes in the two classes accounted for only 3.2% and 6.5% of the sample, respectively, which limited the statistical power of

the study to detect the differences in HCV infection probabilities between these two classes.

The mean age for the class 3 members was slightly lower than that for the class 2 members. The class 3 members had higher probability of using fry and codeine than the class 2 members, which is consistent with previous reports in the 1990s of fry (Modesto-Lowe & Petry, 2001; Peters Jr et al., 2005) and codeine abuse (Elwood, 2001; Peters Jr et al., 2007), especially among teenagers. The results of the present study showed that compared with participants who used crack cocaine and marijuana, those who additionally used fry and codeine did not have a higher probability of HCV infection. One reason may be that people normally take fry by smoking it and codeine in the form of syrup, pill, or drinks (mixed with soda). All these administrative routes have a lower likelihood of blood exposure that may lead to HCV infection and transmission. However, studies have reported an increase of sexual risk behavior among people who use of fry or codeine (Peters Jr et al., 2007), but these studies were not restricted to MSM. The present study, which was restricted to MSM, found that the use of fry or codeine were not associated with sexual risk behaviors.

By comparing latent classes of drug use with different ages, we found an interaction effect between age and drug use types on the probability of HCV infection. This finding indicates that age and drug use types were both associated with HCV infection, and that differences in age were linked to different preference of drug use types. The participants who had multiple use of heroin, speedball, and methamphetamine, in addition to the commonly used crack cocaine and marijuana, were all 42 years old or above, which formed a latent class that had a much higher HCV infection probability than that of other

latent classes. On the one hand, some previous studies revealed that individuals born between 1945-1965 had a higher HCV infection rate than that of other individuals; conversely, other previous studies implied that the use of heroin, speedball, and methamphetamine may relate to HCV infection from several perspectives. First, repeated intranasal use of heroin, cocaine (speedball is heroin mixed with cocaine), and methamphetamine may cause mucosal trauma and hyperemia (Bakhshaei, Khadivi, Sadr, & Esmatinia, 2013; Blaise, Vanhootehem, & De La Brassinne, 2007; Peyrière et al., 2013; Trimarchi et al., 2006), and HCV has been detected in nasal secretions (Aaron et al., 2008) in people with HCV infection. Second, drug use paraphernalia are often shared among people who use drugs, and HCV RNA may remain in the paraphernalia for up to 16 hours (Kamili, Krawczynski, McCaustland, Li, & Alter, 2007). Third, people who use heroin, speedball, and methamphetamine may be exposed to social networks with a higher HCV infection rate than those who use other drugs, because a proportion of people who use heroin, speedball, and methamphetamine inject these drugs, and 40%-90% of people who inject drugs are infected with HCV (Gerberding, 1994; Hagan, Pouget, Des Jarlais, & Lelutiu-Weinberger, 2008). However, some studies have not found that sharing straws or dollar bills when snorting drugs among people who do not report injection drug use is associated with HCV infection (Gyarmathy, Neaigus, Miller, Friedman, & Jarlais, 2002; Howe et al., 2005). More research is needed to determine whether sharing equipment for non-injection drug use is a transmission route of HCV or not.

We cannot directly compare the present LCA findings with those of previous LCA findings because of different recruitment strategies, indicator variables, and the disease

of interest. However, our findings are consistent with other findings demonstrating high rates of infectious diseases, such as HIV, among people who used multiple drugs (Buchacz et al., 2000; Chitwood, Comerford, & Sanchez, 2003; Drumright & Colfax, 2009; Vallejo et al., 2008). LCA studies in MSM have demonstrated that multiple drug use is also associated with increased transmission of STIs by disinhibiting sexual risk behavior (Lim et al., 2015; Yu et al., 2015); the present study did not find an association between multiple drug use and STIs. One reason of this lack of association may be that individuals with HIV and/or HBV infection were excluded from the baseline data of DASH project, which may in turn, lead to the exclusion of individuals also coinfecting with STIs; thus, underestimating the effect of multiple drug use on STIs or risky sexual behavior in our sample of MSM.

This study had some limitations. First, we had small sample size for some drug use subgroups identified by LCA. During analysis, we tested multiple combinations of different variable classifications, and only the reported subgroup solution showed a significant association with HCV infection. However, although it was statistically significant, it also had very large confidence intervals for the significant results; thus, we must interpret the results with caution. Second, for some variables assessing sexual risk behaviors, this study might not have sufficient power to identify their effects on HCV transmission. Third, the route of drug use, and information regarding sharing equipment for drug use were not collected in this study, which may provide crucial information on HCV transmission route in this population (Tortu, McMahon, Pouget, & Hamid, 2004). Fourth, although drug use was verified by lab testing, drug use types and sexual risk behaviors were self-reported, which may have led to underreporting. Fifth, the cross-

sectional study design may not confirm the temporality of the risk behaviors and HCV infection. Lastly, some information potentially related to sexual transmission of HCV was not collected in this study, e.g., drugs related to sex (MDMA, LSD, etc.), and sexual behaviors such as anal sex and group sex. Future studies are warranted with larger sample size, collecting additional information on administrative routes of drug use, sex-related drugs, and detailed sexual risk behaviors of MSM. Further, a longitudinal study design may help clarify the temporality of risk behaviors and HCV infection and explore the transition between drug use subgroups, which may provide insightful understanding of association between drug use behavior and the risk of HCV infection.

Despite these limitations, this study has several strengths. To the best of our knowledge, this is the first study to evaluate the association of latent class of non-injection drug use and HCV infection among HIV-negative MSM by using latent class analysis. Because LCA reduced the dimension of drug use types, this study discovered and evaluated the interaction effect between age and multiple drug use types on HCV infection, which very few studies have reported. In addition, this study excluded individuals with HIV and/or HBV infection; thus, although it led to a smaller sample size for this study, we demonstrated that in the absence of HIV and HBV, there was still a strong association between the interaction of age and multiple drug use types on HCV infection.

In conclusion, we found four distinct latent classes of drug use among MSM: (1) persons ≥ 42 years old who used only crack cocaine, (2) persons about 42 years old who used >2 drugs, (3) persons <42 years old who used >5 drugs, and (4) persons ≥ 42 years old who used >6 drugs. Persons ≥ 42 years old who used >6 drugs was

associated with increased probability of HCV infection. Health education and promotion programs geared towards this subgroup of MSM are needed to increase the awareness of HCV infection, and subsequently increase testing and treatment rates for HCV. Furthermore, drug treatment programs or rehabilitation programs are also needed to reduce the physical damage of multiple drug use and the probability of acquiring or transmitting HCV, especially among heavy multiple drug use MSM.

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Table 1 Characteristics of 118 HIV-negative MSM who reported drug use but did not report injection drug use in Houston, TX

Characteristics	n	%
Latent class indicators ^a		
Crack cocaine	116	98.3
Methamphetamine	17	14.4
Marijuana	105	89.0
Alcohol	101	85.6
Fry	25	21.2
Powder cocaine	67	56.8
Heroin	8	6.8
Speedball	4	3.4
Codeine	26	22.0
42 years old or above	59	50
Sociodemographic characteristics		
African American	98	83.1
Self-reported homosexual or bisexual	98	83.1
Education level (less than or equal to high school)	90	76.3
Marital status (single)	77	65.3
Worked less than 14 days in past 30 days	58	49.2
Income less than 400 dollars in the past month	70	59.3
Homeless	54	45.8
Had been in jail for more than 24 hours	90	76.3
Never received drug treatment	41	34.7
Sexual behaviors		
Had 0 or 1 male sexual partner in the past month	48	40.7
Condom use frequency (<=50%)	71	60.7
Traded sex for money or drugs in the past month	74	62.7
Traded money or drugs for sex in the past month	68	57.6
Diseases status		
Had sexual transmitted disease history	53	44.9
Blood exposure		
Had blood transfusion history	4	3.4
Had occupational blood exposure history	7	5.9

^a These variables refer to the response to the question: "have you ever used this drug"

Table 2 Statistics and entropy of latent class analyses

classes	LL ^a	Free parameters	BIC ^b	LMR ^c	BLRT ^d	Entropy
1	-462.630	10	972.966	NA	NA	NA
2	-430.427	21	961.039	0.0001	0.0000	0.731
3	-418.644	32	989.950	0.0177	0.0100	0.957
4	-406.801	43	1018.742	0.0424	0.0400	0.963
5	-400.104	54	1057.826	0.0115	0.4000	0.957
6	-394.546	65	1099.186	0.1469	0.6200	0.978

Table 3 Bivariate associations between latent class membership and characteristics of 118 HIV-negative MSM who reported drug use but not injection drug use in Houston, TX

Characteristics	Class 4 vs 1 cOR (95%CI)*	Class 4 vs 2 cOR (95%CI)	Class 4 vs 3 cOR (95%CI)	Class 1 vs 2 cOR (95%CI)	Class 1 vs 3 cOR (95%CI)	Class 3 vs 2 cOR (95%CI)
<i>Sociodemographic</i>						
African American vs Caucasian or Hispanic	14621447 (0.0-I)	1.5 (0.1-16.3)	2.7 (0.2-40.2)	0.0 (0.0-I)	0.0 (0.0-I)	0.5 (0.1-2.4)
Homosexual or bisexual vs heterosexual	0.0 (0.0-I)	0.0 (0.0-I)	0.0 (0.0-I)	2.2 (0.4-12.7)	0.9 (0.1-6.3)	2.3 (0.7-7.2)
Less than or equal to high school vs higher than high school	0.0 (0.0-I)	0.4 (0.0-3.7)	0.3 (0.0-3.1)	9175065 (0.0-I)	6382051 (0.0-I)	1.4 (0.4-4.7)
Single vs married, live with partner, separated, divorced, widowed	20.5 (0.0- 2.12E189)	5.5 (0.5-58.6)	4.0 (0.3-47.6)	0.3 (0.0-2.75E187)	0.2 (0.0-2.03E187)	1.4 (0.5-3.6)
Days of working in the past month: <14 days vs >=14 days	1980777 (0.0-I)	17175594 (0.0-I)	27371147 (0.0-I)	8.7 (0.0-1.99E192)	13.8 (0.0-3.17E192)	0.6 (0.2-1.7)
Income in the past month: <400 dollars vs >= 400 dollars	11.6 (0.0-I)	64.8 (0.0-I)	85.0 (0.0-I)	5.6 (0.0-2.27E198)	7.3 (0.0-2.98E198)	0.8 (0.3-2.0)
Ever homeless vs never homeless	0.2 (0.0-3.4)	0.4 (0.0-4.4)	0.5 (0.0-6.2)	2.0 (0.4-9.7)	2.5 (0.4-14.3)	0.8 (0.3-2.1)
Had been in jail for more than 24 hours: Yes vs No	7195742 (0.0-I)	4239687 (0.0-I)	2340792 (0.0-I)	0.6 (0.1-3.0)	0.3 (0.0-2.2)	1.8 (0.5-6.3)
Never received drug treatment vs received drug treatment	0.7 (0.0-12.0)	0.6 (0.1-6.2)	1.2 (0.1-15.6)	0.8 (0.1-4.6)	1.8 (0.3-12.1)	0.5 (0.2-1.5)
<i>Sexual behavior</i>						
No. of male sexual partners in the past month: 0 or 1 vs >1	0.0 (0.0-I)	0.0 (0.0-I)	0.0 (0.0-I)	1.2 (0.2-6.1)	1.0 (0.2-5.6)	1.2 (0.5-3.3)
Condom use frequency while having sex: <=50% vs >50%	0.7 (0.1-10.0)	0.8 (0.1-7.2)	0.6 (0.1-5.8)	1.1 (0.2-5.2)	0.8 (0.1-4.5)	1.4 (0.5-3.9)

Characteristics	Class 4 vs 1 cOR (95%CI)*	Class 4 vs 2 cOR (95%CI)	Class 4 vs 3 cOR (95%CI)	Class 1 vs 2 cOR (95%CI)	Class 1 vs 3 cOR (95%CI)	Class 3 vs 2 cOR (95%CI)
Traded sex for money or drugs in the past month Yes vs No	2.8 (0.2-42.8)	1.7 (0.2-17.8)	1.3 (0.1-16.0)	0.6 (0.1-2.9)	0.5 (0.1-2.7)	1.2 (0.5-3.4)
Traded money or drugs for sex in the past month Yes vs No	2.5 (0.2-39.1)	2.3 (0.2-24.6)	1.2 (0.1-14.9)	0.9 (0.2-4.5)	0.5 (0.1-2.9)	1.9 (0.7-5.2)
Blood exposure history						
Had blood transfusion Yes vs No	12310954 (0.0-I)	14.7 (1.0-220.7)	9.7 (0.0-3.07E257)	0.0 (0.0-I)	0.0 (0.0-I)	1.5 (0.0-4.83E256)
Had occupational blood exposure Yes vs No	2.0 (0.0-I)	0.0 (0.0-I)	6.3 (0.0-I)	0.0 (0.0-I)	3.1 (0.0-I)	0.0 (0.0-I)
Disease history						
Had STI*** Yes vs No	1.6 (0.1-25.4)	4.4 (0.4-46.4)	2.1 (0.2-25.0)	2.8 (0.5-14.0)	1.4 (0.2-7.9)	2.1 (0.8-5.4)
Had HCV infection Yes vs No	7.8 (0.5-134.7)	14.2 ** (1.3-157.4)	20.5 ** (1.4-291.7)	1.8 (0.3-10.6)	2.6 (0.3-21.8)	0.7 (0.2-3.0)

* cOR: crude odds ratio

** P<0.05

*** STI: Sexually transmitted infections

Table 4 Multivariable association between latent class membership with characteristics in 118 HIV-negative MSM who reported drug use but not injection drug use in Houston, TX

Characteristics	Class 4 vs 1 aOR* (95%CI)	Class 4 vs 2 aOR (95%CI)	Class 4 vs 3 aOR (95%CI)	Class 1 vs 2 aOR (95%CI)	Class 1 vs 3 aOR (95%CI)	Class 3 vs 2 aOR (95%CI)
Never received drug treatment vs received drug treatment	0.8 (0.0-17.0)	0.7 (0.1-9.8)	1.2 (0.1-19.7)	0.9 (0.1-5.1)	1.5 (0.2-11.0)	0.6 (0.2-1.9)
Had STIs*** vs Never had STI	1.9 (0.1-33.5)	5.3 (0.4-65.3)	2.7 (0.2-36.6)	2.8 (0.5-14.6)	1.4 (0.2-8.6)	2.0 (0.7-5.3)
Traded money or drugs for sex in the past month vs never traded money or drugs for sex in the past month	2.5 (0.1-48.4)	2.4 (0.2-33.2)	1.4 (0.1-21.6)	1.0 (0.2-4.8)	0.6 (0.1-3.4)	1.7 (0.6-5.0)
Had HCV infection vs Did not have HCV infection	8.5 (0.5-154.0)	16.9 ** (1.4-205.4)	21.8 ** (1.5-322.8)	2.0 (0.3-12.2)	2.6 (0.3-22.2)	0.8 (0.2-3.5)

* aOR: adjusted odds ratio

** P<0.05

*** STI: Self-reported sexually transmitted infections

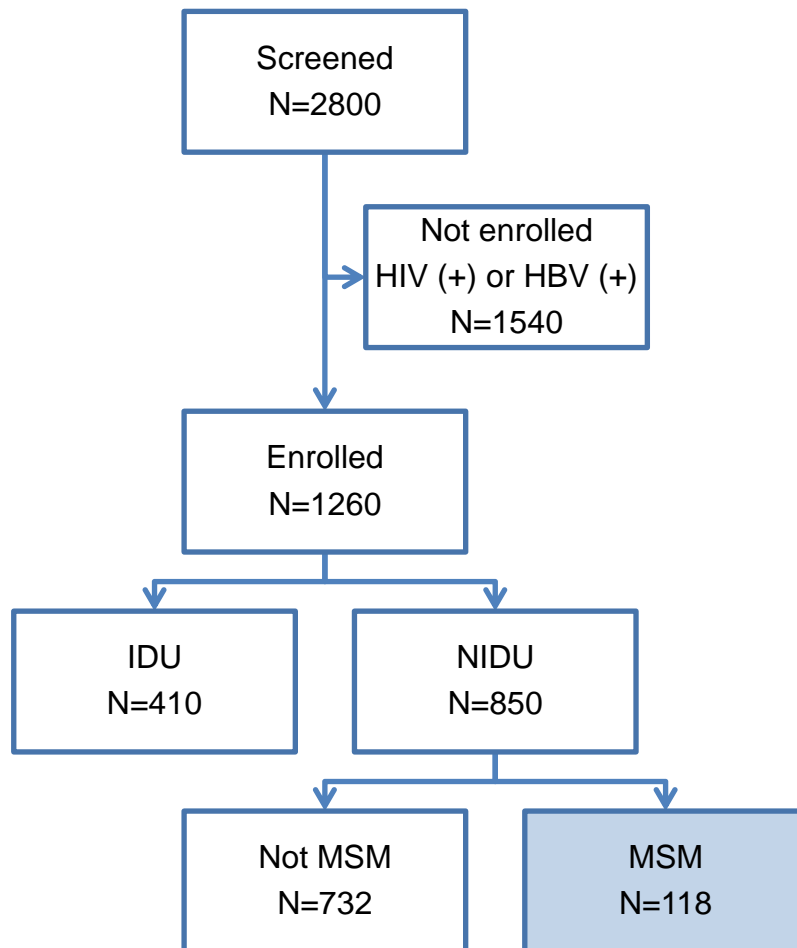


Figure 1. DASH study population flow chart

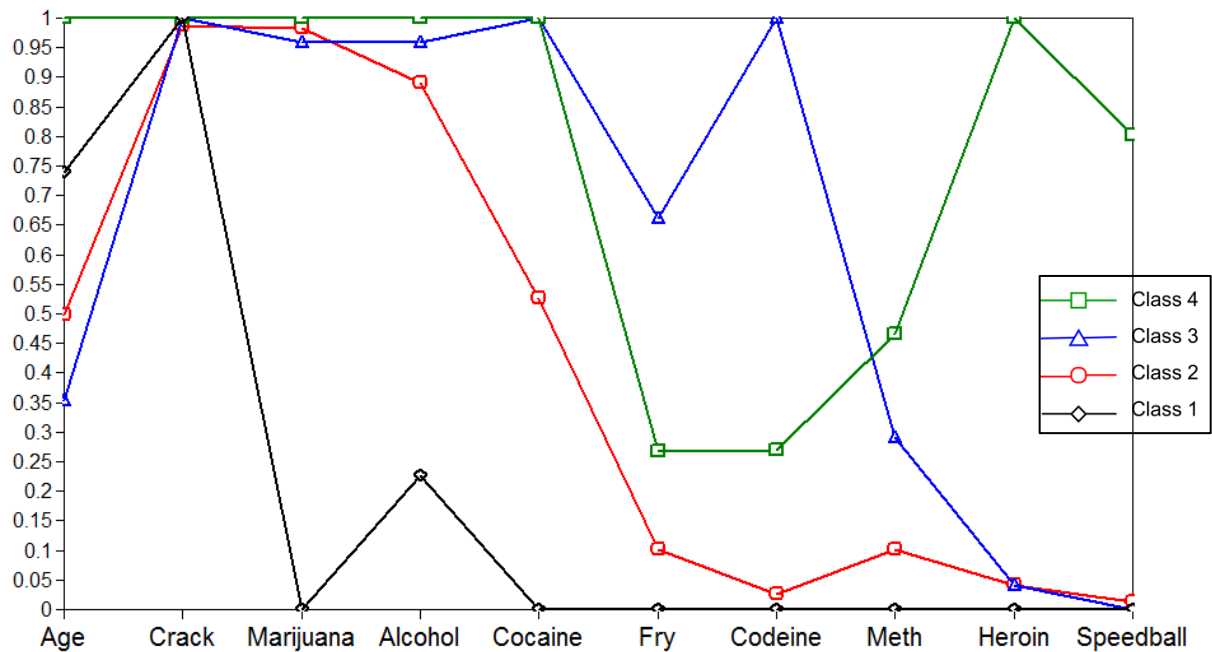


Figure 2 Probability of each indicator variable in each class of 4-latent class model

Note:

Class 1 (6.5%): persons ≥ 42 years old who used only crack cocaine;

Class 2 (70.3%): persons about 42 years old who used > 2 drugs;

Class 3 (20.1%): persons < 42 years old who used > 5 drugs;

Class 4 (3.2%): persons ≥ 42 years old who used > 6 drugs.

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Article III: Risk factors associated with HCV infection in young men who have sex with men reporting drug use not including inject drug in Houston, TX

This article has been formatted for the Journal of *BMC Public Health*

ABSTRACT

Background: Hepatitis C (HCV) infection in men who have sex with men (MSM) has been increasingly reported in recent years. However, little is known about HCV infection in young MSM (YMSM).

Methods: From 2014 to 2017, we recruited YMSM (aged between 17-29 years) who reported drug use, but not injection drug use, in Houston, Texas. We collected information on sociodemographic characteristics and sexual risk behaviors of participants and their sexual partners. We also tested participants for HIV, syphilis, and anti-HCV. Generalized estimating equations were used to assess the association between HCV infection and a variety of exposures.

Results: Among 983 participant-partner dyads, we found that syphilis/HIV coinfection was significantly associated with having anti-HCV of the participants. Compared with the odds of having anti-HCV among reference group (participants' syphilis mono-infection, HIV mono-infection, and neither syphilis nor HIV infection), the odds of having anti-HCV among syphilis/HIV co-infected participants is 4.5times higher (aOR=4.5, 95%CI: 1.05-18.76), controlling for age similarity, participants' HIV status, and whether the participant and his sexual partner used drug before sex.

Conclusion: Syphilis/HIV co-infection was all associated with increased HCV infection. Treatment of syphilis and/or HIV may reduce the disease burden of HCV in YMSM who reported drug use not including injection drug use.

INTRODUCTION

Since 2000, there have been increasing reports of a hepatitis C virus (HCV) epidemic and outbreaks among HIV-positive men who have sex with men (MSM) in Northern Europe, North America, and Australia [1-4]. One meta-analysis reported that the pooled estimated incidence rate of HCV infection among HIV-positive MSM was 19 times that among HIV-negative MSM [5]. Another meta-analysis reported that the pooled HCV prevalence is 8.1% [6], much higher than that in the rest of the general population in the United States (1%) [7]. The epidemic of HCV in MSM has been linked to high-risk sex behaviors, such as group sex with unprotected anal intercourse (UAI) [4, 8], fisting [4, 9]; rectal trauma with bleeding [10]; and potentially underreported non-injection drug use [9, 11, 12].

“Chemsex” is the use of drugs before or during sex to enhance sexual arousal, performance and disinhibition. It has been shown to influence sexual risk behaviors in this population [13-16]. In recent years, a growing number of studies reported chemsex in MSM, and found that the prevalence of chemsex ranged from 3% to 29% among MSM recruited from public venues, gay venues, gay pride event, sexual health clinic, internet, and so on [17]. Chemsex is associated with sexual risk behaviors, including UAI [17-19], being fisted [19, 20], and group sex [20]. Chemsex

is also associated with new HIV infection [21], acute sexually transmitted infections (STI) [18, 21, 22], and HCV infection [18, 21, 23].

Besides “chemsex”, MSM also disproportionately shared the disease burden of syphilis and HIV. The incidence of syphilis and HIV infection in MSM [24, 25], especially in young MSM (YMSM) have been increasing in recent years, which might also contribute to the reported epidemic of HCV in MSM. In the United States, reported primary and secondary (P&S) syphilis increased 10.5% between 2016 and 2017 [26]. Males accounted for more than 90% of new cases of syphilis infection from 2009 to 2013, among whom, MSM who were 25-29 years old had the greatest increase among all age groups (48.4%, 18.2 to 27.0 per 100,000 population) [27]. Moreover, for the incidence of HIV infection in the United States, MSM accounted for two thirds of new infections in 2010 [28]. In reported cases from 2008 to 2011, MSM who were aged 25-34 years accounted for the highest proportion, while MSM aged 13-24 years had the fastest growing rate of infection [29].

Although research on the sexual transmission of HCV in MSM has increased, most studies have focused on HIV-positive MSM and/or MSM who inject drugs. In addition, little is known of HCV risk factors specific to YMSM, which may be a particularly vulnerable subgroup of MSM. Furthermore, most of the information used in such studies is at an individual level, which may not adequately reflect the dynamics of disease transmission. To fill this knowledge gap, we analyzed participant-partner dyadic data of YMSM who reported drug use not including

injection drug use, a subset from the parental study of the Young Men Affiliation Project (YMAP). According to Neaigus, the dyadic link is the primary unit in network development; thus, dyadic data analysis may yield useful results and is feasible among hidden populations, such as MSM [30]. The objective of the study is to assess the associations between the characteristics of participants, sexual partners and characteristics of partnership in a subset of egocentric sexual networks of YMSM and the likelihood that participants are infected with HCV.

METHODS

Study setting

Data were obtained from the Young Men's Affiliation Project (YMAP), a longitudinal network study collected from 2014 to 2017 to investigate social networks and attendance history at social venues and health-promoting venues among YMSM, and to determine how these networks affect HIV and sexually transmitted disease risk and prevention in Houston and Chicago [31-33]. For Houston site, participants were included in this study if they identified as male sex assigned at birth and current male identification, were aged between 17-29 years, reported oral or anal sex with another male in the past 12 months, were residing in and planning to remain in Houston for the following year, and were English-speaking. The study was approved by the institutional review boards at each institution (HSC-SPH-12-0830).

Participant recruitment and data collection

The sampling method in the YMAP study was respondent driven sampling (RDS) [34]. This method has been applied to recruit hard-to-reach populations, such as MSM and people who use drugs. The “seeds” were defined as participants enrolled via representatives at health service providing facilities or at social venues. “Sprouts” were defined as participants who were referred by “seeds”. Four vouchers were given to each participant to recruit other YMSM (sprouts) to produce chained samples.

Interviews were conducted using a computer-based personal-interview combined with a computer-assisted self-interview delivered via Qualtrics (Qualtrics LLC, Provo, Utah). In the computer-assisted personal interviews, the trained data collector read questions from the computer and entered data. We collected information on sociodemographic characteristics, drug use, social and sexual networks, behavior with peers, and participants’ affiliation with community organizations and businesses. For sexual networks, each participant was asked to nominate up to 5 sexual partners in the past 6 months. We collected participants’ perception of each sexual partner’s sociodemographic characteristics, behavioral measures, HIV status, as well as partnership-level information between the participant and each of his partner’s sexual behavioral measures.

Laboratory testing

After the interview, each participant provided biological blood specimen for HIV, HCV, and syphilis testing. HIV tests included fourth generation rapid test, using

Alere Determine HIV-1/2 Ab/Ag combo (Abbott Laboratories, Chicago, IL), viral load quantitative test, using Cobas AmpliPrep/Cobas TaqMan HIV-1 test kit, version 2.0 (Roche Molecular Diagnostics, Pleasanton, California), and confirmatory test, using Geenius HIV -1/2 Confirmatory test (Bio-rad, Marnes-la-Coquette, France). Syphilis tests included a rapid plasma regain (RPR) test, using the Macro-Vue RPR Card test Kit (BD Diagnostics, Franklin Lakes, New Jersey), and fluorescent treponemal antibody FTA test, using Immunofluorescence Assay FTA-Absorption Test System (Zeus Scientific, Branchburg, New Jersey). HCV test was HCV antibody rapid test (Boson Biotech, Xiamen, China).

HIV infection was defined as rapid test positive and viral load detectable, or viral load undetectable but confirmation test positive. Syphilis infection was defined as FTA test positive and RPR titer equal to or greater than 1:8. [35] HCV infection was defined as repeated positive results from rapid antibody test.

Study sample and measures

The study sample was a subset of YMAP baseline data restricted to participants who reported never having injected drugs. The outcome variable was participant's HCV status and the independent variables included three sets: (a) participant's characteristics, (b) perceived sexual partner's characteristics, and (c) dyadic measures between a participant and each of his sexual partner's sexual behaviors.

For participants' measures, we used sociodemographic information (age, education level, race/ethnicity, employment status, living arrangement, insurance status, and

have ever been in jail for more than 24 hours), sexual risk behavioral information (group sex and number of sexual partners in the past 6 months), and disease status (HIV and syphilis infection status). For participants' perception of sexual partner's characteristics, all data were treated as clustered data on the participant, including sociodemographic information (age, gender, education level, and race/ethnicity), and sexual risk behavioral information (unprotected sex, HIV infection status and drug use). For participants' perception of sexual network dyadic measures, all data were also treated as clustered data on the participant, including sexual behavioral measures (whether shared drugs, times that had sex, whether had anal sex, whether the participant ever had receptive anal sex, consistent condom use, whether used drugs before sex, whether engaged in group sex together) and homophily/similarity measures with respect to age, race/ethnicity, and HIV serostatus. We defined age homophily as the value of age difference between a participant and his nominated sexual partner; race/ethnicity homophily as 1=black with black, 2=black with non-black or non-black with black (dissortativity), and 3=non-black with non-black; and HIV serostatus homophily as 1= participant HIV seropositivity and participant's perception about sexual partner's positivity, 2=participant HIV seropositive and participant's perception about sex partner negative, 3=participant HIV seropositivity and participant's perception about sex partner's unknown, 4=participant HIV seronegative and participant's perception about sex partner positive, 5=participant HIV seronegative and participant's

perception about sex partner negative, and 6=participant HIV seronegative and participant's perception about sex partner unknown.

Statistical analysis

The unit of analysis was the sexual dyad, which was a pair composed of a participant and each of his nominated sexual partners. We conducted Chi-square tests and Fisher exact tests to assess the differences of HCV status between the categories of each independent variable. We also conducted bivariate and multivariable generalized estimating equation (GEE), which can deal with clustered observation of participants[36] to statistically test the association between HCV status and independent variables. We used autoregressive correlation structure and robust estimates to address potential misspecification of variance structure. Bivariate analyses were performed between HCV status and each independent variable, showing crude odds ratio and 95% confidence intervals. For variables with p-values less than 0.25 in bivariate analyses, we included all of them, except syphilis mono-infection, into multivariable GEE model. We excluded syphilis mono-infection because this variable and syphilis/HIV co-infection had collinearity. We finally assessed the interaction effect between the selected independent variables in a multivariable model. The statistical significance level was set at 5%. We used SAS 9.4 (Cary, NC) to manage the data and conduct the GEE analysis.

RESULTS

Participants' characteristics

Among 378 participants of YMAP study, we excluded 5 participants who reported never used any drugs, 4 participants who reported injection drug use behavior, 3 participants who did not report injection drug use information. We finally identified a total of 366 MSM who reported drug use not including injection drug use, among whom 12 (3.3%) had anti-HCV. Table 1 shows the characteristics of participants stratified by HCV status. In terms of sociodemographic characteristics, age ranged from 17 years to 29 years with a median of 25 years. Of the participants, 63% had more than a high school education level; 63% were black; 19% were Hispanic; 49% were employed; 18% were homeless in the past month; 59% had insurance; and 40% had ever been in jail for more than 24 hours. In terms of sexual risk behaviors, 28% engaged in group sex; 44% had 2 to 5 sexual partners in the past 6 months. In terms of disease status, 38% were HIV positive and 16% were syphilis positive; 12% were co-infected with HIV and syphilis. Chi-square or Fisher exact tests show that HCV status differed significantly between HIV-positive and HIV-negative participants, as well as between positive syphilis and negative syphilis participants.

Participants' sexual partners' perceived characteristics and dyad measures

A total of 983 sexual partners were nominated by participants. Table 2 shows the participants' perceived characteristics of sexual partners and dyadic measures between a participant and his sexual partners stratified by participants' HCV status. For socio-demographic characteristics of sexual partners, age ranged from 19 years to 65 years, with a median of 26 years; 92% were male; 50% had more than a high school education level; 51% were black; 22% were Hispanic. For behavioral

measures and disease status of sexual partners, 44% had unprotected sex; 11% were participant perceived HIV positive and 27% had unknown HIV status by participants; 39% used drugs. For dyadic measures between participants and their sexual partners, 29% shared drugs with participants; 42% had sex 2 to 9 times with participants; 88% had anal sex with participants; 52% let participants ever had receptive anal sex; 36% had consistent condom use when having sex with participants; 30% used drugs before sex; 8% had group sex together with participants. For the perceived characteristics of homophily, 70% of the dyads had participants' age younger than sexual partners' age; 47% of the dyads were black for both participants and sexual partners; 8% of the dyads were both HIV-positive and 49% were both HIV-negative. The results of Chi-square or Fisher exact tests showed that HCV status differed significantly in the categories of age homophily and HIV status homophily: a participant who was older than his sexual partner had higher probability of having anti-HCV than the participant who was younger than his sexual partner; a participant who was HIV positive regardless of his sexual partner's HIV status perceived by the participant, had higher probability of having anti-HCV than an HIV-negative participant regardless of his sexual partner's HIV status perceived by the participant. Additionally, whether the participants and sexual partners shared drugs ($p=0.071$) and used drugs before sex ($p=0.077$) had small p -value in Chi-square tests.

Bivariate and multivariable analyses

For the results of the bivariate GEE model, Table 3 shows the crude odds ratio, 95%CI, and p-value of Wald tests of each independent variable. As shown, HIV status and syphilis status were significantly associated with HCV status (HIV cOR=5.31, 95%CI: 1.5-19.3; syphilis cOR=6.6, 95%CI: 1.8-23.8). Age homophily (p-value=0.12) and whether the participant and his sexual partner used drugs before sex (p-value=0.19) both had p-values less than 0.25, so they were included in the multivariable model.

For the multivariable GEE model, we included age homophily, HIV status, syphilis status, and whether the participant and his sexual partner used drugs before sex in the model. As in the bivariate GEE model, there was an interaction effect between HIV status and syphilis status, so we used the interaction variable of HIV and syphilis status in the final model. Table 4 shows the adjusted odds ratio and 95%CI in multivariable GEE model. As shown, syphilis/HIV coinfection was significantly associated with having anti-HCV of the participants. Compared with the odds of having anti-HCV among reference group (participants' syphilis mono-infection, HIV mono-infection, and neither syphilis nor HIV infection), the odds of having anti-HCV among syphilis/HIV co-infected participants is 4.5 times higher (aOR=4.5, 95%CI: 1.05-18.76), controlling for age similarity, participants' HIV status, and whether the participant and his sexual partner used drug before sex.

DISCUSSION

In this study, we examined the sociodemographic characteristics and sexual risk behaviors of YMSM and their sexual partners to determine risk factors of having anti-HCV in this potentially vulnerable subpopulation. We found HIV/syphilis co-infection, was significantly associated with participants' anti-HCV, while controlling for age homophily between the participant and his sexual partner, participants' HIV status, and whether the participant and his sexual partner used drugs before sex.

Syphilis infection was found to be associated with HCV infection. This finding is consistent with the findings of two studies among women in Chicago and India, which reported syphilis infection independently associated with HCV infection [37, 38]. Similar studies among MSM were mostly restricted to HIV-positive MSM, one of which indicated that syphilis infection increased the risk of HCV infection about 5 times in HIV-positive MSM [39]. In addition, HIV mono-infection has also been found to be associated with HCV infection. A systematic review showed the risk of HCV infection was 19 times higher among HIV-positive MSM than that among HIV negative MSM[5]. The results of the present study were consistent with prior studies, showing that syphilis mono-infection and HIV mono-infection were associated the increased probability of HCV infection.

Our study indicates that the syphilis/HIV coinfection group had the highest risk of having anti-HCV compared to the risk of having anti-HCV in mono-infection groups, and syphilis/HIV coinfection had more than additive interaction effect on HCV infection. This finding suggests that there is a link between HIV infection and syphilis

infection, which is consistent with prior studies. In the United States, about half of syphilis-infected MSM are living with HIV; those who are mono-infected with syphilis have a 2- to 5- fold increase of HIV infection than those who are uninfected with syphilis[26]. The biological explanations of the overlapped epidemic are syphilis infection may cause sores, ulcers or breaks in the skin or mucous membranes that provide protection against infection[40]. HIV infection causes suppression of immune system. All the aforementioned mechanisms can also be used to explain the effect of syphilis/HIV infection on HCV infection transmitted by blood exposure or fluid contact.

All sociodemographic and risk sexual behaviors at both the individual and dyadic level were not statistically significant in this study. However, it is worth noting that using drugs before sex between the participant and his sexual partner (also referred to as “chemsex”) had a smaller p-value ($p=0.19$) than other sociodemographic and risk sexual behavior measures. Although this variable is not statistically significant in this study, it is of increasing concern in large MSM communities[41]. Prior studies reported that chemsex is associated with HCV infection [18, 21, 23]. However, none of the studies were restricted to YMSM. To better evaluate the effect of “chemsex” on HCV infection in YMSM, further study may include drug use during sex in addition to before sex, and expand the question to any sexual partner instead of restricting to nominated sexual partner, which may collect information on “chemsex” to a greater extent.

This study has several limitations. First, we may not know the HCV status of sexual partners, and thus, cannot provide direct evidence of HCV transmission by sexual behavior. Second, the anti-HCV rate is relatively low in this YMSM population, which may compromise the statistical power. Third, the cross-sectional design of the study cannot provide temporality information to establish causality. Lastly, detailed information on sharing equipment of non-injection drugs was not collected in this study, which could be a risk factor of HCV infection. In order to elucidate HCV transmission in YMSM who reported drug use not including injection drug, further study is needed concentrated on MSM, with a larger sample size, with efforts to obtain HCV infection status for both the respondent and the sexual partner and information on sharing equipment of non-injection drugs.

Despite the limitations mentioned above, this study has multiple strengths. First, this study analyzed dyadic data, which may provide insightful information among sexual partners regarding HCV infection. By incorporating and evaluating dyadic data, this study may infer characteristics of HCV transmission dynamics. Second, the study population, YMSM, represents a growing HCV susceptible subgroup, and the study results may add evidence of the emerging HCV epidemic in MSM in recent years. Third, the HIV, HCV, and syphilis infection status of participants were confirmed by lab test, not self-reported, which reduced the information bias.

In conclusion, we found syphilis mono-infection, HIV mono-infection and syphilis/HIV co-infection were associated with increased risk of HCV infection among a sample of

YMSM living in Houston, who reported drug use not including injection drug use.

Health education and promotion programs geared towards raising the awareness of HCV testing and treatment in HIV and/or syphilis infected YMSM may help reduce the disease burden of HCV directly. Also, programs targeting an increase in syphilis and HIV testing and treatment among YMSM may potentially reduce the transmission HCV in YMSM.

Table 1 Sociodemographic characteristics and sexual risk behaviors of YMSM participants in Houston, TX (N=366)

Covariates	Total	HCV+	HCV-	Fisher test P value
Total	366 (100)	12 (3.3)	354 (96.7)	
Age				0.519*
<25	186 (50.8)	5 (2.7)	181 (97.3)	
≥ 25	180 (49.2)	7 (3.9)	173 (96.1)	
Education level				0.795
High school or less	135 (36.9)	4 (3.0)	131 (97.0)	
Above high school	231 (63.1)	8 (3.5)	223 (96.5)	
Hispanic				0.599
Yes	70 (19.1)	3 (4.3)	67 (95.7)	
No	296 (80.9)	9 (3.0)	287 (97.0)	
Race				0.917
Black	230 (62.8)	8 (3.5)	222 (96.5)	
White	83 (22.7)	2 (2.4)	81 (97.6)	
Multiracial, other	53 (14.5)	2 (3.8)	51 (96.2)	
Working status				0.926
Full time	179 (48.9)	7 (3.9)	172 (96.1)	
Part time	72 (19.7)	2 (2.8)	70 (97.2)	
Not employed	115 (31.4)	3 (2.6)	112 (97.4)	
Homeless in the past 12 month				0.505
Yes	65 (17.8)	3 (4.6)	62 (95.4)	
No	301 (82.2)	9 (3.0)	292 (97.0)	
Insurance				0.260

Covariates	Total	HCV+	HCV-	Fisher test P value
Yes	217 (59.3)	9 (4.1)	208 (95.9)	
No	149 (40.7)	3 (2.0)	146 (98.0)	
Ever been in jail for more than 24 hours				0.637
Yes	146 (39.9)	4 (2.7)	142 (97.3)	
No	220 (60.1)	8 (3.6)	212 (96.4)	
Group sex				0.838
Yes	101 (27.6)	3 (3.0)	98 (97.0)	
No	265 (72.4)	9 (3.4)	256 (96.6)	
No. of sexual partners in the past 6 months				0.933
0-1	104 (28.4)	4 (3.8)	100 (96.2)	
2-5	162 (44.3)	5 (3.1)	157 (96.9)	
>=6	100 (27.3)	3 (3.0)	97 (97.0)	
Continuous scale, include mean (SD, min, max)				
HIV infection				0.006
Yes	134 (37.1)	9 (6.7)	125 (93.3)	
No	227 (62.9)	3 (1.3)	224 (98.7)	
Syphilis infection				<0.001
Yes	56 (15.7)	7 (12.5)	49 (87.5)	
No	300 (84.3)	5 (1.7)	295 (98.3)	
Syphilis/HIV infection status				<0.001
Syphilis/HIV co-infection	43 (12.1)	6 (14.0)	37 (86.0)	
Other ^a	313 (25.9)	6 (1.9)	307 (98.1)	

* P-value in Chi-square test.

^a Other: Syphilis mono-infection, HIV mono-infection, and neither syphilis nor HIV infection

Table 2 Characteristics perceived by participant of pairs of participants and sexual partners stratified by participants' HCV infection status, Houston, TX (N=983)

Covariates	Total	HCV+	HCV-	Chi-square test P value
Sexual partner's characteristics				
Gender				0.299*
Male	904 (92.0)	31 (3.4)	873 (96.6)	
Female or transgender	79 (8.0)	1 (1.3)	78 (98.7)	
Education				0.374*
High school or less	299 (30.4)	11 (3.7)	288 (96.3)	
Above high school	495 (50.4)	18 (3.6)	477 (96.4)	
Unknown	189 (19.2)	3 (1.6)	186 (98.4)	
Hispanic				0.630
Yes	208 (21.6)	8 (3.8)	200 (96.2)	
No	757 (78.4)	24 (3.2)	733 (96.8)	
Race				0.357
Black	501 (51.0)	19 (3.8)	482 (96.2)	
White	297 (30.2)	6 (2.0)	291 (98.0)	
Multiracial, other	185 (18.8)	7 (3.8)	178 (96.2)	
Unprotected sex				0.519
Yes	436 (44.4)	12 (2.8)	424 (97.2)	
No	201 (20.4)	9 (4.5)	192 (95.5)	
Unknown	346 (35.2)	11 (3.2)	335 (96.8)	
HIV infection status				0.276
Positive	108 (11.0)	6 (5.6)	102 (94.4)	
Negative	614 (62.5)	20 (3.3)	594 (96.7)	
Unknown	261 (26.6)	6 (2.3)	255 (97.7)	
Ever use drugs				0.118*
Yes	384 (39.1)	17 (4.4)	367 (95.6)	
No	378 (38.5)	12 (3.2)	366 (96.8)	
Unknown	221 (22.5)	3 (1.4)	218 (98.6)	
Participant and sexual partner's characteristics				
Ever shared drug between the pair				0.071
Yes	287 (29.4)	14 (4.9)	273 (95.1)	
No	688 (70.6)	18 (2.6)	670 (97.4)	
Times that had sex between the pair				0.485
2-9	398 (41.5)	13 (3.3)	385 (96.7)	
>=10	250 (26.1)	11 (4.4)	239 (95.6)	
0-1	311 (32.4)	8 (2.6)	303 (97.4)	
Whether had anal sex between the pair				0.665*
Yes	852 (88.2)	29 (3.4)	823 (96.6)	
No	114 (11.8)	3 (2.6)	111 (97.4)	

Covariates	Total	HCV+	HCV-	Chi-square test P value
Whether the participant ever had receptive anal sex				0.853
Yes	494 (51.5)	17 (3.4)	477 (96.6)	
No	465 (48.5)	15 (3.2)	450 (96.8)	
Consistent condom use between the pair				0.306*
Yes	352 (35.8)	14 (4.0)	338 (96.0)	
No	400 (40.7)	14 (3.5)	386 (96.5)	
Unknown	231 (23.5)	4 (1.7)	227 (98.3)	
Whether use drugs before sex between the pair				0.077
Yes	292 (29.7)	14 (4.8)	278 (95.2)	
No	691 (70.3)	18 (2.6)	673 (97.4)	
Attended group sex together				0.122
Yes	81 (8.2)	5 (6.2)	76 (93.8)	
No	902 (91.8)	27 (3.0)	875 (97.0)	
Homophily of participants and sexual partners				
Age homophily				0.036
Participant ≤ Sexual partner	687 (69.9)	17 (2.5)	670 (97.5)	
Participant > Sexual partner	296 (30.1)	15 (5.1)	281 (94.9)	
Race homophily (participant / sexual partner)				0.397
Black / Black	447 (45.5)	18 (4.0)	429 (96.0)	
Black / non-Black	115 (11.7)	5 (4.3)	110 (95.7)	
non-Black / Black	54 (5.5)	1 (1.9)	53 (98.1)	
non-Black / non-Black	367 (37.3)	8 (2.2)	359 (97.8)	
HIV infection status homophily (participant / sexual partner ^a)				<0.001*
Positive/Positive	77 (7.9)	5 (6.5)	72 (93.5)	
Positive/Negative	137 (14.0)	14 (10.2)	123 (89.8)	
Positive/Unknown	109 (11.1)	6 (5.5)	103 (94.5)	
Negative/Positive	31 (3.2)	1 (3.2)	30 (96.8)	
Negative/Negative	475 (48.5)	6 (1.3)	469 (98.7)	
Negative/Unknown	151 (15.4)	0 (0)	151 (100)	

* P-value in Fisher exact test

^a Partner's status as perceived by participant

Table 3 Results of bivariate GEE model of dyadic data of participant and sexual partner pairs in Houston, TX (N=983)

Covariates	Unadjusted Odds Ratio (95%CI)	P
Participants' characteristics		
Age		0.535
≥ 25	1.48 (0.46-4.77)	
< 25	Reference	
Education level		0.818
High school or less	0.87 (0.26-2.94)	
Above high school	Reference	
Hispanic		0.694
Yes	1.36 (0.36-5.17)	
No	Reference	
Race		0.802
White	0.64 (0.13-3.09)	
Multiracial, other	1.08 (0.22-5.25)	
Black	Reference	
Working status		0.811
Full time	1.53 (0.39-6.04)	
Part time	1.05 (0.17-6.47)	
Not employed	Reference	
Homeless in the past 12 months		0.602
Yes	1.49 (0.39-5.66)	
No	Reference	
Insurance		0.251
Yes	2.05 (0.54-7.70)	
No	Reference	
Ever been in jail for more than 24 hours		0.643
Yes	0.75 (0.22-2.54)	
No	Reference	
Group sex		0.801
Yes	0.84 (0.22-3.15)	
No	Reference	
No. of sexual partners in the past 6 months		0.841
0-1	1.52 (0.33-7.00)	
2-5	1.04 (0.24-4.45)	
≥6	Reference	
HIV infection status		0.019
Yes	5.64 (1.49-21.29)	
No	Reference	
Syphilis infection status		0.020
Yes	8.31 (2.53-27.28)	
No	Reference	

Covariates	Unadjusted Odds Ratio (95%CI)	P
Syphilis/HIV infection status		0.031
Syphilis/HIV co-infection	8.40 (2.57-27.46)	
Other ^a	Reference	
Sexual partners' characteristics		
Gender		0.406
Male	1.02 (0.97-1.08)	
Female or transgender	Reference	
Education		0.307
High school or less	1.00 (0.97-1.04)	
Unknown	0.98 (0.95-1.01)	
Above high school	Reference	
Hispanic		0.654
Yes	1.00 (0.99-1.01)	
No	Reference	
Race		0.892
White, other	1.00 (0.97-1.02)	
Black	Reference	
Unprotected sex		0.705
Yes	0.99 (0.95-1.02)	
Unknown	1.00 (0.96-1.03)	
No	Reference	
HIV infection status		0.705
Positive	0.99 (0.95-1.02)	
Unknown	1.00 (0.96-1.03)	
Negative	Reference	
Ever use drugs		0.522
Yes	1.00 (0.98-1.03)	
Unknown	0.98 (0.96-1.01)	
No	Reference	
Participant and sexual partner's characteristics		
Ever shared drug between the pair		0.374
Yes	1.01 (0.99-1.04)	
No	Reference	
Times that had sex between the pair		0.396
2-9	1.00 (0.99-1.01)	
>=10	1.01 (0.99-1.02)	
0-1	Reference	
Whether had anal sex between the pair		0.712
Yes	1.00 (0.99-1.02)	
No	Reference	
Participant in the bottom when had anal sex between the pair		0.578
Yes	1.00 (0.99-1.02)	

Covariates	Unadjusted Odds Ratio (95%CI)	P
No	Reference	
Consistent condom use between the pair		0.384
Yes	1.01 (0.97-1.04)	
Unknown	0.99 (0.97-1.02)	
No	Reference	
Whether use drugs before sex between the pair		0.192
Yes	1.02 (0.99-1.06)	
No	Reference	
Attended group sex together		0.436
Yes	2.13 (0.55-8.26)	
No	Reference	
Homophily of participants and sexual partners		
Age homophily		0.117
Participant ≤ Sexual partner	0.96 (0.93-1.00)	
Participant > Sexual partner	Reference	
Race homophily (participant / sexual partner)		0.952
Black / Black	1.26 (0.37-4.28)	
Black / non-Black	1.23 (0.36-4.17)	
non-Black / Black	0.99 (0.91-1.08)	
non-Black / non-Black	Reference	
HIV infection status homophily (participant / sexual partner)		NA*

*GEE model cannot estimate parameters due to small cell numbers.

a Other: syphilis mono-infection, HIV mono-infection, and neither syphilis nor HIV infection

Table 4 Results of multivariable GEE model of the dyadic data of participant and sexual partners pairs in Houston, TX (N=983)

Parameter	Adjusted Odds Ratio (95%CI)
Age homophily	
Participant ≤ sexual partner	0.76 (0.55-1.05)
Participant > sexual partner	Reference
HIV infection	
Yes	2.76 (0.55-13.89)
No	Reference
Participant's syphilis/HIV infection status	
Syphilis/HIV co-infection	4.45 (1.05-18.76)
Other ^a	Reference
Participant and his sexual partner used drugs before sex	
Yes	1.21 (0.85-1.71)
No	Reference

^a Other: syphilis mono-infection, HIV mono-infection, and neither syphilis nor HIV infection

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CONCLUSION

In these three studies, we have provided epidemiological evidence that supports findings from previous studies that MSM who use drugs but not injection drugs (NIDU MSM) were at risk for HCV infection. (1) Overall HCV prevalence in NIDU MSM was higher than the rest of general population; (2) NIDU MSM ≥ 42 years old had a higher risk of HCV infection than NIDU MSM < 42 years old; (3) NIDU MSM ≥ 42 years old who used > 6 drugs were associated with increased probability of HCV infection among all NIDU MSM; (4) Among NIDU YMSM, syphilis mono-infection, HIV mono-infection, and syphilis/HIV co-infection were associated with increased risk of HCV infection.

The strength of our studies was the use of NIDU MSM data from two projects (DASH and YMAP) funded by NIDA and NIH. NIDU MSM in DASH project with a median age of 42 years, represented NIDU MSM of older generation, while NIDU MSM in YMAP project with a median age of 25 years represented NIDU MSM of younger generation. By comparing findings from these two data sources, we could compare characteristic that associated with HCV infection in different generations to some extent. We found that syphilis infection was associated with HCV infection in younger generation but not in older generation. One possible reason was that syphilis status was self-reported in DASH project, which may underestimate the effect of syphilis infection on HCV transmission. Another possible reason was that

syphilis infection was increasing fast in recent years, especially in young people, which reflected the increasing evidence of sexually transmitted HCV in recent years.

The strength of our studies also included the use of two statistical approaches which were latent class analysis and dyadic data analysis to analyze NIDU MSM. Latent class analysis made it possible to analyze all information on drug use types in one analysis, by subgrouping the individuals using similar drug types. Dyadic data analysis incorporated characteristics of sexual partnership into the analysis.

Although we could not identify statistically significant characteristics of sexual partnership related to HCV infection, it was the first study to use this approach for HCV study targeting NIDU MSM to the best of our knowledge.

Our studies had some limitations, particularly those pertaining to sample size issue. Because our target population was hard-to-reach population, we could not obtain large sample size to guarantee enough statistical power. Also, the question related to sexual behavior and drug use behavior may also be underreported, which may lead to underestimating the effect of sexual behavior and drug use behavior on HCV transmission.

Further study is warranted specifically among NIDU MSM, with a larger sample size, to more fully examine risk factors related to HCV infection, with efforts to obtain HCV infection status for both the participant and the sexual partner and information on sharing equipment of non-injection drugs.

Finally, we conclude that NIDU MSM ≥ 42 years old with multiple drug use are at risk of HCV infection; YMSM with HIV mono-infection, syphilis mono-infection, and HIV/syphilis co-infection are at risk of HCV infection. Health education should be promoted in these subgroups to enhance the awareness of HCV infection and increase HCV testing rates. In addition, treatment in HIV and/or syphilis infected YMSM may help reduce the disease burden of HCV directly. Also, programs targeting on increasing syphilis and HIV testing and treatment among YMSM may potentially reduce the transmission HCV in YMSM.

APPENDICES

Appendix A: Screening questionnaire for DASH project

SCREENER

I.D.# _____

Date: _____

READ: This is just a screener questionnaire. The information obtained here is voluntary. You will not receive any money for answering these questions. This information will be entered into our computer which will decide if you qualify. Only if you qualify and finish the study will you receive any money.

ASK ALL OF THESE QUESTIONS: Montrose Shotwell

1. Race? _____ 2. Male or Female 3. How old are you?

4. What is your birthday? _____ - _____ - _____

5. Do you currently have a permanent address?

Y N

What is your address? _____ Phone

Are you currently living in a shelter? Y N Are you currently living on the street? Y N

6. Have you used crack cocaine in the last 48 hours? Y N # of times _____

7. Have you used crack cocaine in the last 7 days? Y N # of times _____

8. Have you used powder cocaine in the last 48 hours? Y N # of times _____

9. Have you used powder cocaine in the last 7 days? Y N # of times _____

10. Have you used heroin in the last 48 hrs? Y N # of times _____

11. Have you used heroin in the last 7 days? Y N # of times _____

12. Have you used marijuana in the last 48 hours? Y N # of times _____

13. Have you used marijuana in the last 7 days? Y N # of times_____
14. Have you used meth (crystal) in the last 48 hrs? Y N # of times_____
15. Have you used meth (crystal) in the last 7 days? Y N # of times_____
16. Have you used alcohol in the last 48 hours? Y N # of times_____
17. Have you used alcohol in the last 7 days? Y N # of times_____
18. Have you ever injected drugs? Y N # of times_____ in the past 30 days
 Have you injected drugs in the last 7 days? Y N
 Have you ever shared needles or works while injecting any drug? Y N # of times past 30 days_____
 How many years have you injected drugs? _____
19. Do you smoke cigarettes? Y N If yes, how many in a day? _____
20. Do you have a main sex partner? Y N
21. Have you had sex with a casual sex partner in the last week? Y N
22. Have you had sex with a new sex partner in the last week? Y N
23. Have you had vaginal/oral/anal sex in the last 48 hours? List # of times for each
 # vag_____ # oral_____ # anal_____
 How many men?_____ How many women?_____
24. Have you had vaginal/oral/anal sex in the last 7 days? List # of times for each
 # vag_____ # oral_____ # anal_____
 How many men?_____ How many women?_____
25. How many times have you had vaginal or anal sex in the last 30 days? _____
 How many men?_____ How many women?_____
26. Do you use condoms with all your partners? Y N
27. Of the people you had sex with, what percentage of them did you use a condom with?
 None___ Quarter___ Half___ Three-quarters___ All___

28. Do you trade sex for money/drugs? Y N If No, skip to Question 33
29. Have you traded sex for money/drugs in the last 48 hrs? Y N # of times_____
- How many men?_____ How many women?_____
30. Have you traded sex for money/drugs in the last week? Y N # of times_____
- How many men?_____ How many women?_____
- Have you traded sex for money in the last 30 days? Y N # of times_____
- How many men?_____ How many women?_____
- Have you traded sex for drugs in the last 30 days? Y N # of times_____
- How many men?_____ How many women?_____
31. What part of town do you normally work in? _____
32. Do you work on the streets? Y N
33. Do you consider yourself: Gay____ Straight____ Bisexual____
34. Have you ever been tested for HIV? Y N Status? Positive Negative Don't Know
- If HIV+, are you currently on meds? Y N Are you currently under a physician's care? Y N
- If a vaccine was available for HIV, would you be willing to be vaccinated? Y N
35. In your lifetime, have you ever been tested for a sexually transmitted disease? Y N
- If yes, what types:
- Syphilis____ Gonorrhea____ Chlamydia____ Genital Herpes____ Genital warts____
- Other_____
- In your lifetime, have you ever been diagnosed or treated with a sexually transmitted disease? Y N
- If yes, what types:
- Syphilis____ Gonorrhea____ Chlamydia____ Genital Herpes____ Genital warts____
- Other_____

If you were not treated, what was the reason?

36. Have you been vaccinated against hepatitis B? Y N

If not, are you willing to be vaccinated against hepatitis B? Y N

37. Have you ever been in drug treatment? Y N # of times _____

38. Have you ever received a transfusion with blood or blood products (including clotting factors)? Y N If yes, what was the year of your first transfusion? _____

39. Have you ever been employed as a medical, dental, public safety or other health care worker involved with human blood contact? Y N

What was your job description? _____

What was your degree of blood contact? Frequent _____ Infrequent _____

40. Have you ever been in prison or jail for more than 24 hours? Y N

Interviewer read: I am going to ask you about a place where you may have smoked crack in the last 30 days. One of the places I am going to ask you about is a place where someone pays money or gives the owner some crack to smoke at his/her place. We call this kind of place a crack house. What do you call such a place?

[Interviewer: Record responses other than a 'crack house.' If the respondent calls a place where someone pays money or gives the owner some crack to smoke at his/her place by a different name, use that name in referring to a 'crack house.']

41. In the past 30 days, how many times did you smoke crack in each of the following places?

	At your home	_____
	At a friend's home	_____
At an acquaintance's (someone you did not know well) home		_____
	In a crack house	_____
	In a bar	_____
In a public place, like a park, alley, public restroom		_____
	Times	

If the response to smoking in a crack house was 0, skip to item _____. If the response to smoking in a crack house is 1 or more times, ask:

41a. When you smoked in a crack house, what was the usual number of people present during the times you were smoking?

1 other person	_____
2 to 3 other people	_____

4 to 5 other people _____
5 to 10 other people _____
More than 10 other people _____

If the response to 41a is 1 other person, skip to 41c. If the response is 2 or more people, ask:

41b. How many times did you smoke in a crack house when two or more persons were present? _____
Times

41c. Of the _____ times you smoked in a crack house, how many times did you pay money to smoke there? _____
Times

41d. Of the _____ times you smoked in a crack house, how many times did you give the owner crack to smoke there? _____
Times

41e. Of the _____ times you smoked in a crack house, how many times did you have sex while you were there? _____
Times

42. How many people do you know have tuberculosis right now? _____
Number

If the response to 42 is 0, skip to 42. If two or more, go to 42b. If the response is 1 ask:

42a. What is the relationship of this person to you?

Relative _____
Sex partner _____
Someone you hang out with currently _____
Someone you work with _____
Someone that you were with in jail _____
Someone you were in a shelter with _____
Y/N

42b. How many people you know who have tuberculosis are related to you in the following ways?

Relative _____
Sex partner _____
Someone you hang out with currently _____
Someone you work with _____
Someone that you were with in jail _____
Someone you were in a shelter with _____
number

42c. How many people do you know who are taking medication for tuberculosis right now?

Number

If the response to 42c is 0, skip to 43. If two or more, go to 42e. If the response is 1 ask:

42d. What is the relationship of this person to you?

Relative _____
Sex partner _____
Someone you hang out with currently _____
Someone you work with _____
Someone that you were with in jail _____
Someone you were in a shelter with _____
Y/N

42e. How many people you know taking medications for tuberculosis are related to you in the following ways?

Relative _____
Sex partner _____
Someone you hang out with currently _____
Someone you work with _____
Someone that you were with in jail _____
Someone you were in a shelter with _____
number

43. Who referred you to our study? _____

COMBO TEST RESULTS

	HIV	HBsAG	HCV
Positive			
Negative			

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