Published in final edited form as:

J Med Virol. 2016 March ; 88(3): 512–520. doi:10.1002/jmv.24358.

Correlates to Seroprevalent Herpes Simplex Virus Type 2 Among Rural Appalachian Drug Users

Dustin B. Stephens^{1,2}, April M. Young^{2,3}, Ursula L. Mullins², and Jennifer R. Havens^{1,2,*}

¹Department of Behavioral Science, University of Kentucky College of Medicine, Lexington, Kentucky

²Center on Drug and Alcohol Research, University of Kentucky College of Medicine, Lexington, Kentucky

³Department of Epidemiology, University of Kentucky College of Public Health, Lexington, Kentucky

Abstract

Herpes simplex virus type 2 (HSV-2) is the most common cause of genital ulcer disease and, along with substance abuse, an important HIV risk factor. Therefore, the purpose of this study was to examine HSV-2 seroprevalence in a sample of drug users in rural Appalachia. Rural Appalachian individuals age 18 or older reporting non-medical use of prescription opioids, heroin, crack/cocaine, or methamphetamine in the past 6 months ($n = 499$) were included. Behavioral, demographic, and sexual network data were collected using interviewer-administered questionnaires. Participants' serum was tested for HSV-2 antibodies using the Biokit rapid test (Lexington, MA). The estimated population seroprevalence of HSV-2 was 14.4% (95%CI: 9.6–19.4%). Only 8.8% were aware of being HSV-2+, and unprotected sex was reported in 80% of serodiscordant sexual relationships. In a multivariate model, female gender, age, older age at first oral sex, and frequency of unprotected sex in the sexual network were independently associated with HSV-2 seropositivity. Despite lower seroprevalence than that reported in similar studies of substance abusers, targeted interventions to reduce sexual risk behavior are warranted in this underserved population. Network-informed approaches with particular focus on women, older individuals, and those engaging in frequent unprotected sex are recommended.

Keywords

genital herpes; HSV-2; drug use; HIV risk

INTRODUCTION

Human herpesvirus 2, also known as herpes simplex virus type 2 (HSV-2), is a member of the genus *Simplexvirus*, family *Herpesviridae* [International Committee on Taxonomy of

*Correspondence to: Jennifer R. Havens, PhD, MPH, Center on Drug and Alcohol Research, University of Kentucky College of Medicine, 845 Angliana Avenue, Lexington, KY 40508. jennifer.havens@uky.edu.

Conflicts of interest: The authors have no conflicts of interest to report.

Viruses, 2012]. HSV-2 is the second-most prevalent sexually transmitted infection (STI) in the United States and the most common cause of genital ulcer disease worldwide [Centers for Disease Control and Prevention, 2010]. One out of six Americans age 14–49 (15.7%) has antibodies to HSV-2 [Bradley et al., 2014], with higher prevalence among women (20%), non-Hispanic blacks (39%), and older individuals [Centers for Disease Control and Prevention, 2010]. Over the last two decades, racial disparity with regard to HSV-2 seroprevalence in the United States has increased, and 87% of seropositive individuals nationwide were unaware of their status [Fanfair et al., 2013]. Moreover, disproportionate HSV-2 prevalence among women poses a major public health problem due to the risk of neonatal herpes infection, a condition conferring obstetric complications and high mortality [Brown et al., 1997].

HSV-2 is a well-established risk factor for the transmission and acquisition of HIV. Individuals with prevalent HSV-2 are two to three times more likely to contract HIV [Freeman et al., 2006], and HSV-2 accounted for greater than 50% of the population attributable risk of HIV infection among non-injecting drug users in New York City [Des Jarlais et al., 2014]. In addition, HSV-2 has been utilized as a sentinel for HIV transmission risk in various populations including people who inject drugs (PWID), among whom sexual transmission is likely the most common mode of HIV infection [Des Jarlais et al., 2011]. Thus, the epidemiology of HSV-2 is particularly relevant in the drug-using population, among whom STI risk has been shown to be elevated due to high-risk sexual network structures facilitating viral transmission [Latkin et al., 2003; Semaan et al., 2013].

Accounting for asymptomatic and untreated individuals, the medical cost of HSV-2 in the United States was estimated at \$540.7 million in 2008, a total exceeded only by HIV and human papillomavirus [Owusu-Edusei et al., 2013]. This financial burden is likely to be particularly problematic for smaller underserved communities lacking public health resources, social services, and other preventive programs. Thus, understanding the relevant risk factors among individuals in medically underserved communities is crucial to targeting prevention efforts for HSV-2 and other STIs.

As reviewed by Semaan et al. [2013], prior studies of HSV-2 among drug users in the United States have focused primarily on urban populations and reported prevalences consistently elevated relative to the general population, with values ranging from 38% to 75% [Jones et al., 1998; Ross et al., 1999; Hwang et al., 2000; Plitt et al., 2005; Des Jarlais et al., 2007, 2009, 2010, 2011; Semaan et al., 2010; Hagan et al., 2011]. In population-based data, Oster et al. [2014] found no difference in prevalence among 416 PWID when compared by urban versus rural residency, with 35.3% seroprevalence among individuals living in medium, small, and non-metropolitan counties. Overall, HSV-2 seroprevalence for the general population living in non-metro counties was 16.9%, and among heterosexuals, prevalence was significantly higher in central metropolitan areas relative to rural, smaller metropolitan, and suburban areas [Oster et al., 2014]. Similarly, Hwang et al. [2000] found significantly higher HSV-2 prevalence among drug users based in the Houston metropolis compared to those living in the smaller West Texas city of Lubbock (pop. 230,000). In the HSV-2 literature overall, however, the primary focus has been on urban populations, presenting a gap in the epidemiology of this virus. Moreover, rural individuals have been found to engage

frequently in STI risk behaviors, such as younger age at sexual debut, having multiple sex partners, using drugs before or during sex, excessive alcohol use, engaging in transactional sex, and inconsistent condom use [Yan et al., 2007; Dunn et al., 2008; Crosby et al., 2012], but these behaviors have not been assessed in the context of HSV-2 prevalence specifically in a rural high-risk rural population. Moreover, the potential impact of these risk behaviors is compounded by the limited access to disease screening, STI prevention, and specialized treatment services typical of many underserved rural areas in the United States. For these reasons, epidemiological study and needs assessment research targeting HSV-2 and STI prevention more broadly are needed in low-income rural areas of the United States.

Some of the most economically distressed and medically underserved counties in the United States are located in Central Appalachia, particularly Eastern Kentucky [Appalachian Regional Commission, 2011; Lane et al., 2012]. This region is characterized by high rates of poverty and unemployment, poor access to hospitals, healthcare providers, preventive services, and other public health resources, and a lack of social services and addiction treatment programs [Krause et al., 2008]. In addition, illicit drug use is widespread in Appalachian Kentucky, particularly non-medical use of prescription opioids via injection and concomitant drug overdose [Havens et al., 2011]. The rural Appalachian drug users sampled here were previously found to engage in frequent sexual risk behaviors including unprotected sex with multiple partners, unprotected sex with PWID, and unprotected transactional sex [Crosby et al., 2012]. Despite research suggesting that rural Appalachian drug users tend to be embedded in dense risk networks [Young et al., 2012] that could facilitate rapid transmission of STIs [Semaan et al., 2013], there have been no studies describing HSV-2 prevalence and associated risk factors in this population. Thus, the purpose of this study is to examine HSV-2 seroprevalence and determine relevant demographic, behavioral, and social network correlates in a sample of drug users in rural Central Appalachia.

MATERIALS AND METHODS

Study Sample

Data were collected from drug users recruited into the Social Networks among Appalachian People (SNAP) study. To be eligible participants had to be at least 18 years of age, residents of a rural Appalachian county in Kentucky, and have used prescription opioids, heroin, crack/cocaine, or methamphetamine for the purpose of getting high in the preceding 30 days. Participants were recruited using respondent-driven sampling (RDS) between November 2008 and September 2010, as described elsewhere [Havens et al., 2013]. In light of the low level of educational attainment in this sample, interviewer-administered questionnaires were administered by trained community-based interviewers to 503 participants. Baseline interviews were conducted in the study's field office site between November 2008 and August 2010. Informed consent was obtained for all participants. The protocol was approved by the University of Kentucky Institutional Review Board, and a Certificate of Confidentiality was obtained from the National Institutes of Health.

HSV-2 Testing

Excluding three individuals who declined testing and one who did not return for retesting after a test manufacturer recall, all participants were tested for HSV-2 using a rapid test manufactured by Biokit (Lexington, MA), which determines the presence IgG antibodies to glycoprotein G2 in whole capillary blood. The test is 96% sensitive and 98% specific [Ashley et al., 2000]. Pre- and post-test counseling was provided to all persons consenting to testing. Prior to testing, participants were also asked if they had ever been told by a healthcare provider that they were infected with herpes and/or other STIs.

Demographic and Behavioral Characteristics

Data on participants' gender, race, marital status, sexual orientation, age, years of education, and total income were also collected. Behavioral data collected include recent (past 6 months) drug use, ages at first vaginal, anal, and oral sex, age at sexual initiation, and lifetime and recent number of sexual partners. Data on participants' history of engaging in unprotected sex (vaginal, oral, or anal) with non-primary partners and/or PWID, or engaging in any form of unprotected transactional sex (trading sex for money, drugs, or gifts) during the past 6 months were also collected.

Social Network Data Collection

Participants were asked to list the first name and last initial, gender, and age of individuals with whom they had had vaginal, oral, or anal sex in the past 6 months. Network data collection is described in detail elsewhere [Young et al., 2012]. Briefly, to determine linkages among participants, network members' names and demographic characteristics were cross-referenced against that of other participants with input from community-based interviewers. Overall, 870 sexual partnerships were reported, 33.8% ($n = 294$) of named partners were confirmed to be SNAP participants. As in previous analyses [Young et al., 2012; Havens et al., 2013], only confirmed ties between SNAP participants were used in the network analyses of what is hereafter referred to as the *Sex Network*, as non-duplicity among named partners who were *not* participating in SNAP was unable to be determined with confidence and could result in underestimated network density. Thus, to address possible biases introduced by the analysis of only confirmed network ties, network analyses were supplemented by analysis of individual-level behavioral data that included information on *all* sexual partnerships.

Figure 1 illustrates the computation of the network variables. Participants were asked how often a condom was used during any type of sex with each network member, with responses given on a 4-point scale (0 = *all the time*, 1 = *half the time*, 2 = *less than half the time*, 3 = *never*). These data were used to construct a *Frequency of Unprotected Sex Network* in which ties were assigned the maximum ordinal value reported by either partner. An *Unprotected Sex Network* was also constructed, in which the ordinal variable was dichotomized (1 = *any unprotected sex* and 0 = *no unprotected sex*). Participants were also asked with which network members they talked about condom use and to whom condoms were given in the past 6 months.

In the *Sex*, *Unprotected Sex*, and *Frequency of Unprotected Sex* networks, two measures of network centrality (degree centrality and two-step reach) were computed. Centrality has been shown to be associated with STI risk in previous research [Rothenberg et al., 1998]. *Degree centrality* is a local centrality measure which takes into account the number of links to and from a person [Freeman, 1979]. *Two-step reach* is a count of the number of individuals that each person is connected to within two steps (number of immediate partners and the number of those partners' partners) [Hanneman and Riddle, 2005].

Analysis

To account for possible biases introduced by the respondent-driven sampling methodology, individualized sampling weights generated using RDSAT 7.1 (Ithaca, NY) [Volz et al., 2012] were used in all analyses. Univariate analyses for dichotomous and continuous variables were conducted using Rao-Scott χ^2 and adjusted Wald tests, respectively. Variables significant at the $P < 0.10$ level were considered for inclusion in a multivariate logistic model in a stepwise manual forward-selection process, with calculation of respective variance inflation factors to assess for potential multicollinearity in the final model. Adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) are reported. Stata 12.0 (College Station, TX) was used for univariate and multivariate analyses. UCINET v6 (Harvard, MA) [Borgatti et al., 2002] was used to determine prevalence of unprotected sex, condom communication, and condom distribution within sexual relationships and to compute degree centrality and two-step reach. NetDraw v2.1 (Harvard, MA) [Borgatti, 2002] was used for network visualization.

RESULTS

In this sample of 499 rural drug users, the majority were male (57.1%), white (94.2%), with a mean age of 32.6 years. Fifty-seven individuals (11.4%) tested HSV-2 seropositive; after weighting for respondent-driven sampling, the estimated population prevalence was 14.4% (95% CI: 9.6–19.4%). Women in this sample had significantly higher HSV-2 seroprevalence than men (19.6% and 5.3%), with estimated population prevalences of 24.2% and 6.7%, respectively, after weighting for RDS ($P < 0.0001$). No significant differences in seroprevalence were detected by race or sexual orientation, although statistical power was limited by small sample sizes in these subgroups. Only five (8.8%) seropositive participants were aware of their HSV-2 status prior to the study. Five individuals reported having previously been told by a healthcare provider that they were infected with herpes but did not test seropositive in this study.

Table I displays descriptive characteristics and RDS-weighted univariate analyses. HSV-2 seropositive participants were slightly older ($P = 0.011$), more likely to be female ($P < 0.00001$), and lower reported monthly income ($P = 0.036$). HSV-2 seropositive participants also reported slightly more years since sexual initiation ($P = 0.038$), engaging in unprotected sex of any kind with a PWID in the last 6 months ($P = 0.033$), and moderately older ages at first oral ($P = 0.003$) and vaginal sex ($P = 0.004$). HSV-2 serostatus was not associated with any other demographic, sexual behavior, or network measures at the $P < 0.05$ level of significance, although greater frequency of unprotected sex within the sociometric network

was marginally associated with testing HSV-2 seropositive ($P = 0.088$), as was engaging in unprotected transactional sex of any kind (i.e., for money, drugs, or gifts) during the past 6 months ($P = 0.056$).

Table II displays results of the multivariate logistic model ($n = 486$), excluding 13 participants who denied any lifetime history of engaging in oral sex. Female gender (adjusted OR = 4.2, 95%CI: 2.0–8.9), older age (aOR = 1.1 per year, 95%CI: 1.0–1.1), older age at first oral sex (aOR = 1.1 per year, 95%CI: 1.0–1.2), and greater frequency of unprotected sex of any kind within the network (aOR = 1.2, 95%CI: 1.0–1.3) were independently associated with positive HSV-2 serostatus. Variance inflation factors for variables in this final model were less than 1.2, indicating that any correlation between independent variables had negligible impact on standard error.

Sex Network

Of the 499 participants tested for HSV-2, 300 (60.1%) were connected to another participant in the sex network. The majority of participants in the sex network were members of dyads (59%, $n = 176$). The largest component in the network contained 46 participants, six of whom were HSV-2 seropositive (Fig. 2). In total, there were 194 sexual relationships in the network, of which 170 (87.6%) involved unprotected sex. In 155 (91.2%) of the relationships involving unprotected sex, the couple reported never using condoms. In only 16 (9.4%) of the 170 relationships involving unprotected sex did at least one partner report having given condoms to the other, and in only 22 (12.9%) was condom use discussed.

Of the 194 sexual relationships, 75% ($n = 150$) were among seroconcordant partners, including four between HSV-2 seropositive partners. Of the 41 sexual relationships that existed between serodiscordant partners, 33 (80.5%) involved unprotected sex, and in 32 (78.0%), condoms were *never* used in the past 6 months. Of note, condoms were discussed in 16 of the 41 (39.0%) serodiscordant relationships, and condoms were exchanged in just seven of these relationships.

DISCUSSION

This study is among the first to report HSV-2 seroprevalence and associated risk factors in a sample of rural drug users in the United States. HSV-2 antibodies were detected in 11.4% of study participants, yielding an estimated seroprevalence of 14.4% in the sampled population and 95% confidence interval overlapping the 15.7% prevalence reported in the general population [Bradley et al., 2014]. Given that 94% of this study sample was white, it is worth noting that the 14.4% seroprevalence reported here exceeds the 11.3% observed among non-Hispanic white Americans in race-stratified population-based data [Fanfair et al., 2013]. In contrast, as reviewed by Semaan et al. [2013], prior studies of people who use drugs have reported HSV-2 prevalences considerably higher than the general population, with prevalences typically exceeding 40% among both PWID and non-PWID. Interestingly, the level of serostatus awareness among HSV-2+ participants (8.8%) was lower than that reported for the general population in most previous studies, which have ranged from 12.6% to 18.9% [Centers for Disease Control and Prevention, 2010; Pouget et al., 2010; Fanfair et

al., 2013], although one study reported status awareness of just 1.3% among young drug users in Baltimore [Plitt et al., 2005].

Previous research in this population has proposed an “isolative protection” phenomenon at work in rural Appalachia, shielding the region from high prevalence of STIs such as HSV-2 and HIV [Crosby et al., 2012] despite facilitative risk network structure [Young et al., 2012]. This notion is supported by the correlation observed between HSV-2 seroprevalence and increasing urbanicity in the general population and among heterosexuals in particular, although these differences attained only the level of trend ($P = 0.10$) among PWID [Oster et al., 2014]. Nonetheless, in light of the frequency of unprotected sex, dense connectedness of the sexual network, markedly low HSV-2+ status awareness observed in this sample, and the scarcity of preventive services and other healthcare resources in the region, any potentially protective effect afforded by geographic isolation could be readily breached by mixing with other populations characterized by high prevalence of HSV-2 or other STIs. Furthermore, given the tendency of genital herpes to facilitate sexual transmission of HIV [Freeman et al., 2006; Des Jarlais et al., 2014], increased transmission of HSV-2 in this sample with greater than half of participants reporting recent injection drug use would suggest compounded risk for HIV, as has been observed in the recent outbreak of cases in rural southern Indiana [Conrad et al., 2015].

Consistent with findings from previous research [Wald et al., 1997; Semaan et al., 2013], significant associations were observed between HSV-2 and female gender, older age, and higher frequency of unprotected sex in both univariate and multivariate analyses. Higher HSV-2 seroprevalence among women is reflected in many previous studies of genital herpes [Wald et al., 1997; Centers for Disease Control and Prevention, 2010; Semaan et al., 2013], partially due to anatomical differences rendering male-to-female transmission more likely. The association of older age with seropositive status, as with greater amount of time since sexual initiation, is also typical [Wald et al., 1997; Centers for Disease Control and Prevention, 2010], reflective of longer periods for potential viral exposure. Interestingly, recent injection among study participants themselves was not associated with HSV-2 seropositivity, an unexpected finding implying that injection drug use may not exhibit as robust an association with high-risk sexual behavior in this sample as has been reported in other studies [Strathdee and Sherman, 2003; Celentano et al., 2008], particularly those examining the use of crack [Booth et al., 2000] and methamphetamine [Molitor et al., 1999] among PWID.

Previous studies have reported high sexual risk among rural drug users [Crosby et al., 2012], and the majority of this sample reported engaging in unprotected sex and other risky sexual behaviors. Moreover, awareness of an infected partner’s status has been shown to decrease the risk of transmission [Wald et al., 2006], but less than 9% of HSV-2 seropositive participants in this sample were aware of their status. Furthermore, in the present study, 80% of serodiscordant couples in the sex network reported unprotected sex, and in only 13% was condom use discussed, underscoring substantial STI risk in this population.

Recommended approaches to HSV-2 prevention and control among drug users include promotion of disease screening services, partner disclosure, risk-reduction interventions

including education and counseling, antiviral drug treatment for HSV-2, and highly-active antiretroviral therapy among individuals coinfecting with HIV [Semaan et al., 2013]. Incidence of HSV-2 has been shown to be effectively reduced by daily antiviral treatment among infected individuals [Corey et al., 2004]. However, in resource-deprived Central Appalachia, access to healthcare tends to be limited, and rates of health insurance coverage lag behind the national average [Lane et al., 2012]. In this sample, just one in three individuals reported having any form of health insurance, suggesting limited access to primary care and preventive services including STI screening and treatment. Given these barriers and the high cost of treating HSV-2 [Owusu-Edusei et al., 2013], public health strategies recommended by CDC to prevent and control HSV-2 among people who use drugs are especially relevant in this underserved population, including better access to disease screening in order to increase status awareness and partner disclosure, educational interventions, psychosocial counseling, and options for treatment [Semaan et al., 2013].

In light of previous research and the association of sexual network risk behavior with HSV-2 observed here, creative approaches informed by social network data could enhance STI screening and sexual risk reduction efforts among Appalachia drug users. Previous study of such interventions in primarily urban African-American populations has demonstrated that network-based strategies, in which strategically targeted individuals disseminate harm-reduction and other health-protective messages to peers, are most effective if individually tailored to embrace culturally specific social identity and pro-social roles [Latkin et al., 2003]. However, optimal modes of implementation and potential effectiveness of such strategies in a rural, primarily white population requires further study. In an HIV prevention study among MSM in urban southern Indiana, risk network position was identified as a key criterion when selecting educators and peer change agents, with particular emphasis on those individuals at highly centralized or “bridging” locations within the sexual risk network [Schneider et al., 2015]. Thus, while increasing disease status awareness, partner disclosure, and treatment uptake are promising approaches to decreasing HSV-2 prevalence [Wald et al., 2006; Semaan et al., 2013], network-based interventions targeted to influential risk network members to optimize promotion of safe sex practices among the greatest number of individuals could yield substantial added benefit. Nonetheless, more research is needed to explore the feasibility, acceptability, and optimal design of such network-oriented strategies tailored to the setting of resource-poor rural areas such as Central Appalachia.

While this study offers useful public health insights, there are limitations to consider. First, the data reported here are cross-sectional, limiting causal inference, and the serum antibody test used in this study demonstrates exposure to HSV-2, but not time since infection or frequency and severity of symptoms, if any, among seropositive participants. It is also worth noting that while the test used in this study is 98% specific to HSV-2, herpes simplex virus type 1 (HSV-1) can cause an identical clinical presentation and is a substantial contributor to the overall burden of genital herpes [Lafferty et al., 2000]. In addition, low numbers of male (n = 16), racial minority (n = 2), bisexual/homosexual (n = 9) and individuals testing seropositive limited statistical power and the ability to conduct reliable stratified analyses in these subgroups. Finally, some study measures relied on self-reported risk behavior, which can be subject to bias. While interviewer-administration of sensitive questionnaires has potential to introduce social desirability bias, the length and complex skip patterns of the

questionnaire, the detailed nature of the network inventory process, and low educational level of this population precluded the feasibility of self-administration. Moreover, past research has validated the reliability of self-reported data from people who use and inject drugs with regard to risk behaviors for HIV and other STIs [De Irala et al., 1996], and recall bias is minimized by the primary use of measures with a 6-month recall period.

Although HSV-2 seroprevalence in this high-risk population approximates that of the general population and is lower than that reported in prior studies of drug users, the low level of status awareness and abundant sexual risk behavior reported here, coupled with poor access to healthcare, screening, and preventive resources, suggest that interventions to reduce risk behavior facilitating transmission of STIs such as HSV-2 are warranted in this population. In particular, individuals who are female, older, and those who engage in frequent unprotected sex within their sexual network are ideal candidates for focused intervention. CDC recommendations and network-informed interventions could help mitigate the clinical impact and enhancement of HIV risk conferred by HSV-2 infection, although further research is needed to assess the effectiveness of such interventions in the unique context of resource-deprived rural areas. Moreover, future studies with larger samples of male, racial minority, and non-heterosexual drug users in the rural setting would allow for stratified analyses and help shed additional light on this infrequently studied population. Other promising avenues for further study include the clinical impacts of HSV-2, the prevalence of HSV-1 and the relative contribution of this virus to symptomatic genital lesions in this population, and the background prevalence of HSV-2 in the general Appalachian population for comparison to the drug-using population sampled here. Finally, examination of HSV-2 incidence in this population is also likely to be highly informative, both to monitor for increasing prevalence in this population over time as well as enhance causal inference with regard to covariates associated with HSV-2 acquisition. Nonetheless, the findings presented here provide vital insight into the epidemiology of HSV-2 and sexual network structure in an infrequently studied population to inform public health interventions aiming to control STI transmission in resource-deprived rural areas such as Central Appalachia.

Acknowledgments

Grant sponsor: National Institute on Drug Abuse; Grant number: R01DA024598; Grant sponsor: National Center for Research Resources; Grant sponsor: National Center for Advancing Translational Sciences; Grant sponsor: National Institutes of Health (NIH); Grant number: TL1RR033172; Grant sponsor: National Institute on Drug Abuse; Grant number: T32DA035200

References

- Appalachian Regional Commission. County economic status, fiscal year 2011 Appalachian Kentucky. Washington, DC: Appalachian Regional Commission; 2011.
- Ashley RL, Wald A, Eagleton M. Premarket evaluation of the POCKit HSV-2 type-specific serologic test in culture-documented cases of genital herpes simplex virus type 2. *Sex Transm Dis.* 2000; 27:266–269. [PubMed: 10821598]
- Booth RE, Kwiatkowski CF, Chitwood DD. Sex related HIV risk behaviors: Differential risks among injection drug users, crack smokers, and injection drug users who smoke crack. *Drug Alcohol Depend.* 2000; 58:219–226. [PubMed: 10759032]

- Borgatti, S., Everett, M., Freeman, L. Ucinet for windows: Software for social network analysis. Harvard, MA: Analytic Technologies; 2002.
- Borgatti, SP. Netdraw network visualization Version 2.095. Harvard, MA: Analytic Technologies; 2002.
- Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2-United States, 1999–2010. *J Infect Dis.* 2014; 209:325–333. [PubMed: 24136792]
- Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL, Watts DH, Berry S, Herd M, Corey L. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med.* 1997; 337:509–515. [PubMed: 9262493]
- Celentano DD, Latimore AD, Mehta SH. Variations in sexual risks in drug users: Emerging themes in a behavioral context. *Curr HIV/AIDS Rep.* 2008; 5:212–218. [PubMed: 18838061]
- Centers for Disease Control and Prevention. Seroprevalence of herpes simplex virus type 2 among persons aged 14–49 years-United States, 2005–2008. *MMWR Morb Mortal Wkly Rep.* 2010; 59:456–459. [PubMed: 20414188]
- Conrad C, Bradley HM, Broz D, Buddha S, Chapman EL, Galang RR, Hillman D, Hon J, Hoover KW, Patel MR, Perez A, Peters PJ, Pontones P, Roseberry JC, Sandoval M, Shields J, Walthall J, Waterhouse D, Weidle PJ, Wu H, Duwve JM. Community outbreak of HIV infection linked to injection drug use of oxymorphone-Indiana, 2015. *MMWR Morb Mortal Wkly Rep.* 2015; 64:443–444. [PubMed: 25928470]
- Corey L, Wald A, Patel R, Sacks SL, Tyring SK, Warren T, Douglas JM Jr, Paavonen J, Morrow RA, Beutner KR, Strachounsky LS, Mertz G, Keene ON, Watson HA, Tait D, Vargas-Cortes M. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med.* 2004; 350:11–20. [PubMed: 14702423]
- Crosby RA, Oser CB, Leukefeld CG, Havens JR, Young A. Prevalence of HIV and risky sexual behaviors among rural drug users: Does age matter? *Ann Epidemiol.* 2012; 22:778–782. [PubMed: 22902042]
- De Irala J, Bigelow C, McCusker J, Hindin R, Zheng L. Reliability of self-reported human immunodeficiency virus risk behaviors in a residential drug treatment population. *Am J Epidemiol.* 1996; 143:725–732. [PubMed: 8651235]
- Des Jarlais DC, Hagan H, Arasteh K, McKnight C, Perlman D, Friedman SR. Herpes simplex virus-2 and HIV among noninjecting drug users in New York city. *Sex Transm Dis.* 2007; 34:923–927. [PubMed: 18049425]
- Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman D, Friedman SR. Using hepatitis C virus and herpes simplex virus-2 to track HIV among injecting drug users in New York City. *Drug Alcohol Depend.* 2009; 101:88–91. [PubMed: 19108958]
- Des Jarlais DC, Arasteh K, McKnight C, Perlman D, Hagan H, Semaan S, Friedman SR. Gender and age patterns in HSV-2 and HIV infection among non-injecting drug users in New York City. *Sex Transm Dis.* 2010; 37:637–643. [PubMed: 20838366]
- Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman DC, Semaan S. Associations between herpes simplex virus type 2 and HCV with HIV among injecting drug users in New York City: The current importance of sexual transmission of HIV. *Am J Public Health.* 2011; 101:1277–1283. [PubMed: 21566021]
- Des Jarlais DC, Arasteh K, McKnight C, Perlman DC, Feelemyer J, Hagan H, Cooper HL. HSV-2 co-infection as a driver of HIV transmission among heterosexual non-injecting drug users in New York City. *PloS ONE.* 2014; 9:e87993. [PubMed: 24498235]
- Dunn MS, Ilapogu V, Taylor L, Naney C, Blackwell R, Wilder R, Givens C. Self-reported substance use and sexual behaviors among adolescents in a rural state. *J Sch Health.* 2008; 78:587–593. [PubMed: 18844811]
- Fanfair RN, Zaidi A, Taylor LD, Xu F, Gottlieb S, Markowitz L. Trends in seroprevalence of herpes simplex virus type 2 among non-Hispanic blacks and non-Hispanic whites aged 14 to 49 years-United States, 1988 to 2010. *Sex Transm Dis.* 2013; 40:860–864. [PubMed: 24113408]
- Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: Systematic review and meta-analysis of longitudinal studies. *AIDS.* 2006; 20:73–83. [PubMed: 16327322]

- Freeman LC. Centrality in social networks: Conceptual clarification. *Social Netwks.* 1979; 1:215–239.
- Hagan H, Perlman DC, Des Jarlais DC. Sexual risk and HIV infection among drug users in New York City: A pilot study. *Subst Use Misuse.* 2011; 46:201–207. [PubMed: 21303240]
- Hanneman, R., Riddle, M. Introduction to social network methods. University of California; Riverside: 2005.
- Havens JR, Oser CB, Knudsen HK, Lofwall M, Stoops WW, Walsh SL, Leukefeld CG, Kral AH. Individual and network factors associated with non-fatal overdose among rural Appalachian drug users. *Drug Alcohol Depend.* 2011; 115:107–112. [PubMed: 21126831]
- Havens JR, Lofwall MR, Frost SD, Oser CB, Leukefeld CG, Crosby RA. Individual and network factors associated with prevalent hepatitis C infection among rural Appalachian injection drug users. *Am J Public Health.* 2013; 103:e44–e52.
- Hwang LY, Ross MW, Zack C, Bull L, Rickman K, Holleman M. Prevalence of sexually transmitted infections and associated risk factors among populations of drug abusers. *Clin Infect Dis.* 2000; 31:920–926. [PubMed: 11049771]
- King, AMQ. Adams, MJ. Carstens, EB., Lefkowitz, EJ., editors. International Committee on Taxonomy of Viruses. *Virus taxonomy: Classification and nomenclature of viruses: Ninth Report of the International Committee on Taxonomy of Viruses.* San Diego: Elsevier Academic Press; 2012.
- Jones DL, Irwin KL, Inciardi J, Bowser B, Schilling R, Word C, Evans P, Faruque S, McCoy HV, Edlin BR. The high-risk sexual practices of crack-smoking sex workers recruited from the streets of three American cities. The multicenter crack cocaine and HIV infection study team. *Sex Transm Dis.* 1998; 25:187–193. [PubMed: 9564720]
- Krause, DD., May, WL., Lane, NM., Cossmann, JS., Konrad, TR. An analysis of mental health and substance abuse disparities & access to treatment services in the Appalachian region. *Appalachian Regional Commission: National Opinion Research Center (NORC) at the University of Chicago and East Tennessee State University;* 2008.
- Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: Impact on surveillance and prevention. *J Infect Dis.* 2000; 181:1454–1457. [PubMed: 10762576]
- Lane, NM., Lutz, AY., Baker, K., Konrad, TR., Ricketts, TR., Randolph, R., Tran, C., Beadles, CA. Health care costs and access disparities in appalachia. Washington DC: Appalachian Regional Commission; 2012.
- Latkin CA, Sherman S, Knowlton A. HIV prevention among drug users: Outcome of a network-oriented peer outreach intervention. *Health Psychol.* 2003; 22:332–339. [PubMed: 12940388]
- Molitor F, Ruiz JD, Flynn N, Mikanda JN, Sun RK, Anderson R. Methamphetamine use and sexual and injection risk behaviors among out-of-treatment injection drug users. *Am J Drug Alcohol Abuse.* 1999; 25:475–493. [PubMed: 10473010]
- Oster AM, Sternberg M, Nebenzahl S, Broz D, Xu F, Hariri S, Miles I, Paz-Bailey G. Prevalence of HIV, sexually transmitted infections, and viral hepatitis by Urbanicity, among men who have sex with men, injection drug users, and heterosexuals in the United States. *Sex Transm Dis.* 2014; 41:272–279. [PubMed: 24622641]
- Owusu-Edusei K Jr, Chesson HW, Gift TL, Tao G, Mahajan R, Ocfemia MC, Kent CK. The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. *Sex Transm Dis.* 2013; 40:197–201. [PubMed: 23403600]
- Plitt SS, Sherman SG, Strathdee SA, Taha TE. Herpes simplex virus 2 and syphilis among young drug users in Baltimore, Maryland. *Sex Transm Inf.* 2005; 81:248–253.
- Pouget ER, Kershaw TS, Blankenship KM, Ickovics JR, Niccolai LM. Racial/ethnic disparities in undiagnosed infection with herpes simplex virus type 2. *Sex Transm Dis.* 2010; 37:538–543. [PubMed: 20502391]
- Ross MW, Hwang LY, Leonard L, Teng M, Duncan L. Sexual behaviour, STDs and drug use in a crack house population. *Int J STD AIDS.* 1999; 10:224–230. [PubMed: 12035774]
- Rothenberg R, Sterk C, Toomey K, Potterat JJ, Johnson D, Schrader M, Hatch S. Using social network and ethnographic tools to evaluate syphilis transmission. *Sex Transm Dis.* 1998; 25:154–160. [PubMed: 9524994]
- Schneider JA, Zhou AN, Laumann EO. A new HIV prevention network approach: Sociometric peer change agent selection. *Soc Sci Med.* 2015; 125:192–202. [PubMed: 24518188]

- Semaan S, Neumann MS, Hutchins K, D'Anna LH, Kamb ML. Brief counseling for reducing sexual risk and bacterial STIs among drug users-results from project RESPECT. *Drug Alcohol Depend.* 2010; 106:7–15. [PubMed: 19720471]
- Semaan S, Leinhos M, Neumann MS. Public health strategies for prevention and control of HSV-2 in persons who use drugs in the United States. *Drug Alcohol Depend.* 2013; 131:182–197. [PubMed: 23647730]
- Strathdee SA, Sherman SG. The role of sexual transmission of HIV infection among injection and non-injection drug users. *J Urban Health.* 2003; 80:7–14.
- Volz, E., Wejnert, C., Cameron, C., Spiller, M., Barash, V., Degani, I., Heckathorn, D. Respondent-driven sampling analysis tool (RDSAT) Version 7.1. Ithaca, NY: Cornell University; 2012.
- Wald A, Koutsky L, Ashley RL, Corey L. Genital herpes in a primary care clinic. Demographic and sexual correlates of herpes simplex type 2 infections. *Sex Transm Dis.* 1997; 24:149–155. [PubMed: 9132981]
- Wald A, Krantz E, Selke S, Lairson E, Morrow RA, Zeh J. Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. *J Infect Dis.* 2006; 194:42–52. [PubMed: 16741881]
- Yan AF, Chiu Y-W, Stoesen CA, Wang MQ. STD-/HIV-related sexual risk behaviors and substance use among U.S. rural adolescents. *J Natl Med Assoc.* 2007; 99:1386–1394. [PubMed: 18229775]
- Young AM, Jonas AB, Mullins UL, Halgin DS, Havens JR. Network structure and the risk for HIV transmission among rural drug users. *AIDS Behav.* 2012; 17:2341–2351.

Fig. 1.

This figure presents an example to illustrate the computation of degree centrality measures. This figure displays a participant (A) who reports having vaginal, anal, or oral sex with three partners (B–D). Thus, participant A's degree centrality in the sex network is three (i.e., number of sex partners). The numbers next to the ties indicate how often a condom was used during any type of sex with each partner in the network, as specified by the participant on a 4-point scale (0 = *all the time*, 1 = *half the time*, 2 = *less than half the time*, 3 = *never*). For example, participant A's degree centrality for the frequency of unprotected sex network would equal five (i.e., 2+3). In the dichotomized unprotected sex network, where 1 = *any unprotected sex* and 0 = *no unprotected sex*, the degree centrality would equal two (i.e., the number of relationships involving any form of unprotected sex, as indicated by solid lines).

Fig. 2.

Sex network. Solid lines represent recent (past 6 months) sexual relationships involving unprotected vaginal, anal, or oral sex. Dotted lines represent sexual relationships in which condoms were always used. Nodes are sized by their degree centrality (i.e., number of immediate ties).

TABLE I

Sample Characteristics With Demographic, Behavioral, and Network-Level Correlates to HSV-2 Serostatus Among Rural Drug Users (n = 499)

Characteristic	Sample total n (%)	HSV-2 seronegative ^a % (95%CI)	HSV-2 seropositive ^a % (95%CI)	P-value
Demographic				
Female	214 (42.9)	40.6 (35.4–46.1)	75.2 (60.7–85.6)	<0.00001 **
Male	285 (57.1)	59.4 (53.9–64.6)	24.8 (14.4–39.3)	<0.00001 **
Age (years)-mean (95%CI)	32.6 (31.8–33.3)	32.3 (31.4–33.3)	36.3 (33.4–39.2)	0.011 **
White	470 (94.2)	94.2 (91.2–96.2)	97.9 (89.7–99.6)	0.211
Non-white	29 (5.8)	5.8 (3.8–8.8)	2.1 (0.4–10.3)	0.211
Married	130 (26.1)	76.6 (71.8–80.8)	72.2 (56.5–83.9)	0.537
Education (years)-mean (95%CI)	11.1 (11.0–11.3)	11.2 (11.0–11.4)	10.9 (10.3–11.5)	0.369
Income (USD)-mean (95%CI)	1136.7 (982.8–1290.7)	1052.5 (892.6–1212.3)	773.6 (567.7–979.5)	0.036 **
Insured ^c	168 (33.7)	33.4 (29.0–39.2)	27.6 (16.7–42.0)	0.387
Heterosexual	456 (91.4)	93.9 (91.2–95.8)	90.7 (81.1–95.7)	0.317
Bisexual or Homosexual	43 (8.6)	6.1 (4.2–8.8)	9.3 (4.3–18.9)	0.317
Sexual behavior				
Lifetime # sex partners-mean (95%CI)	36.5 (29.9–43.0)	32.8 (26.3–39.4)	33.8 (21.1–46.5)	0.894
Years since sexual debut-mean (95%CI)	14.4 (14.2–14.6)	17.9 (16.8–18.9)	20.9 (18.2–23.5)	0.038 **
Age at first vaginal sex-mean (95%CI)	14.6 (14.4–14.8)	14.6 (14.4–14.9)	15.5 (14.9–16.0)	0.004 **
Age at first anal sex-mean (95%CI)	21.2 (19.9–22.5)	20.6 (19.3–21.8)	24.2 (20.1–28.3)	0.099 *
Age at first oral sex-mean (95%CI)	16.1 (15.7–16.4)	15.9 (15.7–16.2)	18.0 (16.7–19.4)	0.003 **
No. of sex partners in past 6 months- mean (95%CI)	2.3 (2.0–2.6)	1.9 (1.6–2.2)	1.6 (1.1–2.0)	0.180
Unprotected sex with non-main partner in past 6 months	151 (30.3)	23.5 (19.5–28.0)	29.4 (17.6–44.9)	0.398
Unprotected sex with PWID in past months	152 (30.5)	28.0 (23.6–32.8)	45.0 (29.9–61.1)	0.033 **
Unprotected transactional sex in past months	36 (7.2)	5.1 (3.4–7.6)	11.4 (5.4–22.6)	0.056 **
Drug use (past 6 months)				
Injection drug use	287 (57.5)	55.5 (50.0–61.0)	55.2 (39.6–69.9)	0.972
Heroin use	57 (11.4)	10.2 (7.7–13.4)	4.1 (1.2–13.0)	0.124
Illicit methadone use	373 (74.8)	73.8 (68.7–78.3)	60.6 (43.6–75.3)	0.099 *
OxyContin [®] use	406 (81.4)	79.4 (74.1–83.8)	82.1 (69.3–90.3)	0.655
Other oxycodone use	418 (83.8)	86.5 (82.2–89.9)	81.8 (67.5–90.7)	0.409
Hydrocodone use	451 (90.4)	86.3 (81.4–90.1)	91.9 (72.3–98.0)	0.443
Crack use	124 (24.9)	20.2 (16.6–24.4)	28.5 (16.7–44.2)	0.218
Cocaine use	210 (42.1)	38.2 (33.3–43.4)	40.0 (25.7–56.2)	0.830
Methamphetamine use	47 (9.4)	7.3 (5.2–10.2)	11.2 (5.4–21.8)	0.287

Characteristic	Sample total n (%)	HSV-2 seronegative ^a % (95%CI)	HSV-2 seropositive ^a % (95%CI)	P-value
Oral amphetamine use	81 (16.2)	14.5 (11.3–18.3)	10.5 (5.1–20.3)	0.380
Marijuana use	344 (68.9)	66.4 (61.0–71.5)	65.1 (48.3–78.9)	0.876
Benzodiazepine use	412 (82.6)	79.5 (74.4–83.9)	80.9 (61.7–91.8)	0.866
Network measures-mean (95%CI)				
Sex network				
Degree centrality	0.76 (0.68–0.83)	0.73 (0.65–0.80)	0.97 (0.67–1.28)	0.125
2-step reach	1.16 (1.01–1.33)	1.12 (0.97–1.27)	1.46 (0.85–2.07)	0.284
Unprotected sex network				
Degree centrality	0.67 (0.60–0.73)	0.64 (0.58–0.71)	0.82 (0.61–1.03)	0.113
2-step reach	0.90 (0.79–1.01)	0.87 (0.76–0.99)	1.09 (0.76–1.42)	0.214
Frequency of unprotected sex network				
Degree centrality	2.55 (2.30–2.81)	2.45 (2.19–2.70)	3.21 (2.37–4.06)	0.088 [*]

^aWeighted for respondent-driven sampling.

^bIncludes all legal and illegal sources.

^cIncludes private health insurance, Medicaid, or Medicare.

^dProportions estimated from 64 HSV-2 negative and 17 HSV-2 positive participants (n = 81).

^eProportions estimated from 430 HSV-2 negative and 56 HSV-2 positive participants (n = 486).

^{*}P < 0.10;

^{**}P < 0.05.

TABLE IIRDS-Adjusted Multivariate Correlates of HSV-2 Seropositivity in a Population of Rural Drug Users (n = 486)^a

Variable	Adjusted odds ratio	95% Confidence interval	P-value
Female	4.25	(2.04, 8.86)	<0.0001
Age (per year)	1.05	(1.01, 1.09)	0.009
Age at first oral sex (per year)	1.10	(1.01, 1.21)	0.033
Degree centrality in frequency of unprotected sex network	1.16	(1.01, 1.33)	0.040

^aExcludes 13 participants who did not report a history of oral sex.