Epidemiology of Herpes Simplex Virus

College of Medicine

Diyala University

In partial fulfillment of

The requirement of M.B.Ch.B

Supervised by: Prof Dr. Shahab Ahmed Shakir

Done by: ALI ADNAN NASER

2021-2020 1442-1441

Abstract

Background: Infection with herpes simplex virus (HSV) types 1 and 2 is common infection among human population. Virus transmission is typically restricted to the epithelia and develops persistently in paranoia inducing sensory neurons, reactivating on a regular basis to create localized recurrent infections. Nevertheless, these infections can also cause serious illness, such as chronic keratitis, which can vision loss as well as neonatal encephalitis and systemic disease in people with compromised immune systems. While pharmacological intervention has resulted in significant improvements in the treatment of both primary and recurring infections, sensitivity to currently available drugs and long-term toxicity pose a current and potential challenge that should be tackled through the production of new antiviral compounds focused against novel targets. Several ambitious HSV vaccines have currently been discontinued due to minor or contentious clinical effects in humans. Several promising clinical trials remain in the pipeline and are successful in animal models; these must also be evaluated in humans for adequate therapeutic effects to prompt further production.

Aim: To determine the prevalence of HSV.

Patient and methods: The study design and methods for quarterly follow up, HIV-1 testing and viral-load measurement, along with demographics, risk behavior, and other clinical data. Five hundred and thirteen adolescent (386 females and 127 males) with age from 14 to 19 years old were involved in this cohort study with a period of 1.95 years. In the Reaching for Excellence in Adolescent Care and Health (REACH) center, the cohort was checked for HSV-2 antibodies at baseline and again at the final follow-up visit.

Results: At baseline, 179 (35%) subjects were HSV-2 positive, with an additional 47 (16%) new cases being identified during a median follow-up time of 1.95 years and an incidence rate of 7.35 cases per 100 person years (py). Several risk factors were associated with HSV-2 prevalence (being female, non-Hispanic, uncertainty of sexual preference, and HIV-1 positive) and incidence (using drugs, alcohol, and number of new sexual partners). Among HIV-1 positives, an increase in CD4+ count by 50 cell/mm3 (OR, 1.17; 95% CI 1.04–1.31, p=0.008) was associated with HSV-2 acquisition.

Conclusion: The high prevalence and incidence of HSV-2 infection among adolescents, compared to the general population at this age group suggests a critical need for screening and preventive programs among this targeted group

Keywords: HIV-1, HSV-2, CD4+ count, adolescents

Introduction

Infections with the herpes simplex virus (HSV) are common in humans all over the world. (1-2) the infection is permanent and is marked by reactivations at the infection site on a regular basis. HSV type 1 is mainly transmitted by oral-to-oral contact and is the most common cause of orolabial herpes (cold sores). Type 1 virus may also cause keratitis and other ocular manifestations, as well as encephalitis.(3-4) HSV type 1 genital infection from oral-to-genital contact is on the rise, though reactivations are less common than for HSV type 2. (5–6) HSV type 2 is almost exclusively transmitted sexually, triggering genital herpes. (7) Genital HSV infections can go unnoticed or result in painful genital ulcer disease in some people. Neonates can become infected with HSV by genitally infected mothers during birth and through oral contact with caregivers after birth. (8) While uncommon, neonatal infection has a high fatality and impairment rate in living infants. Numerous early fundamental findings set the basis for today's awareness of HSV. Symptomatic and asymptomatic viral spreading are normal for both HSV type 1 and type 2.(9-12) As a result, infected individuals may be asymptomatic and contagious, causing these viruses to be transmitted unknowingly, a factor that leads to the high global prevalence of HSV infection. To begin, once infected, a person can experience recurrences despite both humeral and cell-mediated immune responses (leading to the recognition that the virus establishes latency and may recur upon various provocative stimuli to produce disease). Secondly, the distinction between HSV-1 and HSV-2 was obvious. HSV-1 was associated primarily with upper body infections, specifically the mouth and eyes, while HSV-2 was associated with infections below the belt, specifically genital herpes. In modern times, however, there is substantial overlap between HSV infection sites and a growing proportion of genital herpes induced by HSV-1. In the United States, more than half of adults are seropositive for HSV-1, and about 15% of sexually active people are infected with HSV-2 (13). These viruses' infections are, for the most part, harmless. Thirdly, there was evidence of person-to-person transmission, especially in boarding houses and among sexual partners. Just toward the end of the twentieth century more understanding about epidemiology, pathogenesis, virulence, and the mechanics of latent infection had spike. The use of two critical methods, type-specific serology and polymerase chain reaction would provide significant insights into pathogenesis (PCR). Consequently, antiviral

therapy, especially acyclovir, became widely available, eventually bringing in the era of HSV disease management. Significant new discoveries concerning pathogenesis have been reported in the twenty-first century.

Epidemiology

Herpes simplex epidemiology is of great epidemiologic and public health importance. About 90% of people worldwide are infected with the herpes simplex virus (HSV-1 and HSV-2). (14) While several people infected with HSV develop labial or genital lesions (herpes simplex), the vast majorities goes undiagnosed or have no physical symptoms—individuals who have no symptoms are referred to as "asymptomatic." or as having subclinical herpes.

The first symptom of a person's own infection in many diseases is horizontal transmission to a sexual partner or vertical transmission of neonatal herpes to a newborn at term. Since the majority of asymptomatic people are unaware of their infection, they are considered to be at high risk of transmitting HSV.

Many studies have been conducted worldwide to estimate the number of people infected with HSV-1 and HSV-2 by assessing whether or not they have produced antibodies against either viral type.

This data shows the population prevalence of HSV viral infections in people with and without active disease. It should be noted that some population subgroups, such as cancer chemotherapy patients, are more susceptible to HSV infections.

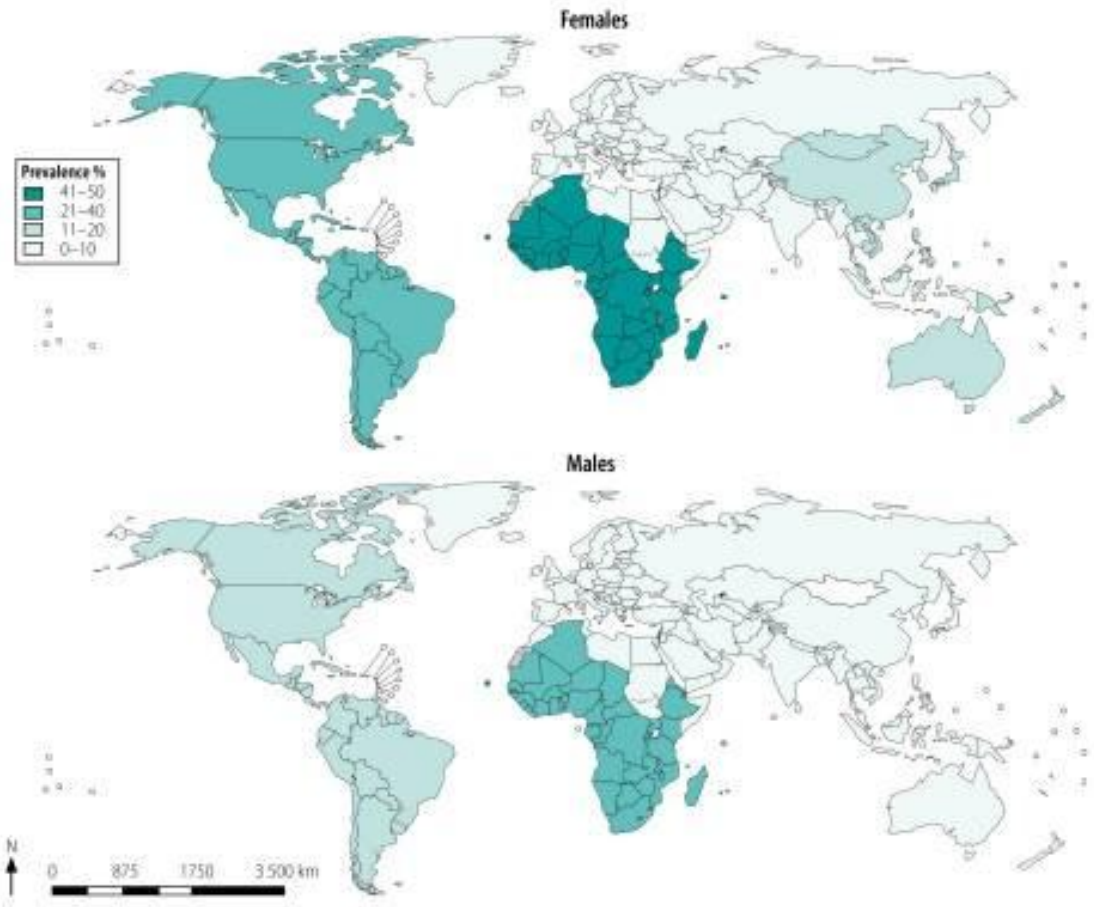
Prevalence

The World Health Organization (WHO) has previously provided global and regional projections of HSV type 2 infection prevalence and incidence (derived from prevalence) among people aged 15 to 49 years old in 2005 and 2012(.15, 16) For 2012, the first observations of HSV type 1 infection at any location in people

aged 0–49 years old, and of genital HSV type 1 infection in people aged 15–49 years old, were made. 1 The Global Burden of Disease (GBD) report has also provided estimates for HSV type 2 infection (again, close to the WHO estimates), most recently for 2017. (17)These figures, however, are not directly comparable to the WHO estimates since they go up to age 99, are not adjusted for assay accuracy, and use different regional groupings than the WHO estimates. Furthermore, the GBD report provides no estimates for HSV type 1 infection, which is becoming an increasingly common cause of genital infection. According to 2016 figures, a total of 491.5 million (95 percent UI: 430.4 million–610.6 million) individuals 15–49 years old worldwide were infected with HSV type 2. (Table 1). Women were affected at a higher rate (313.5 million) than men (178.0 million).while, an approximate 120.4 million (95 percent UI: 114.3 million–130.1 million) people aged 0–49 years were infected with HSV form 1 at any location, representing a 2.1 percent (95 percent UI: 2.0–2.3;). The percentage was highest in Africa and decreased with age, most prominently in countries where incidence was saturated at younger ages.

WHO region by sex	No. of infected people in millions (population prevalence, %) by age group								95% UI[a]
	15–19 years	20–24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	Total	
Total	27.8 (4.8)	49.6 (8.5)	68.6 (11.4)	78.9 (14.3)	83.3 (16.8)	89.6 (18.8)	93.7 (20.8)	491.5 (13.2)	430.4–610.6 (11.5–16.3)

In contrast to 2012 figures, the number of available prevalence data points for HSV types 1 and 2 increased in 2016. This rise, however, did not necessarily result from an increase in the number of countries represented, as the number of participating countries decreased between the 2012 and 2016 figures. The decline was especially noticeable in the WHO Region of the USA.



	African Region	Region of the Americas	Eastern Mediterranean Region	European Region	South-East Asia Region	Western Pacific Region
Female						
Prevalence	43.9%	24.0%	7.6%	10.7%	9.6%	14.6%
Number	102.9 million	57.7 million	12.8 million	22.2 million	48.4 million	65.5 million
Male						
Prevalence	25.4%	11.6%	2.8%	5.3%	7.2%	7.1%
Number	59.3 million	28.0 million	5.1 million	11.1 million	38.5 million	36.0 million

Map of regional estimates of the number and prevalence of herpes simplex virus infections in females and males, 2016

HSV type 1 or 2 infected an estimated 596 million–656 million people, implying that HSV has a significant impact on the sexual and reproductive health of millions of people worldwide. Women and the WHO African Area were disproportionately affected by HSV type 2 infections.

Herpes simplex virus type 1 (HSV-1)

HSV-1 is an extremely contagious virus that is widespread and prevalent around the world. The majority of HSV-1 infections occur during puberty, and the infection is permanent. The most of of HSV-1 infections are oral herpes (infections in or around the mouth, also known as orolabial, oral-labial, or oral-facial herpes), but genital herpes (infections in the genital or anal area). (17-18)

Signs and symptoms of Oral herpes infection is usually symptomless, and the majority of people infected with HSV-1 are unaware they are affected. Oral herpes symptoms involve painful blisters or open sores called ulcers in or around the mouth. (19-20)Before the emergence of sores, infected people often feel tingling, scratching, or burning sensations around their mouth. After the initial infection, the blisters or ulcers can reoccur on a regular basis. (21)The frequency at which recurrences occur varies from person to person. On the other hand, HSV-1 genital herpes may be asymptomatic or have minor symptoms that go unidentified. When signs do appear, genital herpes is distinguished by the presence of one or more genital or anal blisters or ulcers. Symptoms of genital herpes can recur after an initial, serious episode. Unlike genital herpes caused by herpes simplex virus type 2, genital herpes caused by HSV-1 does not normally persist frequently. To cause oral herpes infection, HSV-1 is primarily **transmitted** via oral-to-oral contact, through contact with the virus in sores, saliva, and surfaces in or around the mouth. HSV-1, on the other hand, can be transmitted to the genital area through oral-genital contact and cause genital herpes. Furthermore, HSV-1 can be transmitted via natural oral or skin surfaces in the absence of symptoms. If there are active lesions, however, the risk of transmission is highest. Individuals that have already had HSV-1 oral herpes are unlikely to become infected with HSV-1 in the genital region.

Possible complications

HSV-1 can cause more serious symptoms and recurrences in immunocompromised individuals, such as those with advanced HIV infection. In rare cases, HSV-1 infection may cause more serious complications such as encephalitis (brain infection) or keratitis (eye infection).(22)

Herpes simplex virus type 2 (HSV-2)

HSV-2 infection is common in the world and is almost entirely transmitted sexually, resulting in genital herpes. HSV-2 is the most common cause of genital herpes, while herpes simplex virus type 1 may also cause it (HSV-1) however HSV-2 infection is permanent and untreatable.(23)

Genital herpes infections usually have no manifestations or have mild symptoms that ignored by most of the patients. The majority of sick people are unaware that they are infected. About 10-20% of people with HSV-2 infection have a history of genital herpes. Medical research on people being closely monitored for new infections, on the other hand, show that up to one-third of people with new infections may have symptoms. Genital herpes is distinguished by the presence of one or more genital or anal ulcers.(24)

Symptoms of recent genital herpes infections include fever, body aches, and swollen lymph nodes, with genital ulcers. Incidences appear to become less frequent with time, but they can last for several years. Before the emergence of genital ulcers, people infected with HSV-2 can feel mild tingling or shooting pain in the legs, hips, and buttocks.

HSV-2 is primarily transmitted during sex by contact with infected individuals' genital surfaces, skin, sores, or fluids. HSV-2 can be **transmitted** via normal-looking skin in the genital or anal region, and it is often transmitted in the absence of symptoms.

Possible complications

HSV-2 and HIV have been shown to interact with one another. (25) HSV-2 infection more than triples the chance of contracting a new HIV infection. Furthermore, people who are infected with both HIV and HSV-2 are more likely to transmit HIV to others. HSV-2 is one of the most common infections in HIV

patients, infecting 60-90 percent of that infected.in addition, Infection with HSV-2 in people living with HIV (and other immunocompromised people) can result in a more serious appearance and more frequent episodes. HSV-2 may cause more severe, but uncommon, complications in advanced HIV disease, such as meningoencephalitis, esophagitis, hepatitis, pneumonitis, retinal necrosis, or disseminated infection.

Treatment

The roles of treatment for both type of herpes simplex infection being studied with two drugs are: **pritelivir** and **brincidofovir**.(26-28)

1) **Pritelivir** is a helicase primase inhibitor that is required for HSV DNA replication. Pritelivir is highly active in cell culture and has been shown to have substantial efficacy against genital HSV infections in two clinical trials. To date, medication has been limited to the treatment of genital herpetic infections in the short term, rather than long-term inhibiting therapy. Long-term toxicity evaluations are being conducted to assess the suitability of long-term suppressive management. Pritelivir is currently being tested for its efficacy against acyclovir-resistant HSV infections in immunocompromised patients.
2) **Brincidofovir**, a lipophilic analog of cidofovir, has a similar molecular mechanism to cidofovir but without the corresponding nephrotoxicity. The drug was initially created to treat human cytomegalovirus infections in hematopoietic stem cell transplant recipients. However, because of gastrointestinal tract toxicity, the drug is no longer being tested for this indication. It is uncertain if this drug would eventually be available for human administration in certain circumstances.

Vaccination

Another important point to discuss is that there a wide range of vaccination trails had been conducted; they have ultimately yielded disappointing results in human

trials, leading to termination of vaccine development. The most recent of these are as follows.

In June 2018, The VICal HSV-2 program was suspended after a VICal vaccine trial "did not reach proper end point" in reducing HSV-2–induced infections. This vaccine contains plasmids encoding HSV-2 viral proteins glycoprotein D, VP11/12 encoded by UL46, and VP13/14 encoded by UL47, both of which are combined with the cationic lipid–based adjuvant Vaxfectin. Although the vaccine had been well accepted during the human trial and had previously been shown to be successful against recurrent lesions in animal models, the extent of the impact in the test population—HSV-2–infected individuals who reactivated reasonably regularly (four to nine times per year)—did not warrant further research.

Another trail carried out by Genocea (Cambridge, MA, USA) will apparently no longer grow its GEN-003 vaccine solely after the outcome of a partially finished phase III trial showed only modest clinical efficacy. This vaccine is made up of HSV-2 gD without the transmembrane domain and a truncated form of infected cell polypeptide 4 (ICP4) formulated in a Matrix M-2 adjuvant.

To determine if any of these promising leads would eventually result in an effective HSV-1 or HSV-2 vaccine, significant reductions in lesions in human clinical trials will be needed. This has historically been a formidable barrier to tackle.

Patient and Methods:

Five hundred and thirteen adolescents (386 females and 127 males) with age from 14to19 years old and end of follow up HSV-2 serology data were a period of 1.95 years. In the Reaching for Excellence in Adolescent Care and Health (REACH) center, the cohort was checked for HSV-2 antibodies at baseline and again at the final follow-up visit. The prevalence of HSV-2 infection at baseline and the incidence (per individual year) were determined. A subgroup study was also performed among HIV-1-positive individuals to determine risk factors for HSV-2 infection. The odds ratios (OR) and p-values (p) for associations between CD4+ T-cell (CD4+) count, HIV-1 viral load (VL), and HSV-2 acquisition were estimated using conditional logistic regression, after controlling for antiretroviral therapy use, other sexually transmitted infections, gender, race, and number of sexual partners.

Results:

Of the eligible participants, 343 were HIV-1 seropositive, and 170 were HIV-1 seronegative. At baseline, prevalent HSV-2 infection was present in 179 (35%), and 47 (16%) incident cases were identified during a median follow-up period of 1.95 years, resulting in an incidence of 7.35 cases/100 py. Incidence rates tended to be higher among females (7.70 vs. 6.64/100 py), African Americans (7.62 vs. 6.89/100 py), and HIV-1-positive participants (8.50 vs. 5.58/100 py); however, none of these differences were statistically significant.

Persons with prevalent HSV-2 infection were more likely to be heterosexual (81% vs. 69%), female (91% vs. 67%), black non-Hispanic (78% vs. 64%), HIV-1 positive (82% vs. 59%), and co-infected with chlamydia (25% vs. 16%). Perhaps surprisingly, fewer HSV-2 infected participants reported smoking cigarettes (47% vs. 59%) than HSV-2-negative subjects; however, 58% of HSV-2 seronegativs at baseline who reported smoking became HSV-2 seropositive at the end of the study (Table 1).

Table 1

Differences between a) HSV-2 sero-prevalent and HSV-2 negative adolescents at baseline and b) HSV-2 sero-incident and HSV-2 negative adolescents at the end of follow-up

	a) Baseline			b) End of follow-up		
	HSV-2 negative (n=334)	**HSV-2 positive (n= 179)**	**P**	**HSV-2 negative (n=287)**	**HSV-2 positive (n=47)**	**p**
Female	66.77 (223)	91.06 (163)	**<0.0001**	66.20 (190)	70.21 (33)	0.59
Age[#]	16.76 ± 1.17	16.86 ± 1.12	0.37	18.84±1.55	19.36±1.63	**0.04**
Race/Ethnicity			**0.0014**			0.89
Black	64.07 (214)	77.53 (138)		63.76 (183)	65.96 (31)	
White	5.69 (19)	2.25 (4)		5.92 (17)	4.26 (2)	
Hispanic	23.95 (80)	11.80 (21)		23.76 (68)	25.53 (12)	
Other	6.29 (21)	8.43 (15)		6.62 (19)	4.26 (2)	
Sexual Preference			**<0.0001**			0.47
Heterosexual	69.33 (226)	81.07 (137)		68.68(193)	73.33 (33)	
Bisexual	10.74 (35)	4.73 (8)		10.32 (29)	13.33 (6)	
Homosexual	16.56 (54)	4.73 (8)		17.08 (48)	13.33 (6)	
Not Sure	3.37 (11)	9.47 (16)		3.91 (11)	0	
HIV positive	58.98 (197)	81.56 (146)	**<0.0001**	57.14 (164)	70.21 (33)	0.09
Gonorrhea[*]	7.07 (21)	12.42 (19)	0.06	9.41 (27)	21.28 (10)	**0.02**
Chlamydia[*]	15.72 (47)	25.00 (39)	**0.02**	26.48 (76)	29.79 (14)	0.64
Anal HPV[~]	31.72 (85)	35.82 (48)	0.41	36.24 (104)	46.81 (22)	0.17
Survival Sex[*]	5.99 (20)	3.35 (6)	0.20	7.32 (21)	14.89 (7)	0.08
Number of Sexual Partners at baseline			0.57[†]			0.15[†]
median (IQR)	6 (3, 14)	7 (4, 14)		6 (3, 14)	8.5 (3, 21)	
mean (SD)	13.96 (24.55)	15.54 (30.94)		13.18 (24.32)	18.91 (25.73)	
Engaged in receptive anal sex[*]	36.39 (119)	28.24 (48)	0.07	17.41 (50)	25.53 (12)	0.19
Homeless[*]	23.35 (78)	26.40 (47)	0.44	21.60 (62)	34.04 (16)	0.06
Ever Smoked cigarettes[*]	59.33 (194)	47.06 (80)	**0.009**	80.49 (231)	85.11 (40)	0.45
Ever drank alcohol[*]	71.25 (233)	64.12 (109)	0.10	32.06 (92)	51.06 (24)	**0.01**
Ever used drugs[*]	86.93 (266)	80.26 (122)	0.06	36.93 (106)	57.45 (27)	**0.008**
New sexual partners during follow-up						**0.04**[†]
median (IQR)				2 (0, 4)	2 (0, 6)	
mean (SD)				3.44±7.98	6.57±15.84	

Table 2: Associations between demographic or risk behavior characteristics and a) prevalence b) incidence of HSV-2 infection. Odds ratios (OR) and 95% CI are estimated .

	a) Baseline (Odds Ratio)				b) End of Follow-up (Odds Ratio)			
	Crude	95% CI	Adjusted	95% CI	Crude	95% CI	Adjusted	95% CI
Female	5.07	(2.89, 8.89)	**7.46**	**(3.12, 17.83)**				
Race Ethnicity								
Black	1.89	(1.25, 2.86)						
White	0.38	(0.13, 1.13)						
Hispanic	0.43	(0.25, 0.71)	**0.42**	**(0.21, 0.84)**				
Other	1.36	(0.68, 2.72)						
Sexual Preference								
Not Sure	2.88	(1.31, 6.35)	**3.87**	**(1.31, 11.42)**				
Bisexual	0.24	(0.11, 0.52)						
Homosexual	0.40	(0.18,						
Heterosexual	1.56	(1.03, 2.36)						
HIV positive	3.20	(2.06, 4.96)	**2.94**	**(1.75, 4.96)**	1.77	(0.91, 3.45)		
Gonorrhea*	1.86	(0.97, 3.58)			2.60	(1.17, 5.81)		
Chlamydia*	1.79	(1.11, 2.88)						
Engaged in receptive anal sex*	0.69	(0.46, 1.03)						
Ever Smoked cigarettes*	0.61	(0.42, 0.89)						
Ever used drugs*	0.61	(0.36, 1.03)			2.31	(1.23, 4.31)	**2.31**	**(1.23, 4.34)**
Age at end of study					1.24	(1.01, 1.52)		
Survival sex*					2.22	(0.89, 5.55)		
Homeless*					1.87	(0.96,		

Likewise, upon comparison of HSV-2 incident cases and HSV-2 seronegatives, the seroincident subjects were older (19.4 vs. 18.8 years), and during follow-up, were more likely to have been infected with gonorrhea (21% vs. 9%), had ever consumed alcohol (51% vs. 32%), used drugs (57% vs. 37%), or had a greater number of sexual partners (mean 6.57 vs. 3.44) than HSV-2-seronegative subjects (Table 1). In the multivariable model, only having used drugs during the follow-up time (OR, 2.31; 95% CI, 1.23–4.34)) remained significantly different between seroincident and seronegative persons (Table 2).

Discussion

HSV-2 prevalence rates were higher in the REACH cohort (35%) compared to adolescents (1.6%) of similar age (14–19) from NHANES, during the study period. (21) Most factors associated with HSV-2 seroprevalence at study baseline are similar to those reported in previous studies. As in prior studies, the prevalence was relatively higher (39%) among black non-Hispanics than among Hispanics (21%). In the most recent data from NHANES III, overall HSV-2 seroprevalence was 39.2% in black non-Hispanics (48% in women vs. 29% in men) as compared to 12.3% (15.9% in women and 8.7% in men) in white non-Hispanics and 10.1% (13.2% in women and 7.5% in men) in Mexican Americans,2 similar to rates in suburban primary care offices.(22) HSV-2-prevalent individuals were also more likely to be females (r2, 0.53 with being heterosexual) and HIV-1 positive. The cohort is comprised of 76% females and a stratified analysis by gender could not be conducted due to limited power; however a sensitivity analysis among females showed similar results to those presented in this study (data not shown). Adolescents who reported to be unsure of their sexual preference were also likely to be HSV-2 seroprevalent. (24) These individuals were more likely to be HIV-positive, engage in anal sex, and be involved in survival sex and had a higher number of sex-partners which could indicate that they were engaging in sexual acts to help determine their sexuality (data not shown).(25)

Despite the high initial prevalence of HSV-2 among participants, HSV-2 incidence rates were high in the REACH cohort (7.35 per 100 py) compared to the general

U.S. population (0.18 per 100 py) ; however, it was at the lower end of what has been reported in some special populations. These estimates of HSV-2 incidence are conservative since HSV-2 was tested only at two visits, the first and last, and thus the actual date of seroconversion was likely sooner than the date of the final follow-up visit. Among HIV-1-negative individuals attending U.S. STD clinics (RESPECT cohort), an incidence of 11.7 per 100py was reported. Likewise, studies among women attending STD clinics in the U.S. have reported incidence ranging from 5.7–20.5 per 100 woman years and similarly 4.9–14.2 per 100 person years in other populations. (26)

Factors associated with HSV-2 seroprevalence at baseline differed from factors associated with HSV-2 seroincidence. HSV-2-seroprevalent cases differed demographically, such as with race and gender, and risk behaviors such as sexual preferences, and HIV status from HSV-2-seronegative individuals at baseline. Persons who experienced HSV-2-seroincidence during follow up were more likely to report drug use and a higher numbers of new sexual partners when compared to individuals who remained HSV-2-seronegative. Seroincident cases were more likely to be HIV-1-seropositive, and the trend was similar for drug use and co-infection with gonorrhea as in seroprevalent individuals. (27) Having only had such data at the time of initial evaluation and at the end of the follow-up period, acknowledge the lack of precision in the evaluation of time-dependent factors. Here, they used the baseline measurements for the prevalence study; but for the seroincident study, either could only ascertain variables such as drug and alcohol use cumulatively for all follow-up visits or used the data reported at the time of the last visit. Future studies should assess HSV-2 serology at each visit to correspond to the risk factor at respective visits. (28)

Recommendations

The present study is a multicenter study and unlike other studies from specific clinics or sites, where data may disproportionately represent certain social and sexual networks, our estimates may be more representative for at-risk adolescents in the U.S., in general. The results indicate that adolescents were engaging in activities that made them susceptible to HSV-2 infection even after being infected

with HIV-1 and add to the recommendation for continuing risk reduction counseling for persons with HIV, i.e "prevention for positives"

Conclusion

Herpes simplex virus infection, also known as herpes, may be caused by either herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2) (HSV-2). HSV-1 is primarily transmitted by oral-to-oral communication, resulting in infection in or around the mouth (oral herpes). HSV-1, on the other hand, may be transmitted by oral-genital contact and cause inflammation in or around the genital region (genital herpes). HSV-2 is almost predominantly acquired during sex by genital-to-genital contact, resulting in infection in the genital or anal region (genital herpes).

Reference

1. Looker KJ, Magaret AS, May MT, Turner KME, Vickerman P, Gottlieb SL, et al. Global and regional estimates of prevalent and incident herpes simplex virus type 1 infections in 2012. PLoS One. 2015

2. Looker KJ, Magaret AS, Turner KME, Vickerman P, Gottlieb SL, Newman LM. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. PLoS One. 2015.

3. Higgins CR, Schofield JK, Tatnall FM, Leigh IM. Natural history, management and complications of herpes labialis. J Med Virol. 1993;41(S1)

4. Whitley R, Baines J. Clinical management of herpes simplex virus infections: past, present, and future. F1000 Res. 2018.

5. Ayoub HH, Chemaitelly H, Abu-Raddad LJ. Characterizing the transitioning epidemiology of herpes simplex virus type 1 in the USA: model-based predictions. BMC Med. 2019.

6. Tuokko H, Bloigu R, Hukkanen V. Herpes simplex virus type 1 genital herpes in young women: current trend in Northern Finland. Sex Transm Infect. 2014.

7. Brijwal M, Rawre J, Dhawan B, Khanna N, Choudhary A, Dar L. Herpes simplex virus type 1 genital ulcer disease at a tertiary care hospital in north India. Clin Infect Dis. 2019. May 2;68(10):1783–4.

8. Khadr L, Harfouche M, Omori R, Schwarzer G, Chemaitelly H, Abu-Raddad LJ. The epidemiology of herpes simplex virus type 1 in Asia: systematic review, meta-analyses, and meta-regressions. Clin Infect Dis. 2019. February 15;68(5):757–72.

9. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med. 1994.

10. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med. 1983. June;98(6):958–72.

11. Anonymous: Redbook, 31st ed. American Academy of Pediatrics.2018.]

12. Kimberlin DW, Whitley RJ, Wan W, et al. : Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med. 2011;365(14):1284–92.

13. Whitley RJ, Alford CA, Hirsch MS, et al. : Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med. 1986;314(3):144–9.

14. Whitley R: Herpes Simplex Virus. In Scheld W, Whitley R, Marra C (ed), Infections of the Central Nervous System,3rd ed. LWW, Philadelphia.2004;123–144.

15. Rowley AH, Whitley RJ, Lakeman FD, et al. : Rapid detection of herpes-simplex-virus DNA in cerebrospinal fluid of patients with herpes simplex encephalitis. Lancet. 1990;

16. Lakeman F, Whitley RJ: Diagnosis of herpes simplex encephalitis: results of PCR on CSF from biopsy positive and biopsy negative patients. p. In (ed).

17. Whitley R: Herpes Simplex Virus Infections. In Singhi P, Griffin D, Newton C (ed), Infections of the CNS in Children.Mac Keith Press.2014.

18. Jouan Y, Grammatico-Guillon L, Espitalier F, et al. : Long-term outcome of severe herpes simplex encephalitis: a population-based observational study. Crit Care. 2015;19(1):345.

19. Raschilas F, Wolff M, Delatour F, et al. : Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis. 2002;35(3):254–60.

20. Gnann JW, Jr, Sköldenberg B, Hart J, et al. : Herpes Simplex Encephalitis: Lack of Clinical Benefit of Long-term Valacyclovir Therapy. Clin Infect Dis. 2015;61(5):683–91.

21.Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006;296:964–73.

22. Leone P, Fleming DT, Gilsenan AW, et al. Seroprevalence of herpes simplex virus-2 in suburban primary care offices in the United States. Sex Transm Dis. 2004;31:311–6.

23. Gottlieb SL, Douglas JM, Jr, Foster M, et al. Incidence of herpes simplex virus type 2 infection in 5 sexually transmitted disease (STD) clinics and the effect of HIV/STD risk-reduction counseling. J Infect Dis. 2004;190:1059–67.

24. Gallo MF, Warner L, Macaluso M, et al. Risk factors for incident herpes simplex type 2 virus infection among women attending a sexually transmitted disease clinic. Sexually transmitted diseases. 2008;35:679–85.

25. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. Annals of internal medicine. 2005;143:707–13.

26. Cachay ER, Frost SD, Poon AF, et al. Herpes simplex virus type 2 acquisition during recent HIV infection does not influence plasma HIV levels. J Acquir Immune Defic Syndr. 2008;47:592–6.

27. Tobian AA, Charvat B, Ssempijja V, et al. Factors associated with the prevalence and incidence of herpes simplex virus type 2 infection among men in Rakai, Uganda. J Infect Dis. 2009;199:945–9.

28. Tassiopoulos KK, Seage G, 3rd, Sam N, et al. Predictors of herpes simplex virus type 2 prevalence and incidence among bar and hotel workers in Moshi, Tanzania. J Infect Dis. 2007;195:493–501