Time Trends in First Episode Genital HSV infections in an Urban STD Clinic

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Abstract

Background: Genital HSV-1 has emerged as a more common cause of first episode genital herpes in the last few decades. We examined trends in etiology of first episode genital HSV infection in a 21-year period and determined risk factors for genital HSV-1 versus genital HSV-2 infection.

Methods: Using an electronic database, we identified persons who visited Public Health – Seattle & King County STD Clinic from 1993 through 2014 with genital ulcers. We selected persons diagnosed with a first episode of culture positive genital HSV. Poisson regression was used to determine risk factors for first episode genital HSV-1 versus HSV-2 infection.

Results: Of 52,030 patients with genital ulcers, 3,199 (6.15%) patients had culture-proven first episode genital HSV infection: 1,059 (33.1%) with HSV-1 and 2,140 (67.9%) with HSV-2. Overall, 1,213 (37.9%) patients with first episode genital HSV were women. The median age was 27 (range 13-81) years of age. 1,959 (61.2%) patients were white, and 377 (11.8%) were men who have sex with men. Over time, the number of patients with HSV-2 has declined 6% per year, from 223 in 1993 to 39 in 2014 (RR=0.94 per year, 95% CI=0.93, 0.95) while the number of patients with HSV-1 remained stable at about 50 per year (RR=1.0; 95% CI: 0.99, 1.01), resulting in an increasing proportion attributed to HSV-1 over time, from 16.9% in 1993 to 44% in 2014. Among patients with first-episode genital HSV, age <30 years (RR=1.40; 95% CI: 1.20, 1.63), white race (RR=3.03; 95% CI: 2.37, 3.87), and reporting homosexual practice (RR=1.42; 95% CI: 1.19, 1.71) were associated with genital HSV-1 infection compared with genital HSV-2 infection.

Conclusions: We observed a significant decrease in first episode genital HSV-2 in the last 21 years with a stable number of first episode genital HSV-1 infections. Understanding changing epidemiology in genital HSV infection may inform prevention strategies.

Background

Genital herpes simplex virus (HSV) – caused by HSV-1 and HSV-2 – is one of the most prevalent sexually transmitted infections (STIs) in the United States, with 776,000 incident HSV-2 infections in 2008 (Satterwhite, 2013). Genital HSV-2 is estimated to infect one of every five people in the United States (Satterwhite, 2013). Although genital HSV-1 is less prevalent than HSV-2, the proportion of anogenital first episode genital herpes due to HSV-1 has increased in developed countries from 29% in the 1990s to 42% in the 2000s (Ryder, 2009; Wald, 2006; Scoular, 2002). HSV-1 is also prevalent in genital HSV infections among university students, accounting for as much as 80% of genital HSV infections (Horowitz, 2010). Further, between 1993 and 1997, approximately 20% of first episode genital herpes in patients from the Public Health Seattle & King County (PHSKC) STD Clinic were caused by HSV-1 (Lafferty, 2000). However, as of 2000, HSV-2 continued to cause a higher proportion of overall genital HSV infections, particularly recurrent genital HSV, than does HSV-1 (Lowhagen, 2000).

Despite the changing epidemiology of genital HSV infection, there have been few studies looking specifically at risk factors for acquiring genital HSV-1 versus HSV-2. Receptive oral sex is associated with HSV-1 infection, with up to 2.8 fold increased odds compared to HSV-2 (Cherpes, 2005; Lafferty, 2000; Janier, 2006). In another analysis, MSM (men who have sex with men), heterosexual women, those who received oral sex, and those who reported white race had a higher risk of genital HSV-1 infection (Cherpes, 2005). Vaginal sex, however, was associated with HSV-2 infection (Lafferty, 2000). While these risk factors have already been identified, they may be changing over time.

When diagnosing HSV, the first clinical presentation of genital HSV ulcerations is classified as the "first episode" infection and any subsequent episodes are classified as "recurrences." Symptomatic first episodes exhibit painful ulcers or lesions. Many people with HSV-2 infection are asymptomatic, but even patients who do not have genital herpes symptoms exhibit viral shedding about 10% of the time (Tronstein, 2011; CDC, 2015). Rates of viral shedding are higher in those with symptomatic infection, as viral shedding is associated with lesions (Tronstein, 2011; Wald, 1995). Genital HSV-1 infections have fewer recurrences and less frequent shedding than HSV-2 (Benedetti, 1994; Langenberg, 1999); therefore, typing genital HSV infection provides useful clinical information regarding prognosis, and consequently typing is recommended by the CDC STD Treatment Guidelines (CDC, 2015).

To evaluate time trends in genital HSV infection, we assessed the changes in first episode genital herpes due to HSV-1 and HSV-2 between 1993 and 2014 in the Public Health Seattle-King County STD Clinic. We also wanted to determine whether demographic characteristics – such as gender, age, and race – and sexual practices were associated with first episode genital HSV-1 or HSV-2 infection. Our analysis of patients presenting to an STD clinic with genital herpes can help to identify considerations when approaching strategies for preventing, diagnosing, and treating genital herpes.

Methods

Study population. The Public Health-Seattle & King County (PHSKC) STD Clinic at Harborview Medical Center provides confidential STD and HIV evaluation, screening, testing, and treatment on a sliding fee basis. Those who present with a genital ulcer and suspected

genital herpes have their lesions swabbed for HSV culture. Patients who visited between 1993 and 2014 and who met any of the following criteria were included in the dataset: 1) diagnosis of genital ulcers, 2) collection of a swab for viral culture, 3) physical exam findings consistent with lesions due to genital herpes. We then selected those with a positive genital HSV culture and first episode genital HSV for further analysis. We defined patients as having "first episode" genital herpes if the physician and patient had not reported previous episodes.

Demographic and sexual history collection. The PHSKC STD clinic uses standard collection instruments for all clinical encounters, including demographic information (age, gender, race), detailed sexual history, physical exam findings, and laboratory testing. Until October 2010, clinicians assessed and recorded all clinical and behavioral information using face-to-face interviews entered into an electronic medical record database (Khosropour, 2016). After October 2010, an expanded set of behavioral and self-reported clinical information was collected directly from patients using the computer-assisted self-interview (CASI) kiosk system. If patients did not complete the kiosk due to language barriers or logistical issues, behavioral measures were collected by clinicians. The kiosk questions are more detailed than the face-to-face interview, and include specific information about sexual partners, practices, and timing of the sexual encounters.

We extracted the following information: demographic information (age, gender, race), sexual history (gender of sexual partners, number of lifetime sex partners), and sexual practices (including receptive oral sex, vaginal intercourse, and insertive and receptive anal intercourse). The analysis was approved by the UW Human Subjects Division.

Laboratory methods. Samples for viral cultures underwent shell vial centrifugation in MRC-5 cells and were processed using Trinity MicroTrak monoclonal antibody reagents (Trinity Biotech, 2014). Cultures were typed as HSV-1 or HSV-2 using type-specific monoclonal antibodies.

Statistical Analysis. A descriptive analysis to examine time trends in etiology of first episode genital HSV was performed. We selected *a priori* predictors of genital HSV-1 infection, including gender, race, age, and gender of sexual partner. We performed univariate and multivariate analyses using Poisson regression models. Stata (13) software was used to conduct analyses. Two-sided 95% confidence intervals (CIs) and p-values were calculated, with p-values <0.05 considered statistically significant.

We used a Poisson model because our outcome variable of interest is binary, and we wanted to use risk ratios as our outcome is not rare. We included variables from the univariate model in our multivariate model, removing those with $p>0.05$. We did not include sexual practices in the model, as a large proportion of the sexual practices reporting was missing.

Results

A total of 52,030 patients had a diagnosis or physical findings of genital ulcers (Figure 1). We excluded 4,117 (7.9%) persons who had recurrent genital HSV. Of the remaining 47,913 patients presenting with genital ulcers, 33,786 (70.5%) did not have cultures collected and were excluded. An additional 10,721 (22.4%) had cultures that were negative for HSV and were excluded. Finally, of the remaining 3,406 (7.1%) patients with positive HSV cultures, 87 were oral, 3 had both HSV-1 and HSV-2, and 117 were not typed; these were also excluded. This left

3,199 patients with culture-proven first episode genital HSV infection. Of these, 1,059 (33%) infections were HSV-1 and 2,140 (67%) were HSV-2.

Of the final group of 3,199 persons with culture-proven first episode genital HSV infection, the median age was 27 years (range 13-81 years) (Table 1). Among patients with first episode genital HSV, 1,213 (37.9%) were women; 363 (34.3%) of those who acquired HSV-1 and 850 (39.7%) of those who acquired HSV-2 were women. Overall, 1,959 (61.2%) patients identified as white –793 (74.9%) of 1,059 acquiring HSV-1 and 1,166 (54.5%) of 2,140 acquiring HSV-2. Additionally, 705 (22.0%) patients identified as black; 88 (8.3%) of those acquiring HSV-1 and 617 (28.8%) of those acquiring HSV-2. In terms of sexual partners, 973 (80.2%) of the 1,213 women engaged in sexual relations with men only and 66 (5.4%) engaged in sexual relations with women or both sexes, with 165 (13.6%) of unknown sexual preference. Of the 1,986 men, 377 (19.0%) engaged in sexual relations with men; 1,287 (64.8%) men engaged in sexual relations solely with women, and 328 (16.5%) had missing data.

The mean number of patients seen at the clinic with confirmed first episode genital HSV-1 per year was 48 (range 28-68) (Figure 2). The mean number of patients with first episode genital HSV-2 per year was 66 (range 35-223). However, the number of patients with genital HSV-2 per year decreased steeply from 223 in 1993 to 75 in 2000, and then further decreased to 39 in 2014 (Figure 2). Each year the overall risk of having genital HSV-2 declined by 6% (RR=0.94, 95% CI: 0.93, 0.95; $p<0.0001$), while the risk of having genital HSV-1 was not found to change with each increasing year (RR=1.00, 95% CI: 0.99, 1.01; $p=0.28$).

When stratified by gender, similar results were seen. In men, there was a range of 22-51 patients with genital HSV-1 per year. In contrast, there were 184 men diagnosed with first

episode genital HSV-2 in 1993, which declined to 43 in 2000 and 27 in 2014. A similar trend was seen in women, with a mean of 19 women with genital HSV-1 per year (range 12-34); compared to 98 women with HSV-2 in 1993, declining to 12 women in 2014 (Figure 3).

We stratified first episode genital HSV-1 and HSV-2 by patients who self-identified as white or black (Figure 4). There was a significant decrease in HSV-2 infection in white patients, from 128 to 44 from 1993 to 2000, then to 17 in 2014. Genital HSV-2 also declined steadily in persons who identify as black, with 65 infections in 1993 and 12 in 2014. In comparison, persons with genital HSV-1 and identifying as white did not experience a significant change in pattern, ranging 21-55 acquisitions per year during those two decades. There was little change in the number of persons who acquired HSV-1 per year when stratified by race.

The medical records include patient responses to sexual practices – including oral, vaginal and anal sex (insertive and receptive) (Table 2). Of 650 women with reported sexual practice, 627 (96.5%) reported receipt of oral sex and 965 (99.8%) of 967 reported receiving vaginal sex. Similarly, 660 (99.2%) of 665 men reported receptive oral sex. All of the 614 men who provided information regarding insertive vaginal sex practiced the behavior. Of the 188 men who reported male sexual partners and acquired genital HSV-1, 35 (18.6%) practiced insertive anal sex and 32 (17.0%) practiced receptive anal sex. Sexual practice reporting was not available for well over half of participants; and these measures were therefore not included in further models.

When stratifying by sexual partners, men having sex with women (MSW) or men (MSM) follow a very similar trend to one another within the HSV type grouping (Figure 5). HSV-2 in

MSM declined fairly steadily from 1993 through 2014, from 108 to 21. A similar trend was seen in MSW/WSM, from 98 to 12. HSV-1, on the other hand, maintained a fairly stable number each year, with an average of 19 in MSM and 20 in MSW/WSM.

In order to represent the potential association of age with genital HSV infection risk, we represented age in categories (Table 3). The age categories clearly demonstrate that there are fewer patients with HSV-1 in each age group as compared to HSV-2. There were relatively higher proportions of HSV-1 in persons under the age of 30 compared to those older than 30. The age deciles represent a similar trend, with slightly higher proportion of HSV-1 in the young adult age groups. Ultimately, we categorized age into <30 years old and $\geq$30 years old. It makes sense to represent age in this manner as about half of those with HSV-1 fall below age 30 and about half fall at or above age 30.

We performed univariate regression to determine whether potential predictors were associated with acquisition of HSV-1 versus HSV-2. Younger age (<30 years) is associated with 1.23 times the risk of having genital HSV-1 compared to being 30 or more years of age (95% CI: 1.08, 1.4; p=0.002) (Table 4). Women are 0.85 times as likely to acquire HSV-1 than men (95% CI: 0.75, 0.97; p=0.015). White patients are 3.24 times more likely to acquire genital HSV-1 than black patients (95% CI: 2.60, 4.04; p<0.0001). Homosexual practice was associated with 1.76 times the risk of acquiring HSV-1 as compared to heterosexual practice (95% CI: 1.51, 2.05; p<0.0001). A person has 1.04 times increased risk of having genital HSV-1 each subsequent year after 1993 (95% CI: 1.03, 1.05; p<0.0001).

In order to generate a multivariate analysis to look at associations with HSV-1 infection, we first considered potential effect modifiers. In particular, we were concerned that gender

could be an effect modifier to gender of sexual partner in determining the outcome of genital HSV. We visually modeled the two variables to see whether there could be an interaction (Figure 6). Stratifying by gender showed that heterosexual versus homosexual partners follow similar patterns regardless of whether the person is a man or woman. This visual presentation suggested there is no interaction between gender and sexual partners, and therefore we did not include an interaction term in our model.

In multivariate analysis, those who are <30 years of age are 1.40 times more at risk of having genital HSV-1 than those who are 30 or more years of age (95% CI: 1.20, 1.63; p<0.0001); women had 0.89 times the risk of having genital HSV-1 than men (95% CI: 0.76, 1.05; p=0.17); those who were white are 3.03 times more likely to have genital HSV-1 than those who are black (95% CI: 2.37, 3.87; p<0.0001); those who engage in homosexual relations are 1.42 times at risk of having genital HSV-1 than those participating in heterosexual relations (95% CI: 1.19, 1.71; p<0.0001); and a person is 1.04 times at risk of having genital HSV-1 each subsequent year following 1993 (95% CI: 1.03, 1.05; p<0.0001).

Although the study focused on patients with first episode, culture-positive genital HSV, the total population of patients visiting the clinic was also explored (Figure 7). Overall, there was a decline in patients seen yearly at the clinic. In addition, there was a large proportion of patients who did not have genital HSV cultures obtained.

Figure 1. Flowchart of methods of patient exclusion.

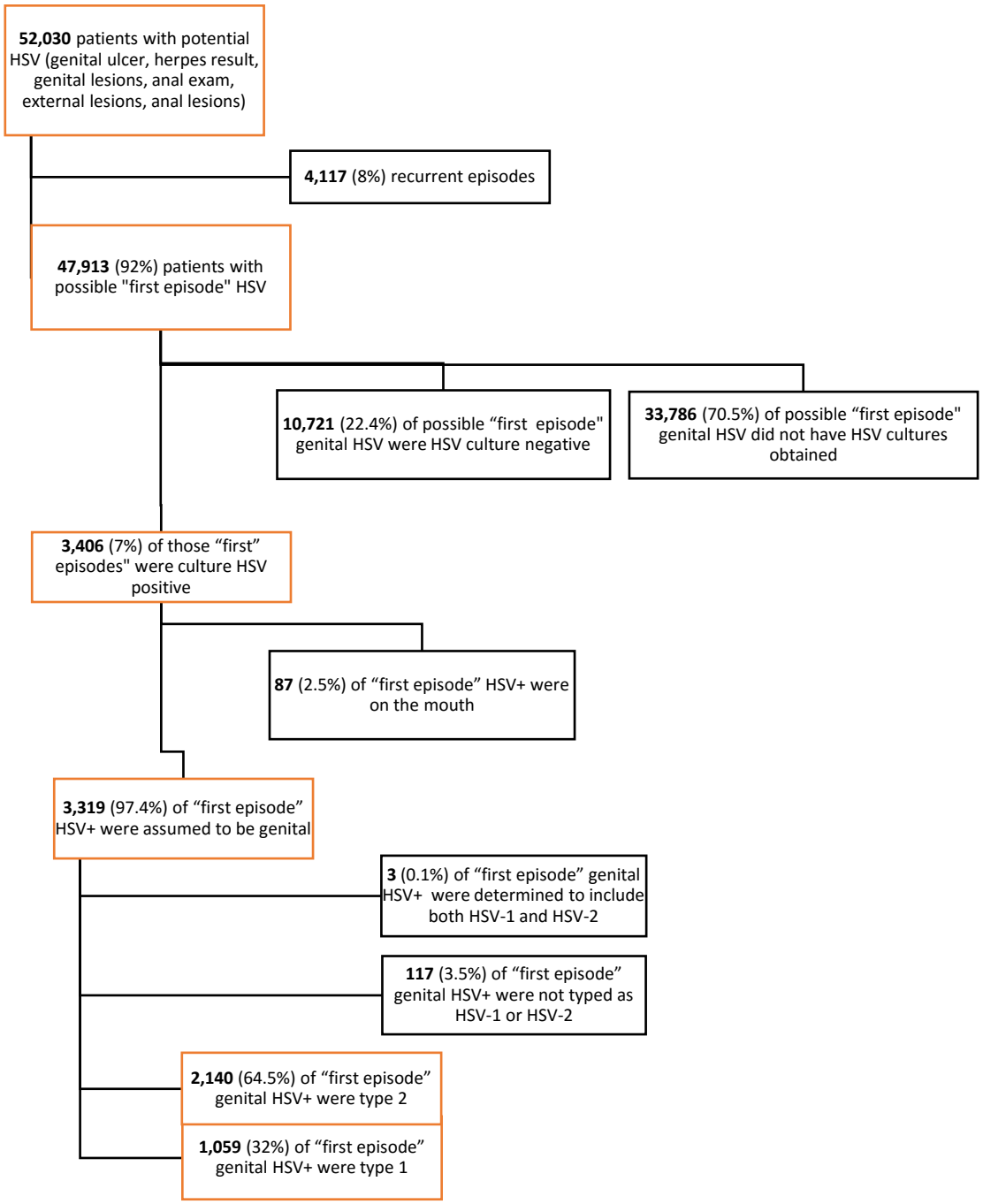


Table 1. Demographic and sexual partners of patients with "first episode" genital HSV

		HSV 1 (n=1,059)	% HSV 1	HSV 2 (n=2,140)	% HSV 2	Total (n=3,199)
Gender[a]						
	Women	363	34.3	850	39.7	1213
	Men	696	65.7	1,290	60.3	1986
Race[a]						
	White	793	74.9	1,166	54.5	1,959
	Black	88	8.3	617	28.8	705
	Asian	70	6.6	79	3.7	149
	Multi	44	4.2	98	4.6	142
	Decline/Unknown	32	3	61	2.8	93
	Pacific Islander	14	1.3	12	0.6	26
	Hispanic	11	1	68	3.2	79
	Native American	7	0.7	39	1.8	46
Sexual Partner[a]						
	WSM	274	25.9	699	32.7	973
	WSW/B	34	3.2	32	1.5	66
	MSW	369	34.8	918	42.9	1,287
	MSM/B	188	17.7	189	8.8	377
	"None"	1	0.09	2	0.09	3
	Unknown	193	18.2	300	14.0	493
Age[a]						
	<30 years	679	64.1	1,227	57.3	1,906
	≥30 years	380	35.9	913	42.7	1,293

[a]Total in each variable group is n=3,199

WSM=women sex men; WSW/B=women sex women/both; MSW=men sex women; MSM/B=men sex men/both

Table 2. Sexual practices of patients with "first episode" genital HSV

		HSV 1 (n=1,059)	% of practice	HSV 2 (n=2,140)	% of practice	Total
Women (n=1,213)		N=363		N=850		
Rec Oral[a]	Yes	232	63.9	385	45.3	627
	No	5	1.4	19	2.2	23
	Unknown	126	34.7	446	52.6	573
Rec Vag[a]	Yes	267	73.5	698	82.1	965
	No	1	0.27	1	0.12	2
	Unknown	95	26.2	151	17.8	246
Rec Anal[c]	Yes	34	9.4	62	7.3	96
	No	7	1.9	7	0.82	14
	Unknown	322	88.7	781	91.9	1103
Men (n=1,986)		N=696		N=1290		
Rec Oral[a]	Yes	248	35.6	412	31.9	660
	No	3	0.43	2	0.15	5
	Unknown	445	63.9	876	67.9	1321
Ins Oral[b]	Yes	172	24.7	227	17.6	399
	No	5	0.72	13	1	18
	Unknown	519	74.6	1050	81.4	1569
Ins Vag[a]	Yes	128	18.4	486	37.7	614
	Unknown	568	81.6	804	62.3	1372
Rec Anal[b]	Yes	32	4.6	31	2.4	63
	No	5	0.72	4	0.31	9
	Unknown	664	95.4	1259	97.6	1923
Ins Anal[b]	Yes	35	5.0	39	3.0	74
	No	49	7.0	87	6.7	136
	Unknown	612	87.9	1164	90.2	1776

[a]Total in each variable group (n=3,199)

[b]Total in men (n=1,986)

[c]Total in women (n=1,213)

Table 3. Genital HSV 1 by age categories

Age Categories	HSV 1 (n=1,058)	Total HSV 1 & 2 in age group	Proportion of HSV1 in age group
10-14	1	7	14.3%
15-19	63	234	26.9%
20-24	305	852	35.8%
25-29	310	813	38.1%
30-34	149	507	29.4%
35-39	97	312	31.1%
40-44	59	217	27.2%
45-49	39	126	30.9%
50-54	19	67	28.3%
55-59	6	30	20%
60-64	6	20	30%
65-69	2	10	20%
70-74	1	1	100%
75+	2	3	66.7%

(n=3,199)

Table 4. Univariate and multivariate analysis (Poisson) of risk factors for genital herpes simplex virus type 1 in 3,199 patients with "first episode" genital herpes infections

	RR HSV1	p	RR HSV1	p
Women (Men as ref)	0.85 (0.75, 0.97)	p=0.015	0.89 (0.76, 1.05)	p=0.17
White (black as ref)	3.24 (2.6, 4.04)	p<0.0001	3.03 (2.37, 3.87)	p<0.0001
Other (black as ref)	1.01 (0.86, 1.18)	p=0.94		
<30yrs (≥30 as ref)	1.23 (1.08, 1.4)	p=0.002	1.40 (1.20, 1.63)	p<0.0001
Homo/bi (hetero as ref)	1.76 (1.51, 2.05)	p<0.0001	1.42 (1.19, 1.71)	p<0.0001
Year	1.04 (1.03, 1.05)	p<0.0001	1.04 (1.03, 1.05)	p<0.0001
Constant			0.11 (0.08, 0.13)	P<0.0001

Figure 2. Genital HSV trend from 1993-2013 (n=3,199)

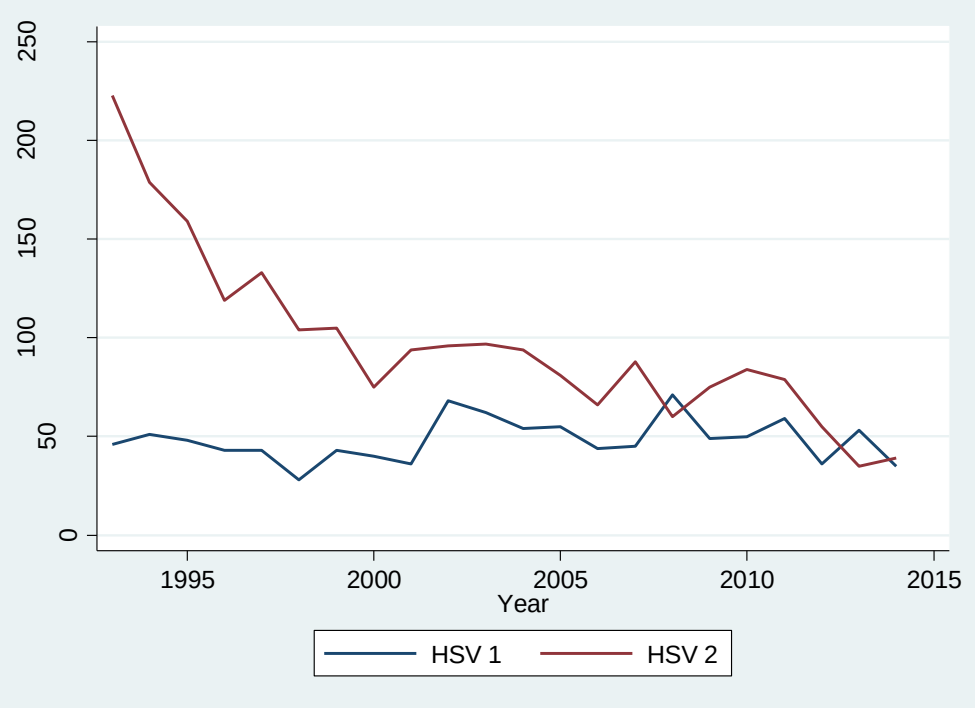


Figure 3. Genital HSV trend from 1993-2013, stratified by gender (n=3,199)

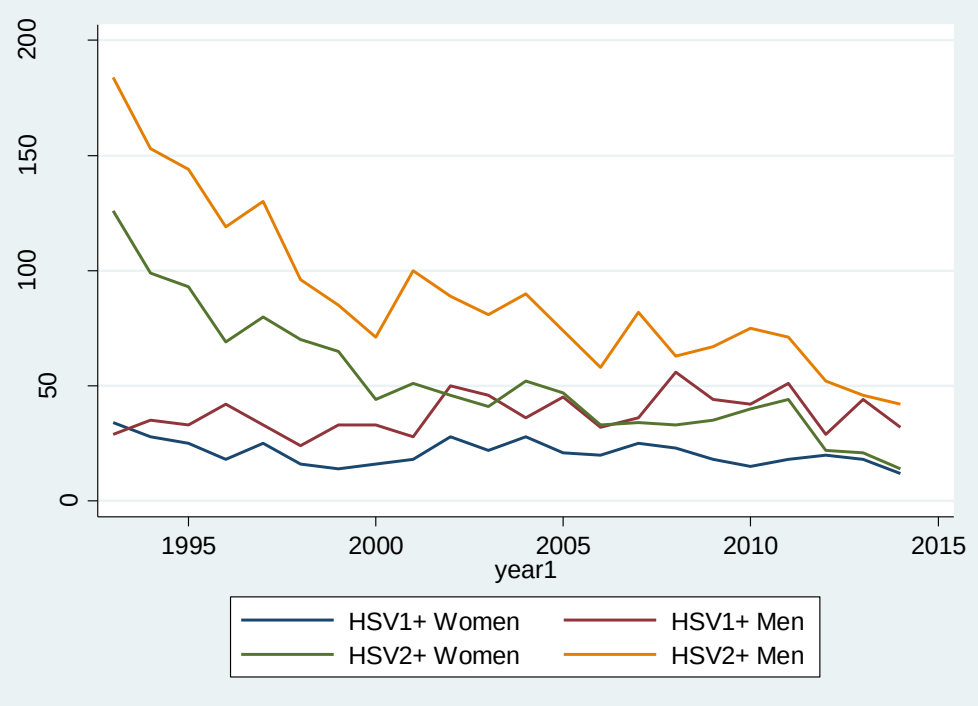


Figure 4. Genital HSV trend from 1993-2013, stratified by race (n=3,199)

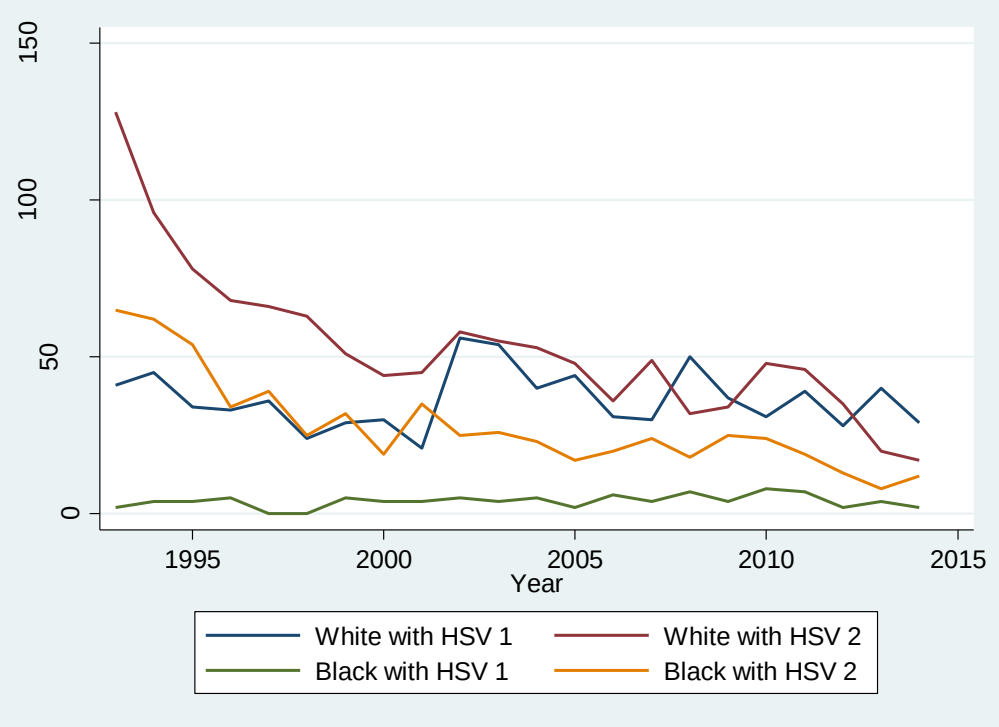
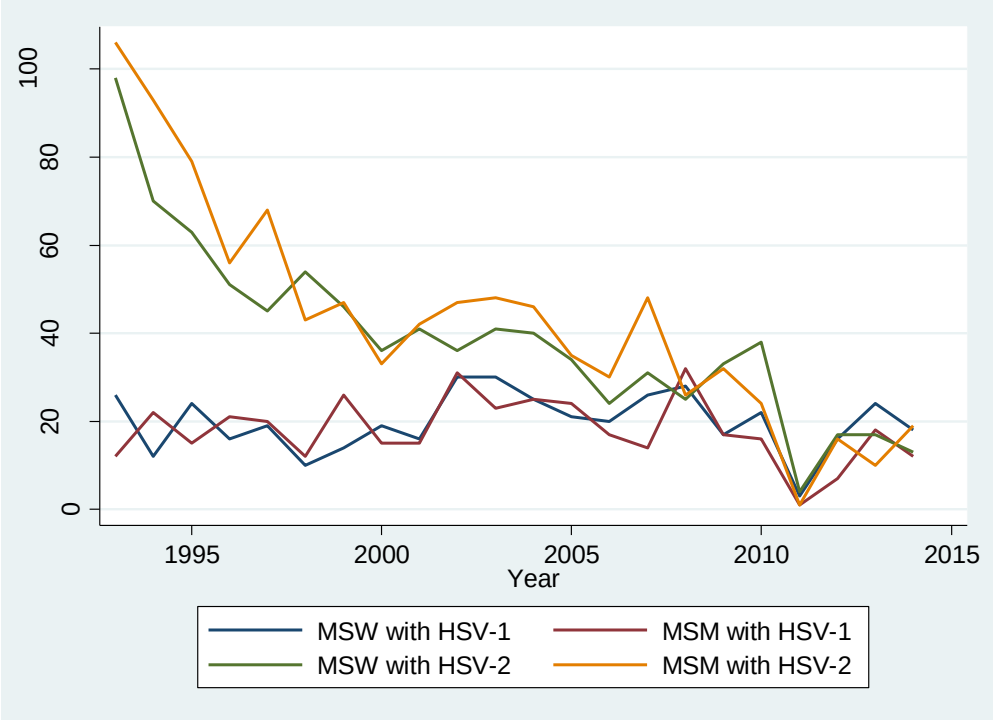


Figure 5. Genital HSV trend from 1993-2013, stratified by sexual partner (n=1,986), among men



MSW=men sex women; MSM/B=men sex men/both

Figure 6. Potential interaction of sexual partners and gender

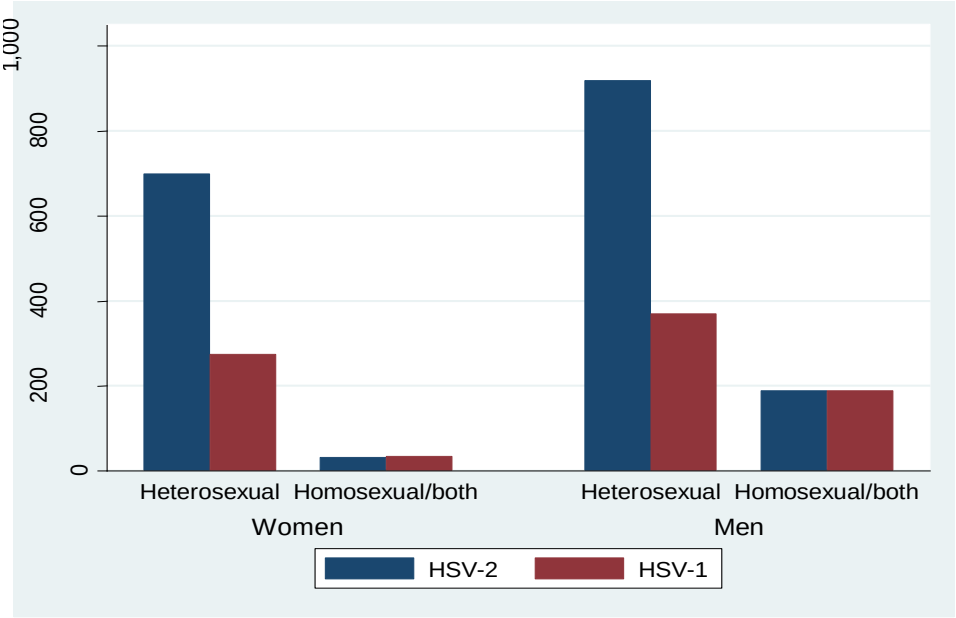
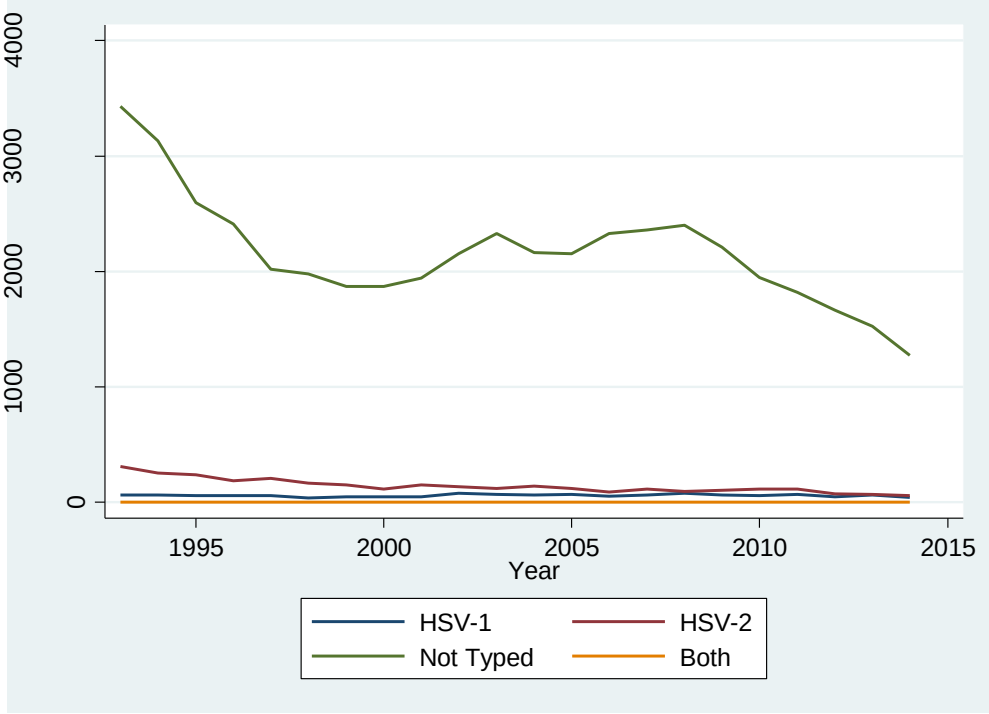


Figure 7. Genital HSV trend from 1993-2013 of all patients in our analysis



Discussion

The number of persons presenting to an urban STD clinic with culture proven first episode genital HSV-2 infection has declined from 1993 through 2014, while first episode genital HSV-1 has remained fairly stable. We identified several risk factors for first episode genital HSV-1, with increased risk in persons <30 year of age, younger age, men, and white race.

We were surprised to find that the increasing proportion of first episode genital HSV-1 infection was due to a decrease in diagnoses of genital HSV-2 rather than an increase in HSV-1. However, these findings are consistent with those from National Health and Nutrition Examination Surveys and seroprevalence in pregnant women, showing declining HSV-2 seroprevalence (Fanfair et al, 2013; Delaney et al, 2014). Whether these changing trends reflect changing sexual practices or improved awareness and decreased transmission of HSV-2 due to interventions such as suppressive therapy and condom use is unknown. It would be helpful to understand the drivers of these trends to determine targeted prevention strategies.

Acquisition of HSV-1 infection now occurs during adolescence and young adulthood rather than being acquired orally during childhood – as was previously common – potentially leading to increased risk of pregnancy complications, including neonatal herpes simplex. Moreover, the increase in proportion of first episode genital HSV-1 infection may be due to changing sexual practice, such as increased reliance on practicing oral sex as a contraceptive method. However, the finding that the number of persons with genital HSV-1 is stable and HSV-2 is decreasing over time suggests that perhaps changing practices are leading to declines in HSV-2. Further study is needed.

Dissemination of results is particularly important because of public health implications. Public health and primary care providers may be able to use these results to aid in diagnosing and counseling patients. Because of the increasing proportion of HSV-1 in genital herpes infection, HSV-2 type-specific serologic assays underestimate the incidence of genital HSV infection – likely by about 15% (Lafferty, 2000). If genital HSV-2 prevalence is in fact decreasing, physicians may need to test for both HSV-1 and HSV-2 when diagnosing a patient with genital HSV symptoms. Potential HSV vaccine formulations may also need to protect against HSV-1 and HSV-2. This is particularly important since first episode genital HSV is generally most symptomatically and clinically severe than recurrences (Wald, 2007).

This research had various strengths, including a large dataset with many patients. Additionally, we accessed the thorough electronic record maintained by the PHSKC STD Clinic to retrieve our data. Staff at the STD Clinic were invaluable in assisting us in understanding the measures recorded. We developed a multivariate analysis with significant results, and interpreted each variable carefully to account for different methods of categorization.

There are some limitations we encountered that ultimately affected the study analysis. Due to a decades-long strong herpes virus research group in Seattle with close collaborations with the PHSKC STD clinic which may affect the trends seen, these results may not be generalizable. Additionally, there was a significant amount of missing response regarding sexual practices of patients, leading to inability of utilizing sexual practices as one of the risk factors in the multivariate analysis. However, the vast majority of patients for whom data was available received oral sex, which has previously been identified as a risk factor for genital HSV-1 acquisition. Unfortunately, there were many patients who had a diagnosis of genital ulcers

who were not tested for HSV culture, and we were unable to include these patients. Finally, there may be other factors leading to the trends that we identified. For instance, there may also be more STD clinics in this area, increasing availability of clinical care in locations other than the PHSKC STD Clinic and decreasing trends in the number of patients seen at the PHSKC STD Clinic (PHSKC, 2016).

We observed a significant decrease in first episode genital HSV-2 in the last 21 years, with a stable number of first episode genital HSV-1, resulting in an increased proportion attributed to HSV-1. Understanding changing epidemiology in genital HSV infection may inform prevention strategies.

Acknowledgements

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