Comorbidities associated with HPV and HSV infections among people living with HIV-1 in the Southeastern US: a retrospective clinical cohort study

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Research article

Keywords: HPV, HSV, HIV, LSIL, HSIL, Cancer

Posted Date: August 28th, 2019

DOI: https://doi.org/10.21203/rs.2.13654/v1

Version of Record: A version of this preprint was published on February 14th, 2020. See the published version at https://doi.org/10.1186/s12879-020-4822-5.

Abstract

Background The southeastern US is a domestic epicenter for incident HIV with high prevalence of human papillomavirus (HPV) and herpes simplex virus (HSV) co-infections. However, epidemics of HPV and HSV- associated clinical conditions (CC) among people living with HIV-1 infection (PLWH) are not fully known. Methods Electronic medical records (EMR) of PLWH attending one of the leading HIV clinics in the southeastern US between 2006 and 2018 were reviewed and analyzed. The retrospective study was nested within the University of Alabama at Birmingham HIV clinical cohort, which has electronically collected over 7000 PLWH's clinical and sociobehavioral data since 1999. Incidence rates of HPV-related CC including anogenital warts, penile, anal, cervical, and vaginal/vulvar low- and high-grade squamous intraepithelial lesions (LSIL and HSIL) and HSV- related CC including anogenital herpetic ulcers were estimated in per 10000 person years. Joinpoint regressions were performed to examine temporal changes in the trends of incident CC. All rates and trends were stratified by gender and race. Results Of the 4,484 PLWH eligible individuals (3,429 men, 1,031 women, and 24 transgender), we observed 1,038 and 425 patients with HPV-and HSV-related CC respectively, and 163 patients with both conditions. The mean log10 viral load (VL) was higher in all of the case groups than the non-cases with neither conditions (5.0) (whereas the median nadir CD4 counts (cells/uL) was higher in the non-cases than in any of the case groups (P<0.05). Anogenital warts, anal LSIL, HSIL, and cancer were more likely to be diagnosed among HIV-infected men than women. White men presented more frequently with anal LSIL and anal and penile cancers than black men (P<0.03). White women were also more likely to be diagnosed with cervical HSIL (P=0.023) and cancer (P=0.037) than black women By contrast, herpetic ulcers were more frequent in women than men. Conclusions There were significant differences between gender and race with incidence of HPV- and HSV-related CC among HIV patients. EMR-based studies provide insights on understudied epidemics; however, large-scale studies in other regions are needed to generalize current findings and draw public health attention to co-infection induced non-AIDS defining comorbidities among PLWH.

Background

Human papillomavirus (HPV) and herpes simplex virus (HSV) are two common sexually transmitted infections (STIs) in the general population and specifically among people were living with HIV infection (PLWH) [1][2]. While both infections are treatable, they have chronic sequelae. The prevalence of anogenital HPV infection in 2013–2014 was estimated at 42.5% among US adults aged 18–59 years, with more than 14 million new diagnoses [3]]. Genital HPV infection is 1.5–2.5 times higher in HIV+ women than HIV- women. Anal HPV infections among HIV+ women and MSM are 3 times higher than their HIV- counterparts. Likewise, CDC estimated that 1 in every 6 people aged 14–49 years have anogenital herpes [3, 4]. In 2015, there were about 299,000 initial clinic visits due to anogenital herpes infections [4]. A multi-site prospective study, the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study) reported HSV-seroprevalence was 3 times greater among PLWH than the general US population [5].

HPV infection is common in the US, with over 80% of sexually active individuals being infected at least once during their lifetime [2]; however, most resolve on their own There are 12 types of low-risk HPV (LR-HPV) and at least 13 types of high-risk HPV (HR-HPV) [6]. LR-HPV cause warts and very mild cell changes in infected tracts, whereas persistent infection with HR-HPV cause low- (LSIL) and high- grade squamous intraepithelial lesions (HSIL) that can progress to cancer. Anogenital cancers, including 99.7% of cervical, 95% of anal, 65% of vaginal, 50% of vulvar, and 35% of penile cancers are linked to HR-HPV infections [7]. HPV-associated cancers are diagnosed in 17,600 women and 9,300 men every year in the US [7, 8].

Anogenital herpetic ulcerations are caused by HSV–1 and –2. Although HSV–2 causes most anogenital ulcerations, recent studies have demonstrated that HSV–1 can also be transmitted to anogenital tracts and cause ulcerations [3, 4]. HSV–2 prevalence is 16.2% in the general population [3, 4], and is much higher among PLWH, varying between 50–90% in different studies [9]. HSV infection may be persistent and induce considerable inflammatory responses. Similar to HIV, this infection continues to disproportionally burden blacks with a prevalence of 39.2% of the total HSV–2 diagnoses, with black women accounting for 48.0% of the total [3, 4].

In the state of Alabama, racial disparities in new HIV infections and STDs have been documented; black women and men are highly susceptible to incident HIV [10]. While the epidemiology of HIV infection in the state is well-studied and reported, HPV- and HSV-related clinical conditions (CC) among PLWH have not been comprehensively characterized. Neither the country nor the state of Alabama implements mandatory screening programs for anogenital HSV- and HPV-related (excluding cervical cancer) conditions. Therefore, there is a substantial lack of knowledge of the comorbidities among the PLWH. In this study, we retrospectively studied PLWH at risk of HPV- and HSV-related CC for over 12 years from the patients in the University of Alabama at Birmingham (UAB) 1917 Clinic, an academic institute with the largest HIV patient catchment in Alabama, and estimated HPV- and HSV- CC incidence rates and comorbidity trends.

Methods

Study Design and Population

Electronic health records between January 1st, 2006 and March 30th, 2018 from the UAB 1917 Clinic were reviewed. It is the largest HIV clinic in the state of Alabama [11] with extensive referral network. The prospective clinic cohort has collected more than 7,000 patients' sociodemographic, psychosocial, and clinical information since its establishment in 1992 [12, 13]. More than 3,500 patients currently receive their routine HIV care from the clinic, representing 30% of all PLWH in the state [12].This retrospective study was nested within the UAB 1917 Clinic Cohort and approved by the UAB Institutional Review Board.

In this study, eligible patients were patients who: 1) attended the clinic at least twice for receiving primary HIV care during the 12-year study period; and 2) were at least 18 years old at HIV diagnosis.

Study Variables

HPV-related CC were categorized into nine groups: anal LSIL and HSIL; cervical LSIL and HSIL; anal, cervical, vaginal/vulvar, and penile cancers; and anogenital warts. HSV-related CC were defined as anogenital herpetic ulcers. Cases were verified by reviewing medical charts. Washout periods were given as two years for HPV-related CC and one year for HSV-related CC. Thus, we excluded patients with same HPV- and HSV- related CC (two years and one year, respectively) prior to the case presentation during the study period. A condition was recognized as an incident case only if the subject was free of the condition at baseline but developed the condition during follow-up.

Statistical Analysis

Univariate analyses were conducted to compare demographic and clinical characteristics between patients with HPV- and/or HSV-related CC to patients with neither condition during the entire follow-up period. Chi-squared- and t-tests were used to compare categorical and continuous variables between the diseased and disease-free group, respectively.

Incidence rates (cases per 10,000 person-years) were computed for each HPV- and HSV- related CC separately and compared between different sexes and races. Annual incidence for each condition was estimated followed by trend analyses using the Joinpoint Trend Analysis Software program (JTAS) [14]. Briefly, the Joinpoint regression model started with the minimum number of joinpoints and kept adding more until the number of joins was sufficient to distinguish between two unique and consecutive linear trends [14]. Monte Carlo permutation and Bayesian Information Criterion (BIC) were used for the goodness-of-fit test to find the best fitted curves over time [15]. The permutation method identified a time point that revealed an apparent change in trend. The final selected model comprehended the minimum number of joinpoints and smallest value of BIC.

The annual percent rate change (APC), with an assumption of a constant percentage change of the rate of the previous year was computed by the joinpoint regression. Incidence was log-transformed to diminish the effects of potential outliers in the linear regression. All APCs were then summarized to estimate an average annual percent change (AAPC) over a fixed interval. The AAPC over any fixed interval was calculated using a weighted average of the slope coefficients of the underlying joinpoint regression line with the weights equal to the temporal length of each segment over the interval. The weighted average of slope coefficients was transformed to an annual percent change in the final step [16]. T-statistics were calculated for both APC and AAPC to assess the changes of slopes in the linear association.

Age-standardized incidence rates were initially estimated. The present study population was projected to the standard population of the 2016 US population from the Surveillance, Epidemiology, and End Results program (SEER). However, JTAS prohibits the calculation of age-adjusted rates with a dependent variable equal to zero cases under log transformation. Instead, crude incidence with a Poisson variance was used. Our main objective was to test whether there were any substantial changes on trends regarding incident HPV-and HSV-related CC during the study period.

Results

A total of 4,803 PLWH attended the 1917 Clinic between January 1st 2006 and March 30th, 2017. There were 4,484 patients; however, 4,341 patients met the inclusion/exclusion criteria with 3,333 (76.8%) men, 985 (22.7%) women, and 23 (0.5%) transgender individuals, 2,580 (59.4%) blacks, 1,588 (36.6%) whites, and 173 (4.0%) others. Among the patients, 1,038 (23.1%) presented with HPV-related CC and 425 (0.0022%) with HSV-related CC, 163 presented with both clinical conditions, and 3,098 PLWH had neither condition (Table 1). The mean ages at the time of HPV-and HSV-related CC presentation over the study follow-up were 41.8 (±10.6) years and 42.9 (±10.4) years, respectively. The median follow-up (years) since the enrollment was significantly shorter for non-cases (4.3 years) than HPV- (7.0 years) and/or HSV (8 years) and 9.4 years for both conditions (P<0.05). The mean log10 VL (copies/mL) were higher in all of the condition groups as compared to the non-case group (HPV CC:5.3±5.9 copies/mL; HSV CC:5.5±6.0 copies/mL; and both conditions: 5.6±6.2 vs. 5.0±0.4 copies/mL for neither) whereas the median nadir CD4 counts (cells/uL) were higher in the non-cases (318, IQR: 151–853) than in any of the HPV CC (237 [IQR: 72–701]), HSV CC (268 [IQR:54–695]) or both conditions(130 [IQR:16–641]) (P< 0.05). Compared with women, men had much higher rates of HPV-related warts, anal LSIL, HSIL, and any HPV-related cancer (P<0.0001 for each comparison, Table 2). Overall, whites were more likely to be diagnosed with anal LSIL and cancer (P<0.05, Table 2). Among women, whites were more likely to present cervical HSIL and cervical, vaginal and vulvar LSIL (P<0.0001 for each comparison). In contrast with HPV-related CC, the rate of herpetic ulcers was much higher in women than men (P<0.0001).

HIV+ men had a higher rate than women to present anogenital warts (IR 190.4 vs 68.5 per 10,000 person-years), anal LSIL (188.2 vs 14.7 per 10,000 person-years), HSIL (43.2 vs 5.5 per 10,000 person-years), and cancer (25.8 vs 0 per 10,000 person-years) (Table 2). White men presented more frequently with anal LSIL and anal and penile cancers than black men (P<0.03 for each comparison) (Table 2). By contrast, IR of HSV-related anogenital ulcers was much higher in women than men (IR = 216.8 vs 130.2 per 10,000 person years; P<0.0001) (Table 2). No racial disparity was observed in incident ulcers.

HPV-related anogenital warts showed significant upward trends in both genders (AAPC: 19.5, P<0.0001) and races (AAPC: 20.4, P<0.0001) (Figure 1). However, there were no distinct patterns between these two trends (P>0.05 for test for parallelism, Table 3). The AAPC of anal HSIL among black men also showed an increasing incidence trend (AAPC: 25.6, P<0.0001). Cervical HSIL and cancer did not show significant changes over time, but APC gave the joins that reflected periodic changes between 2006–2013 and 2016–2018 (P<0.05 for each period) (Table 3, Figure 2). Similarly, although anogenital herpetic ulcers failed to demonstrate statistically significant changes over the follow-up (P>0.05 for both gender and race comparisons), there was a noticeable decrease between 2013 and 2016 for both races, followed by an increase after 2016 (APC = 192, P<0.0001).

Discussion

In the present study, among PLWH visiting a southeastern US HIV clinic between 2006 and 2018, HPV-related CC, particularly anal lesions and cancer were much more frequently diagnosed among men than women. By contrast, the rate of HSV-related ulcers was greatly elevated among HIV+ women compared to men. The incidence rate of anogenital warts constantly increased over the study period. Although cervical HSIL and herpetic ulcers did not have monotonic

trends, significant periodic increases in trends were detected. Although crude rates were reported, we computed the age-adjusted rates for warts and herpetic ulcers, which did not generate 0 cases over the follow-up. The alternative rates were similar to our results (data not shown). These observations and trends have never been reported in a clinical setting and this study with sufficient follow-up provides the broader scenario of these conditions among PLWH in the area. Our findings attempt to help clinicians better understand the burden of these comorbidities and drive better care in clinical settings.

HPV-related conditions were observed predominantly in men as compared to women. Although the sub-population for HPV analyses only had 59.2% MSM, 64.4% of incident HPV cases were diagnosed among them. HIV+ men had almost a 3-fold greater risk of anogenital warts compared with women (Table 2), with no racial disparity observed. The trend of warts, however, increased approximately 20% each year (Table 3) regardless of gender and race.

HIV+ men were also 8 and 25 times more likely to be diagnosed with anal HSIL and cancers, respectively, than HIV+ women (Table 2). By contrast, HPV-related anal lesions and cancers are more common in women than men in the general population [17]. There is a huge gap in screening guidelines for non-AIDS defining comorbidities, such as HPV-related anal precancerous lesions and cancers.. The current HPV screening guidelines, the cervical cancer screening program, are only applicable to women [18]. The present study consisted of 76% men with limited anal cancer screenings. MSM were particularly susceptible for HPV-related CC. MSM are known to have an elevated risk of HIV acquisition. HIV+ MSM tend to be more likely infected with other STIs, such as HPV and HSV [19].

One of the largest HIV cohort, Multicenter AIDS Cohort Study (MACS), reported an overall incidence rate of anal cancer of 7 per 10,000 person-years among HIV+ MSM between 1984 and 2006 [20]. The finding from our study was over 3-fold greater than that rate (IR = 25.8 per 10,000 person-years among men) between 2006 and early 2018. In spite of the better immune status of PLWH in our cohort compared to MACS, specifically before ART regimen in 1996[24], the median nadir CD4 counts were still significantly lower in patients with HPV-related CC than the non-cases (Table 1). Further, the rates of anal lesions and cancers increased exceptionally compared to the MACS. Geographically, the MACS, which predominantly includes white men, did not include a site in the Deep South of the US, and our findings provides evidence of the severity of HPV comorbidities in this high-risk population. Overall, there have not been many studies conducted among black MSM in the south regarding HIV and HPV comorbidities.

Although, we did not observe a monotonic trend of cervical HSIL or cancer, we were able to identify the periodic changes. For example, both conditions seemed to be growing in numbers of new diagnoses between 2016 and 2018 (Table 3) in both races. However, we have to take the screening programs implemented into account. In March 2016, the US Health Resources and Services Administration issued new screening guidelines for cervical cancer among HIV+ women, which included both cytology pap smears and serologic testing [18]. As an academic clinic, the UAB 1917 Clinic actively advocates HPV-related screenings for HIV+ women. The implementation of the new screening program could temporarily boost the number of new diagnoses of HPV-related cervical lesions and cancers. However, it does not necessarily mean an increase in cervical HPV infections.

In contrast to HPV-related CC, our data suggest that more women with HIV experienced symptomatic anogenital herpetic ulcers than men. Unlike HPV-CC in the present study, the HSV-cohort consisted of 59.8% MSM and 51.8% of them presented incident herpetic ulcers during the follow-up. To our knowledge, only one study has reported that HIV+ men are more likely to develop HSV-related anogenital ulcers [21]. Most published studies implicate that anogenital herpetic ulcerations are more likely to be clinically manifested in HIV+ women [22–24]. Unlike HPV, HSV is not an oncogenic virus and does not generally lead to any fatal disease sequelae. Thus, preliminary studies have usually focused on its serologic impacts on PLWH. In our study, women showed a 1.8x higher incidence rate of anogenital ulcers than men. Similarly, a study in Uganda estimated the prevalence of anogenital ulcers was 1.4 times higher in women, and HIV viremia was found to be higher among people with symptomatic anogenital ulcers (mean log10 VL = 4.4 copies/mL) [25]. A similar association between higher viral load and symptomatic herpetic ulcers was observed in our cohort (mean log10 VL = 5.5 copies/mL, $P<0.05$ compared with people with neither conditions). This could imply that PLWH with active HIV viral replication were more likely to have outbreaks of symptomatic anogenital ulcers. By contrast, most previous studies only reported the risk of the patients who presented symptomatic herpetic ulcers before they became HIV infected [22–24].

This southeastern US region bears a heavy public health burden of HIV and STDs [26]. The incidence rates of HPV- and HSV-related CC in our study were much higher among PLWH than the general population, based on national statistics. Both infections are incurable, but interventions alleviate symptoms and prevent the HPV-related neoplasia and chronic herpetic ulcers. We had a long clinical follow up in this clinical cohort, which allowed us to estimate incidence rates, while most other studies were only able to report incident HPV- and HSV-related CC as percentages of new cases among PLWH. We specifically used the Joinpoint regression analysis to examine trends, which enabled us to report the statistical significance of changes in trends as well as compare trends between different sexes and races.

It is important to note that clinical diagnoses were based on patient willingness to seek medical attention. Unlike cervical cancer screening, anogenital screenings and examinations are primarily recommended by providers and thus could reflect potential bias. While this can under-estimate the number of cases, with a pro-active screening approach in this academic clinic setting, our estimated incidence shows a substantially higher rate than the estimates from the previous HIV studies. HPV- and HSV- related CC are often initiated from self-reported pain and physical presentations of lesions, warts, and ulcers. It is common practice to make prompt diagnoses and immediate treatment for most HPV and HSV-related CC without testing for viral infections.

Conclusions

Impaired immune systems as shown by nadir CD4 count and high viral load exacerbate the HSV and HPV disease outcomes. It is known that HPV-related anogenital HSIL and HSV-related anogenital ulcers are more difficult to regress in PLWH than immunocompetent people [27]. In addition, PLWH face more complicated treatment options when the co-infections become symptomatic and develop chronic sequela. Since most of these infection related conditions except for cervical cancer and persistent herpetic ulcers are non-AIDS-defining, the Ryan White funding program provides limited coverage in the clinic. Additional comprehensive studies in other clinics in other areas of the country would be helpful to understand the hidden epidemic of clinical conditions caused by HPV and HSV infection among PLWH, which could help guide screening and prevention strategies.

List Of Abbreviations

HIV: human immunodeficiency virus; PLWH: people living with HIV infection; CC: clinical condition; HSV: herpes simplex virus; HPV: human papillomavirus

Declarations

Ethics approval and consent to participate

The study was approved by the UAB Institutional Review Board for Human Use (IRB–170329001), and performed in accordance with the ethical guidelines of the Declaration of Helsinki. All informed consent were signed by the patients. Animals were not used in the study.

Competing Interest

The authors declare no competing interests.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available upon request in https://www.uab.edu/medicine/1917cliniccohort/.

Funding

The ability to complete this work was supported by the UAB Center for AIDS Research (CFAR) [grant P30-AI27767 to MSS from the National Institute of Allergy and Infectious Diseases; https://www.niaid.nih.gov/]; the CFAR Network of Integrated Clinical Systems (CNICS) [grant 1R24 AI067039–1 to MSS from the National Institute of Allergy and Infectious Diseases; https://www.niaid.nih.gov/]; and the Mary Fisher CARE Fund (https://www.uab.edu/medicine/cfar/mary-fisher). This work was also supported by the Quetelet Endowed Professorship Research Fund (SS).

Author Contributions

YY, GB, and SS conceived the study. HW participated in statistical approach. YY processed and analyzed the data. YY and SS interpreted the data and wrote the manuscript. All authors have reviewed and approved the manuscript.

Acknowledgement

We thank all study patients from the UAB 1917 Clinic. We also thank the UAB Research and Informatics Service Center (RISC) for data access (https://www.uab.edu/medicine/1917cliniccohort/).

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Tables

Table 1. Demographics and clinical characteristics of study patients stratified by HPV- and HSV-related clinical condition (CC)[a] status

Characteristics	Ever with HPV CC (N=1038)	Ever with HSV CC (N=425)	Both (N=163)	Neither (Non-cases) (N=3098)
Age at baseline	38.3 (10.0)[c]	39.2 (9.8) [c]	37.9 (8.5) [c]	41.4 (11.5)
Age at HIV diagnosis	31.6 (8.8) [c]	32.0 (9.0) [c]	30.1 (7.6) [c]	35.5 (10.8)
Age at first HPV or HSV CC	41.8 (10.6)	42.9(10.4)	--	--
Race				
Black	596 (57.4) [c]	262 (61.7) [c]	98 (60.1) [c]	1861 (60.1)
White	430 (41.4) [c]	153 (36.0) [c]	64 (39.3) [c]	1084 (35.0)
Others	12 (1.2) [c]	10 (2.3) [c]	1 (0.6) [c]	153 (4.9)
Median years of follow-up	7.0 (4.3-12.1) [c]	8.0 (4.4-12.1) [c]	9.4 (5.5-12.1) [c]	4.3 (1.8-11.9)
Gender				
Male	779 (75.0)	273 (64.2) [c]	104 (63.8) [c]	2423 (78.2)
Female	249 (24.0)	151 (35.5) [c]	59 (36.2) [c]	662 (21.4)
Transgender	10 (1.0)	1 (0.3) [c]	0 [c]	13 (0.4)
HIV risk factors				
MSM	646 (63.2) [c]	207 (49.0) [c]	91 (55.8)	1505 (50.2)
Heterosexual	299 (29.2) [c]	187 (44.2) [c]	59 (36.2)	1214 (40.5)
IVDU	77 (7.5) [c]	29 (0.68) [c]	13 (8.0)	275 (9.2)
Others	1 (0.1) [c]	0 (0.0) [c]	0 (0)	5 (0.1)
Mean Log VL (copies/mL) [‡]	5.3 (5.9) [c]	5.5 (6.0) [c]	5.6 (6.2) [c]	5.2 (5.8)
NadirCD4 (cells/μL)[‡+]	237 (72-701) [c]	268 (54-695) [c]	130 (16-641) [c]	318 (151-853)

[a]: Clinical conditions: clinically and/or symptomatic presented condition

*: All continuous variables in mean (SD); categorical variables in count (%).

[+]: Median (25-75 percentiles)

[c]: P<0.05 when comparing the variable to the one in the "Neither" column

[‡]: Prior to HPV or HSV CC or last clinical visit for controls

Table 2. Incidence rates (IR) of HPV-related anogenital warts, Anal LSIL and HSIL in men and Cervical LSIL and HSIL in women, and HSV-related anogenital ulcerations

	# Cases	# Total	Follow-up time (person-years)	IR (95%CI)	*P*-Value‡
HPV-related Clinical Conditions (by gender)					
Anogenital warts	478	4,484	29,646.2	161.2 (146.8-175.7)	--
Men	420	3,429	22,286.2	188.5 (170.4-206.5)	
Women	51	1,038	7,507.9	67.9 (49.3-86.6)	<0.0001
Anal LSIL	425	4,484	21,854.0	194.5 (176.0-213.0)	--
Men	411	3,429	21,842.3	188.2 (170.0-206.4)	
Women	8	1,031	5,436.6	14.7 (12.1-24.9)	<0.0001
Anal HSIL	75	4,484	22,195.0	33.8 (26.1-41.4)	--
Men	72	3,429	16,665.5	43.2 (33.2-53.2)	
Women	3	1,031	5,434.8	5.5 (0-11.8)	<0.0005
Anal cancer	43	4,484	22,188.2	19.4 (13.6-25.2)	--
Men	43	3,429	16,680.7	25.8 (18.1-33.5)	
Women	0	1,031	5,416.0	0	<0.0001
Bowen's disease	6	4,484	22,232.1	2.7 (0.55-4.9)	--
Men	5	3,429	16,701.2	3.0 (0.37-5.7)	
Women	1	1,031	5,436.3	1.8 (0-5.6)	0.66
HSV-related Ulceration (by gender)					
Anogenital ulcers	425	4,341	28,063.9	151,4 (137.0-165.8)	--
Men	273	3,333	20,975.7	130.2 (114.7-145.6)	
Women	151	985	6,965.9	216.8 (182.2-251.3)	<0.0001
HPV-related Clinical Conditions (by race)					
Anogenital warts	478	4,484	29,646.2	161.2 (146.8-175.7)	--
Black	312	2,676	18,360.7	169.9 (151.1-188.8)	
White	160	1,632	10,382.2	154.1 (130.2-178.0)	0.32
Anal LSIL	425	4,484	21,854.0	194.5 (176.0-213.0)	--
Black	182	2,676	12,892.1	141.2 (120.7-161.7)	
White	238	1,632	8,447.4	281.7 (207.8-317.5)	<0.0001
Anal HSIL	75	4,484	22,195.0	33.8 (26.1-41.4)	--
Black	40	2,676	13,053.3	30.6 (21.1-40.1)	
White	34	1,632	8,628.5	39.4 (26.5-53.3)	0.28
Anal cancer	43	4,484	22,188.2	19.4 (13.6-25.2)	--
Black	18	2,716	13,030.0	13.8 (7.4-20.2)	
White	24	1,632	8,643.7	27.8 (16.7-38.9)	0.025
Cervical LSIL	171	1,031	7352.3	232.6 (197.7-267.4)	--
Black	132	767	5679.6	232.4 (192.8-272.0)	
White	38	236	1610.2	250.3 (102.1-290.9)	0.69
Cervical HSIL	80	1,031	7404.7	108.0 (84.5-131.7)	--
Black	54	767	5721.3	94.4 (69.2-119.6)	
White	25	236	1529.5	163.5 (99.4-169.6)	0.023
Cervical cancer	12	1031	5304.8	22.62 (9.8-35.4)	--
Black	6	767	4018.1	14.9 (3.0-26.9)	
White	6	235	1203.4	49.9 (3.0-38.9)	0.037
Vaginal/Vulvar cancer	15	1,031	5,304.3	28.3 (14.0-42.6)	--
Black	11	767	4,018.1	27.4 (11.2-43.6)	
White	4	236	1,202.9	33.3 (0.67-65.8)	0.74
Penile cancer	4	3,429	16,493.2	2.3 (0.049-4.8)	
Black	3	886	8,769.5	3.4 (0-7.3)	
White	0	1,396	7,298.4	0	<0.0001
Bowen's disease	6	4,484	22,232.1	2.7 (0.55-4.9)	--
Black	3	2,676	13,070.1	2.3 (0-4,9)	
White	3	1,632	8,647.5	3.5 (0-7.4)	0.61
HSV-related Ulcerations					
Black	262	2,580	17,367.7	150.9 (132.6-169.1)	
White	153	1,588	9,813.1	155.9 (131.2-180.6)	0.75

‡P: comparison between races and genders

Table 3. Race and gender stratified trends of incident HPV-related anogenital warts,

LSIL, HSIL, and cancer (men only), Cervical LSIL and HSIL, and cancer, and HSV-related anogenital ulcers between 2006-2018.

	Cases	Joins	Joinpoint Year	AAPC (95% CI)	*P*-Value
HPV-related CC					
Anogenital warts	--		--		
Men	420	0	--	19.5 (13.9-25.3)	<0.0001
Women	51	0	--	19.5 (13.9-25.3)	<0.0001
Black	312	0	--	20.4 (15.5-25.5)	<0.0001
White	160	0	--	20.4 (15.5-25.5)	<0.0001
Anal HSIL (men only)	71	0	--		
Black	38	0	--	25.6 (9.7-43.9)	0.0040
White	33	0	--	23.1 (-0.2-52.0)	0.052
Anal cancer (men only)	43	0	--	5.6 (-4.9, 17.2)	0.29
Black	18	0	--	--	--

	White	24	0	--	---	--
Cervical HSIL			2	2013,2016	22.5 (-4.5-57.1)	0.11
	Black	54	2	2013,2016		
	White	25	2	2013,2016		
			--	2006-2013*	29.8 (11.6-50.9)	0.002
			--	2013-2016*	-38.3 (-73.9-45.7)	0.25
			--	2016-2018*	179.6 (20.9-546.7)	0.020
Cervical cancer		12	2	2012, 2016	15.9 (-9.7-48.7)	0.2
	Black	6	2	2012, 2016	--	--
	White	6	2	2012, 2016	--	--
			--	2006-2012*	17.1 (-2.4-40.6)	0.084
			--	2012-2016*	-26.4 (-58.7-31.3	0.27
			--	2016-2018*	177.5 (1.3-660.0)	<0.0001
HSV-related CC						
Anogenital ulcers						
	Men	329	2	2013, 2018	8.5 (-9.5-30.2)	0.38
			--	2006-2013*	3.2 (-5.8-13.1)	0.42
			--	2013-2016*	-44.2 (-73.9-19.2)	0.11
			--	2016-2018*	250.1 (57.3-679.4)	0.010
	Women	176	0	--	9.5 (-1.5-21.8)	0.089
	Black	322	2	2013, 2016	9.6 (-10.8-34.7)	0.38
	White	174	2	2013, 2016	9.6 (-10.8-34.7)	0.38
			--	2006-2013*	6.0 (-3.9-16.9)	0.23
			--	2013-2016*	-38.4 (-68.8-21.4)	0.15
			--	2016-2018*	192.9 (30.4-557.8)	0.013

*: when joinpoints were identified, APC were also reported for the periodic changes.

Figures

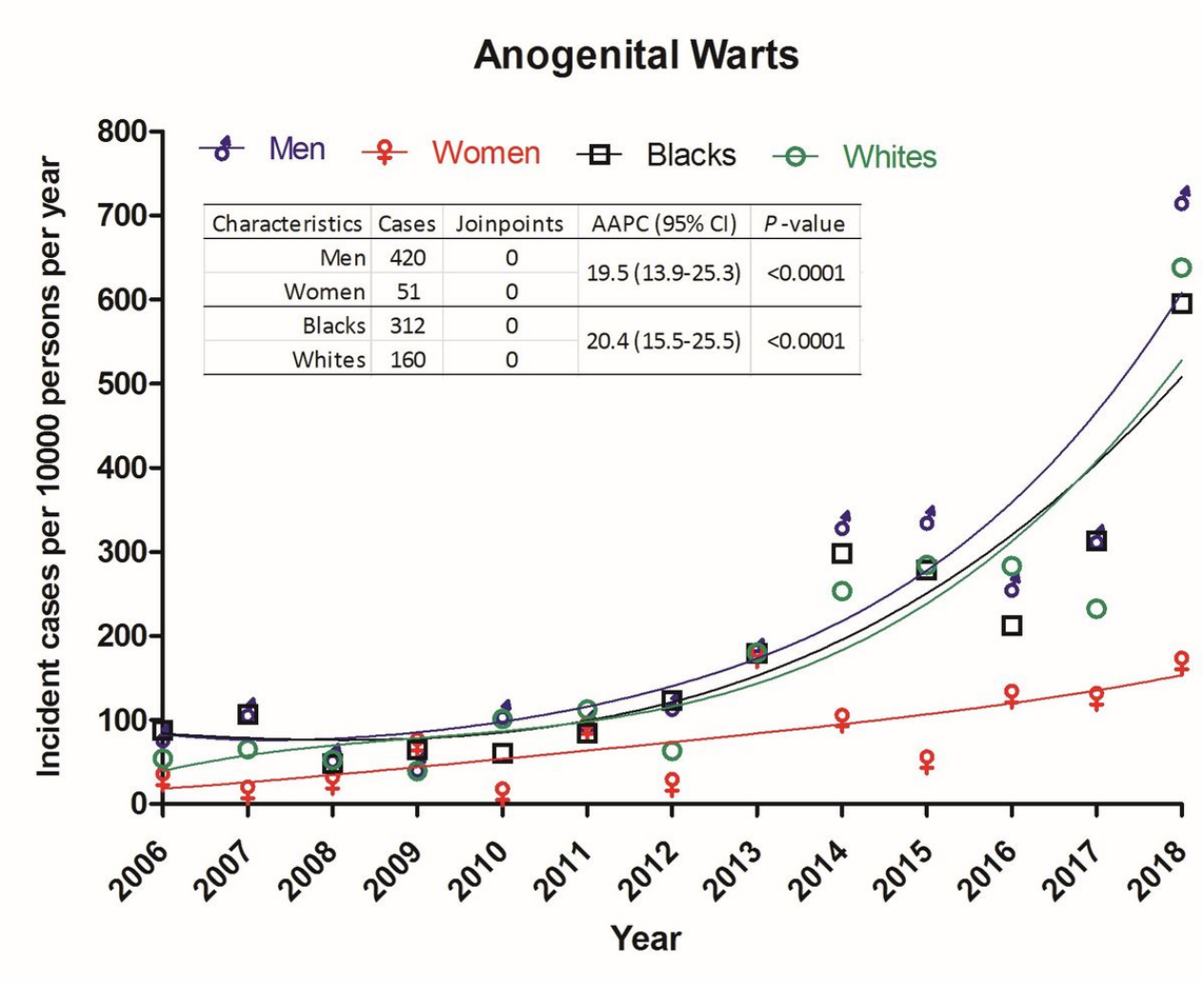
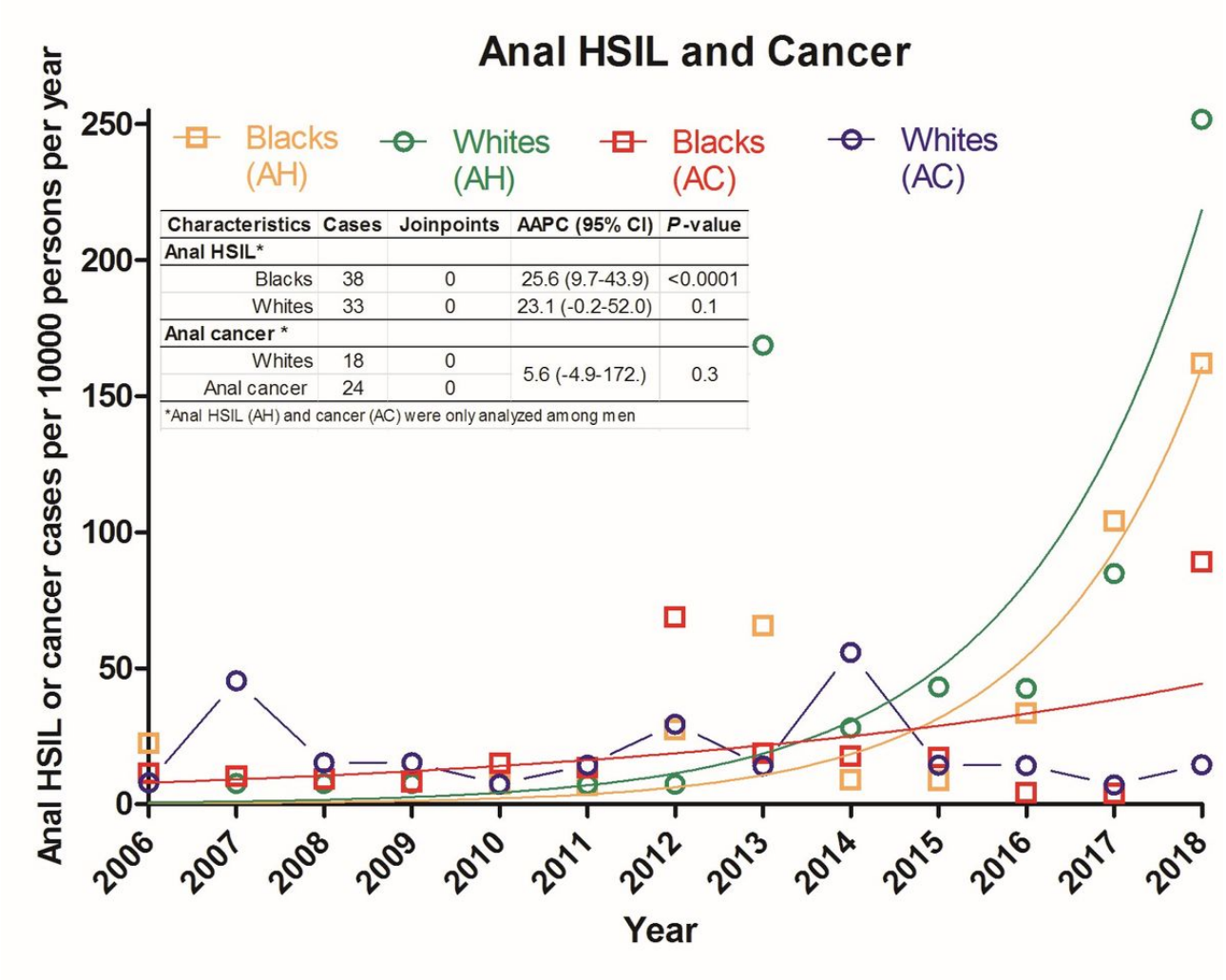


Figure 1

Trend [Office3] of incident HPV-related anogenital warts stratified by genders and races between January 2006 and March 2018.



Characteristics	Cases	Joinpoints	AAPC (95% CI)	*P*-value
Anal HSIL*				
Blacks	38	0	25.6 (9.7-43.9)	<0.0001
Whites	33	0	23.1 (-0.2-52.0)	0.1
Anal cancer *				
Whites	18	0	5.6 (-4.9-172.)	0.3
Anal cancer	24	0		

*Anal HSIL (AH) and cancer (AC) were only analyzed among men

Figure 2

Trend of HPV-related [Office4] incident anal HSIL and cancer stratified by genders and races between January 2006 and March 2018.