The Prevalence of Oral HPV infection and Oral lesions in People Living with HIV in a HIV Primary Care Clinic

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Study Team

Dr Cynthia S Firnhaber MD, MSc, DTM&H
Vivent Health Care-Denver/University of Colorado Medical School Anschutz Medical Center
5250 Leetsdale Drive suite 300
Denver CO 80246
303-393-8050 wk
303-917-0613 cell
Cynthia.firnhaber@cuanschutz.edu
Cindy.firnhaber@viventhealth.org

Blaine Wajdowicz, NP
Vivent Health Care-Denver
5250 Leetsdale Drive suite 300
Denver CO 80246
303-393-8050 wk
Blaine.Wajdowicz@viventhealth.org

Daniel Taylor, PA-C
Vivent Health Care-Denver
5250 Leetsdale Drive suite 300
Denver CO 80246
303-393-8050 wk
Daniel.Taylor@viventhealth.org

Alexis Moore, MPH
Vivent Health Care-Denver
5250 Leetsdale Drive suite 300
Denver CO 80246
303-393-8050 wk
Alexis.Moore@viventhealth.org

Billie Thomas, CCRC
Vivent Health Care-Denver
5250 Leetsdale Drive suite 300
Denver CO 80246
303-393-8050 wk
Billie.Thomas@viventhealth.org

Collaborator

Anna R. Giuliano, PhD
Director Center for Immunization and Infection Research in Cancer American Cancer Society
Clinical Research Professor
P – 813-745-6820 F – 813-745-5606
Anna.Giuliano@Moffitt.org

Study Background

Human Papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States (Centers for Disease Control and Prevention, 2022) and can cause varying degrees of changes to host tissue. Approximately fifteen HPV strains are known to be oncogenic, including types 16 and 18 which account for the majority of both precancerous tissue changes (known as squamous intraepithelial lesions, or SIL) and cancers of the anogenital tract and possibly the oral cavity. While HPV has been known to be associated with SIL of the cervix and the anus, only cervical samples are routinely co-tested for the presence of HPV in the United States. This is despite increasing rates of oropharyngeal squamous cell carcinoma (SCC; defined as malignancy involving the base of the tongue, the tonsils, and the pharynx) between 1999 and 2015 which listed oropharyngeal SCC as the most common HPV-associated cancer in the United States in 2015 (Van Dyne et al., 2018). In 2015, age adjusted incident rates per 100,000 persons in the United States in 2015 were 3,438 in women and 15,479 in men (Van Dyne et al., 2018). For context, the incidence rate of head and neck SCC is approximately 60,000/year for the United States and Europe (Vokes et al., 2015).

Oropharyngeal SCC incidence rates are increasing despite decreases in other head and neck cancers (such as laryngeal cancers) associated with corresponding decreasing rates of tobacco (both smoked and smokeless) and alcohol use (Vokes et al., 2015). As high as 70% of these cancers are estimated to maybe directly attributed to oncogenic strains of HPV, most commonly HPV type 16 (Vokes et al., 2015). While generally these cancers are recognized to have better prognoses and respond to chemoradiation, late detection of these cancers (i.e. when metastasis is present) can lead to poorer outcomes (Vokes et al., 2015). Recognizing this possible increase in HPV associated oropharyngeal SCC, much has been studied on risk factors for acquisition of HPV associated oropharyngeal SCC. These risk factors include immunodeficiency, tobacco, and alcohol use. Grulich et al. (2007) found comparable rates of increased cancer risks between people living with HIV (PLWH) and people on immunosuppressant therapy (i.e. after solid organ transplant). Patel et al. (2008) report that compared to the general public, PLWH had an incidence rate of oropharyngeal cancer that was 2.6 times greater. While studies are ongoing to differentiate whether this increased risk is now due to decreases in AIDS-associated malignancies with the advancement of antiretroviral therapy (ART), interestingly PLWH are diagnosed at younger ages with HPV associated oropharyngeal SCC compared to the general public (Shiels et al., 2017; Deeken et al., 2012).

Interestingly, while research has focused on HPV associated head and neck cancers, there are significant literature gaps on risk factors for oral HPV acquisition, specifically in PLWH. This is likely attributable to the fact that oral HPV status is confirmed through either immunohistochemistry (ICH) analysis or PCR typing of fine needle biopsy samples of oropharyngeal masses and lesions and there is no recommended routine screening for oral HPV in the absence of confirmed masses/lesions. Chaturvedi et al. (2018), in their cross-sectional study within the National Health and Nutrition Examination Survey (NHANES; cycles 2011 to 2013), were able to use an oral rinse screen to determine the prevalence rates of oral HPV DNA of types 16,18, 6, and/or 11 based on self-reported HPV vaccination status. They report statistically significant reduction by an estimated 88.2% of prevalence of the four types of HPV strains between vaccinated and unvaccinated groups. The current recommended vaccination against HPV is a nonvalent vaccine manufactured by Merck Pharmaceuticals (Gardasil®-9) and recommended between ages 9-26 and can be administered up to age 45.

Given the lack of recommended routine screening for oral HPV in the absence of established masses or lesions, there is a wealth of opportunities to investigate risk factors associated with the presence and prevalence of oral HPV which, in turn, can potentially be used to inform screening and treatment protocols. This proposal is designed to evaluate the prevalence of oral HPV infections and associated oral lesions and associated demographics in HIV treatment clinic.

Study Setting and Population

Vivent Health is a non-profit medical home model dedicated to the primary care of People Living with HIV (PLWH) and also provides pre-exposure prophylaxis (PrEP), Hepatitis C, and sexually transmitted infection (STI) treatment. The organization has clinics in Wisconsin (multiple cities), Denver, St. Louis, Austin and Kansas City. All insurances except Kaiser are honored and non-insured people are able to be seen. The Denver medical clinic is a designated medical home that provides adult primary medical and specialty care to approximately 1000 + PLWH. In additional to medical care, this clinic has an onsite pharmacy, case management, HIV and Hepatitis C prevention department, syringe access program, legal department, housing specialists, food bank, a mental health program and dental services. Vivent Health in Denver cares for a diverse population with approximately 11% African-American, 13% Latino, and a recently increasing percentage of women around 13%. This clinic has a strong Electronic Health Record System (EHR- Epic) which provides ample opportunity to recruit a robust study population to investigate the following co-morbidities which might increase the risk of oral HPV infection and related lesions such as:

1. Demographic factors (such as sex, race, and age)

2. Modifiable health behaviors (such as patterns of tobacco, drug, and alcohol use)

3. HIV infection (including CD4 nadir, recent CD4, and recent viral load)

4. History of anal and cervical dysplasia

Study Procedures

Inclusion Criteria

1. Documented HIV test on any FDA-approved HIV test
2. Ability and willingness of participant to provide informed consent
3. Capable of performing an oral swish and spit sample collection
4. Willingness to have an oral exam by Denver Vivent Health Dentist
5. Has had at least two visits at the Vivent Health Denver clinic
6. Study participant allows demographics and medical history/laboratory results in electronic medical records to be confidentially evaluated.

Exclusion Criteria

1. Any medical or mental health diagnosis that the study team concludes would prohibits participation of the protocol
2. CD4 count < 200 cells/ml
3. History of Oral/tongue cancer

Once consent is signed, the study team will collect participants' demographics, health history--including HIV and previous anal/cervical dysplasia information, substance use history, and dental hygiene care. Laboratory studies will be done as per standard of care and the laboratory results will be collected from the EMR.

The study participant will be asked to provide an oral swish and spit sample. This sample collection will follow the procedure published by (Herrero et al 2013). The specimen is collected by a 15-second rinse followed by a 15-second gargle using 15 ml of an alcohol-based mouth wash such as a commercially available product, Scope. The 15-ml samples will then be stored at -20 and then shipped on dry ice to Dr. Anna Giuliano's laboratory in Tampa Florida for HPV testing. At present Dr. Giuliano's laboratory is using the DDL SPF10 LiPA assay for sample analysis. An oral exam will be performed for each patient by the Vivent Dentist within 30 days of the collection of the HPV sample. If a referral is needed to an oral surgeon or Ears, Nose, and Throat specialist this will be done within 60 days of the dentist visit. The HPV results will not be shared with the participants as these are research study results and not part of standard of care.

The following protocol for the oral exam is used at our Vivent Dental department:
For each patient coming in for a comprehensive exam, a head and neck evaluation will be performed as we discuss medical/dental history and take vitals. The patient is then placed in a 12 O'clock recline position. Then palpation of the Temporal Mandibular Joint (TMJ), muscles of mastication, lymph nodes along mandible and neck occurs. The patient's face is then inspected for any asymmetry. Next an intraoral exam is performed to inspect sides of tongue, buccal mucosa, roof of mouth, floor of mouth, oral vestibule, and hard and soft palate. If any lesion is noted, the client will be asked for any known history. If they are unaware of the lesion, we will have the client return in 2 weeks and try to see if there is any causative factor that we can mitigate. If lesion persists, we will either perform the biopsy at our office or send to an oral

surgeon if complicated. All lesions are sent to an oral pathologist for diagnosis as per standard of care, which is then reviewed with the client. If further evaluation and treatment is needed that is outside of the clinic's scope, referral to outside specialist will be completed.

Schedule of Events

	Inclusion/ Exclusion Criteria	Consent Signed	Demographics/health hx/laboratory results collected	HPV sample collected	Oral exam by Vivent Dentist
Study Visit	X	X	X	X	X

Statistical Analysis

The study will evaluate 300 PLWH that attend the Vivent clinic for HIV care. We will use descriptive statistics to characterize our population and include age, race/ethnicity, sex at birth, tobacco use, alcohol use, other comorbidities, HPV vaccination status, other HPV disease, and lab values such as CD4 count and HIV viral load. We will compare results of variables between participants who are HPV positive and negative. We will also use a logistic regression model to evaluate the relationship between HPV oral infections and lesions and the variables above to better understand possible predictors of HPV infections and lesions.

As per data between 2011-2014 of NHANES, prevalence of any oral HPV for non-HIV adults aged 18-69 was 7.3% and for high-risk (oncogenic) HPV was 4.0% (McQuillan et al., 2017) and we think that the PLWH will have higher prevalence of HIV. We have decided on a sample of 300 as per budget allows as this would give us enough sample to determine a prevalence in our clinic population and begin to evaluate other variables associated with HIV infection. The data will be analyzed by the PI and study team.

Study Safety

As this is an observational study without study drug/vaccine no adverse reporting will be required

HUMAN SUBJECTS

Protected Health Information: The protection of the personal and confidential information of our study participants is one of our highest priorities. Therefore, care will be taken to protect the personal health information of the participants. All records will be kept in Vivent's HIPAA compliant EHR Epic. Consents will be maintained in EHR Epic, and a printed hard copy will be stored in the study file under lock and key. Collaborators will not have access to protected health information of the participants. All laboratory specimens, evaluation forms, reports, and other records entered into the data base and/or access will be identified by a coded number only to maintain subject confidentiality. All computer entries will be linked with a participant study number. Clinical information will not be released without written permission of the subject.

IRB APPROVAL:

This protocol, the informed consent documents, and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed informed consent will be obtained from each subject per Vivent's SOP. This study will be submitted to the central IRB we work with, Advarra, and will not be conducted until all aspects of this study have been approved. The consent form will describe the purpose of the study, study procedures and the confidential use of the study records. A copy of the consent form will be given to the subject. Patients will not be prejudiced in any way if they decline to participate in the study and be offered to receive an oral exam at the clinic of their choice.

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