PREVALENCE OF AND RISK FACTORS FOR ANAL HUMAN PAPILLOMAVIRUS IN HETEROSEXUAL MEN

by

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This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

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Alan Nyitray

DEDICATION

... to my Dad, who encouraged me to explore the natural world.

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ABSTRACT

Introduction: The incidence of anal cancer, whose primary cause is human papillomavirus (HPV) infection, has increased in United States (US) men almost three-fold in three decades; however, little is known about the epidemiology of anal HPV, especially in heterosexual men. Furthermore, advancements in knowledge about the epidemiology of anal HPV may be hampered by measurement error in the collection of sexual behavior data.

Methods: From two US cities, behavioral data and anal biological specimens were collected from 253 men who acknowledged sexual intercourse with a woman in the previous year. PCR and genotyping were used to assess the presence of HPV DNA. In addition, two HPV questionnaires were assessed for test-retest reliability: the first was a self-administered questionnaire associated with the collection of the biological specimens while the second was a computer-assisted self-interview (CASI) with 1069 men in Brazil, Mexico, and the US.

Results: Based on DNA analysis, overall anal HPV prevalence was 24.8% in 222 men who acknowledged no prior sexual intercourse with men. Risk factors independently associated with anal HPV were lifetime number of female sexual partners and frequency of sex with females in the past month. Based on kappa and intraclass correlation coefficients (ICC), both HPV questionnaires were found to be highly reliable with low refusal rates; however, three discrete measures in the multi-national interview asking for the number of sexual partners had lower reliability. The ICC of these questions increased to ≥ 0.79

when a small number of extreme outliers (≤ 3) were removed. Predictors of unreliable reporting were age and lifetime number of female sexual partners while years of education was inversely associated with unreliable reporting.

Discussion: These results suggest anal HPV is common in heterosexual men. Risk factors associated with anal HPV did not explain how HPV was transmitted to the anal region. Both instruments used to collect sexual behavior data were highly reliable including the CASI instrument used in three culturally and linguistically distinct countries; however, caution is warranted with discrete measures that ask participants to report the number of sexual partners.

I. INTRODUCTION

A. Explanation of the problem

HPV is a sexually transmitted infection and the primary cause of anal cancer (1, 2). While male anal cancer incidence in the United States (US) has increased almost threefold in three decades (3, 4), anal HPV prevalence and risk factors in men, especially heterosexual men, remain largely unknown.

Increasing incidence of anal cancer, also noted in Europe (5), is likely due to increased anal disease occurring in immuno-compromised persons and in men who have sex with men (6, 7, 8). Appropriately, most male anal HPV research to date has targeted men who have sex with men (MSM) and persons with Human Immunodeficiency Virus (HIV) given their increased risk for anal disease. However, it is a concern that healthy heterosexual men comprise a large majority of the male population and that no research regarding anal HPV has targeted them. Research indicates that heterosexual men with HIV, even in the absence of receptive anal intercourse, may have a high prevalence of pre-cancerous anal lesions associated with HPV (9). Also, more clearly understanding the risks associated with anal HPV in heterosexual men may provide important contrasts that help clarify the picture of anal HPV-related morbidity and mortality in other populations.

Investigations of the prevalence of and risk factors for HPV rely on accurate detection of the virus and the collection of accurate data that describe human characteristics and sexual behaviors. Improvements in the diagnostics for HPV detection have been able to rely on the existence of increasingly sensitive

and accurate assays that have provided a 'gold standard' that supports the further improvement of these assays (10). No such clear cut validity standard exists for the measurement of human behaviors, including sexual behaviors that typically occur in private. Consequently, the accurate measurement of sexual behaviors has lagged behind that of HPV detection and has clouded investigations of behaviors that may increase risk for HPV infection (11).

B. Goals and objectives

The long term goal of this research is to increase understanding of anal HPV in heterosexual men so that prevention approaches such as vaccination can be developed and implemented to reduce anal cancer burden. The focus of this research is to determine the prevalence and risk factors for anal HPV in heterosexual men. The objectives of this research are

1. to assess the test-retest reliability of a self-administered questionnaire used to measure the sexual and non-sexual behaviors in a community sample of 334 heterosexual men;
2. to estimate the type-specific anal HPV prevalence of and risk factors for 222 heterosexual men recruited in Tucson, Arizona and Tampa, Florida using the instrument assessed in objective 1.; and
3. to assess the test-retest reliability of a computer-assisted self-interview survey used to measure HPV-related sexual behaviors in a

multinational group 1069 men in preparation for impending research that builds upon this dissertation research.

C. Role of the author in the research

This project is an investigation of the prevalence and risk factors for anal HPV in heterosexual men with accompanying assessments of instruments used to gather HPV-related sexual behavior data. To determine prevalence and risk factors for anal HPV, the dissertation will analyze data from the Human Papillomavirus Detection in Men Study funded by the Centers for Disease Control and Prevention of the United States Public Health Service (MM-0579-03/03). The study was led by two members of the author's Dissertation Committee, Drs. Robin B. Harris and Anna R. Giuliano. The study collected anogenital exfoliated skin cells and sexual behavior data from men in an effort to 1) determine the optimal sites for anogenital HPV detection in men, 2) estimate the prevalence of anogenital HPV in men, and 3) assess risk factors for anogenital HPV in men. The dissertation author recruited participants for the study first as a volunteer and then as paid staff while also participating in regular meetings involved in the management of the study. Later, the author analyzed the study's data as a Research Assistant which led to an anal HPV prevalence and risk factor analysis. Since summer 2006, the author has maintained all study-related data.

Concurrent to this cross-sectional HPV study, Harris and Giuliano led a natural history study of HPV in men called HPV Infection in Men: A Prospective

Cohort Study. Funded by the Arizona Disease Control and Research Commission (HSC #03-120) and recruiting men only in Tucson, the study is known in this dissertation as the ADCRC study. Like the cross-sectional study above, the author recruited for this study and supported its ongoing management through participation in study-related meetings. The ADCRC study used the same survey instrument as the cross-sectional study. The author assessed this instrument for reliability and predictors of unreliable reporting in order to better understand the role of measurement error in the estimation of prevalence and risk factors in the cross-sectional anal HPV study.

The third study connected with this dissertation research is the ongoing multinational Natural History of HPV in Men Study: The HIM Study. Led by Dr. Anna Giuliano (and her Brazilian and Mexican collaborators Drs. Luisa Villa and Eduardo Lazcano), this National Institutes of Health (NIH) study (RO1 CA098803) is a prospective cohort recruiting a total of 3750 men from Tampa; Cuernavaca, Mexico; and Saõ Paulo, Brazil. This parent study will provide the biological specimens and behavioral data for the author's follow-up studies of anal HPV in men. The author has secured NIH (National Cancer Institute – 1R03CA134204-01) and industry funding (Merck Investigator-Initiated Study for Gardasil #33707) for these ancillary studies. The HIM Study uses a computer-assisted self-interview (CASI) to collect sexual behavior data from study participants. This interview was based on the paper and pencil self-administered survey used domestically in the ADCRC study. For the final phase of this

dissertation research, the author conducted a test-retest reliability study of the CASI in preparation for his continued investigations of anal HPV as part of the HIM Study.

All three studies discussed above have received approval from human subjects review committees in each of the locales where participants were recruited. Where required, human subjects review committees of other involved agencies, like funding agencies, have also provided approval for activities described in this dissertation. The specific institutional review boards involved are listed in the PRESENT STUDY section. In addition, this dissertation research has received approval for its activities from the Institutional Review Board of the University of Arizona.

II. BACKGROUND

A. HPV biology and impact

1. Virion structure and biology in the host

HPV is a double-stranded DNA virus of about 8000 base pairs that preferentially infects stratified epithelium of the skin, anogenital tract, or oral cavity. The virus has eight open reading frames designated E1, E2, E4, E5, E6, E7, L1, and L2 that control various functions like cellular integration and viral replication (12).

The virus infects the basal cells of the squamous epithelium, most likely through tears or micro tears in the skin or mucosa. Each infected basal cell is thought to have approximately 50-100 copies of the virus. As a basal cell divides into daughter cells, one of the daughter cells remains at the basal layer while the other moves up to a suprabasal layer. The viral particles in an infected basal cell segregate themselves into each daughter cell and replicate to re-establish 50-100 viral copies in each cell (13).

In uninfected suprabasal cells, the cells lose their ability to support DNA replication as they leave the basal layer and move closer to the epithelial surface, becoming keratinized along the way; however, after interference from the virion (a single viable virus), HPV-infected cells maintain their DNA replicating machinery and, thus, support the creation of new virions. These cells make their way to the epithelial surface where newly created HPV is sloughed off, potentially leading to a new infection at another anatomical site or in another person.

Alternatively, the virion remains in place at the epithelial surface and is transmitted through direct contact with the epithelial surface of another person (13).

2. Papillomavirus taxonomy

Human papillomaviruses are of the family *Papillomaviridae* which includes viruses that are thought to infect most mammals and birds. A new taxonomy for papillomaviruses was proposed in 2004 that classifies these viruses according to genera, species and type (14). Within the family, 16 genetically distinct genera (alpha- to pi-papillomavirus) help illustrate relationships among papillomavirus species and types. Alpha-, beta-, gamma-, mu-, and nu-papillomaviruses occur in humans, the only papillomavirus host that has been extensively studied with regard to papillomavirus infection and disease (14).

Each genus is composed of a number of species, and each species is composed of a number of genotypes. The species classification is useful in that it groups together papillomavirus types that typically have similar biological and pathological properties. For example, species 9 in the alpha-papillomavirus genus includes genotypes 16, 31, 33, 35, 52, and 58 which are all types thought to have carcinogenic activity in humans (14, 15).

Several hundred papillomavirus genotypes have been detected through isolation of incomplete DNA sequences, while approximately 120 human papillomavirus genotypes have been fully described. Within each genotype,

genetically distinct subtypes and variants have been isolated (14). The distinct pathological characteristics of subtypes and variants are currently under study.

HPV is also classified according to its carcinogenic potential; however, there is modest disagreement as to which types have this potential. The International Agency for Research on Cancer of the World Health Organization identifies 13 types with carcinogenic potential: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 (15). Other HPV researchers add types 26, 53, 68, 73, and 82 as either high risk types or probable high risk types (16).

3. Transmission

Human papillomaviruses are tissue specific with about 40 types known to infect the genitals, anus, and oral cavity. In addition to these 40 genotypes, other HPV types are responsible for warts on the hands or feet (17). Occasionally, these non-anogenital HPV types have been found on the genitals (18). Conversely, anogenital types have been found on the hands (19, 20, 21).

HPV has been presumed to be transmitted primarily through vaginal and anal intercourse. This conclusion comes from studies that assess HPV concordance among couples (22, 23, 24, 25, 26) and other research that detects strong associations between HPV infection and various sexual behaviors including lifetime number of sexual partners, number of recent new sexual partners, and frequency of sexual intercourse (21, 26, 27, 28, 29). In addition, anal intercourse is associated with detection of anal HPV in MSM but its

association with anal HPV in women is less consistent (30, 31, 32). While the routes by which HPV is able to infect the anus are not fully understood, it is clearly possible for HPV to infect the anus in the absence of receptive anal intercourse (9, 28, 33, 34).

It is worth noting that while HPV concordance studies in heterosexual couples have helped establish the sexually transmitted nature of HPV, most such studies find far from perfect concordance between male penile HPV and female cervical HPV (22, 24, 25, 26, 29). There may be several reasons for lower concordance including testing methods with low sensitivity, a differing natural history among males and females that results in clearance of HPV types in one partner but not the other, and non-monogamous relationships (26).

There also is evidence for transmission that is non-sexual. Besides two studies identifying type-specific concordant HPV infection on the hands and genitals of men and women (19, 20), a recent small study among putative monogamous heterosexual couples offered more convincing evidence of non-sexual transmission with HPV (21). In 25 couples, both the male and female were tested for HPV on the hands, genitals, and anus every two months for up to six visits. In 16 couples that showed evidence of HPV infection, the study documented what appears to be sequential, type-specific HPV transmission from body part to body part including autoinoculation. For instance, in one couple, HPV-39 was detected only at the female anal canal at time 1 and 2; then, at time 3, the same type was detected at the male's scrotum, then his penile shaft and

glans at time 4, and then the female anal canal again at time 6 (21). The study raises interesting questions about other possible transmission routes to the anal canal.

4. Outcomes associated with anogenital HPV

No matter what the transmission route may be, a large majority of sexually active men and women in the US will acquire HPV infection (35). It is the necessary cause of cervical cancer (36), and the necessary, or at least primary, cause of anal canal cancer (1, 2). Other cancers associated with HPV are cancers of the penis, vagina, vulva, and oral cavity (37). Additional outcomes associated with anogenital HPV that are important clinically and in research are persistence, subclinical lesions and clinical lesions.

HPV types 16 and 18 are responsible for about 70% of new cases of cervical cancer worldwide (38). HPV types 16 and 18 have also been implicated as the primary etiologic agents for anal cancer, although most investigations have been limited to persons with anal cancer in the US and Europe (1, 2, 39, 40, 41, 42, 43). After infection with HPV DNA, the virus will exist in the individual for some period of time and then typically will be cleared by the immune system. Alternatively, it may persist in a clinically silent form, or it may produce subclinical or clinical lesions. HPV that is not cleared by the body is said to be persistent and is usually defined as any two consecutive HPV DNA tests that are positive for the same HPV genotype. There is no agreed upon temporal definition

of persistent infection; however, it is believed to be a necessary condition for the development of cervical cancer (44, 45) and probably anal cancer given the similarity of tissue (46).

HPV persistence may lead to subclinical lesions which can be seen using a strong light and magnifying glass after the application of 5% acetic acid on keratinized skin (or 3% acetic acid on mucous membranes such as the anal canal) (47). Occurring on both skin and mucosal tissue, subclinical lesions are caused by both oncogenic and nononcogenic types of HPV. Most will spontaneously regress and, therefore, are not useful in predicting the risk of cancer (45).

The severity of subclinical cervical HPV-associated lesions are cytologically and histologically classified to facilitate therapeutic decisions. Unlike low-grade squamous intraepithelial lesions (LSIL), which indicate an active HPV infection but are not considered a precursor to cancer, high-grade squamous intraepithelial lesions (HSIL) are considered a true precursor (44). The same classification system is used with lesions identified on the cervix and in the anal canal (48). The histologic equivalent of LSIL and HSIL in cervical abnormalities is cervical intraepithelial neoplasia (CIN) 1 and CIN 2/3, respectively. With anal disease, the correlates are anal intraepithelial neoplasia (AIN) 1 and AIN 2/3, respectively (48). These classification schemes lead to standard lesion management techniques (see below).

Condyloma acuminata, or anogenital warts, are clinical lesions. Approximately 75% - 90% are caused by nononcogenic HPV types 6 and 11 (47).

While 1% of the population in Western countries may have clinically apparent genital or anal warts, they will spontaneously regress in up to 40% of affected persons (49). Rarely, oncogenic HPV types have been associated with anogenital warts (49).

Over a period of several decades, subclinical lesions, if left untreated, can progress to invasive cancer. The primary anogenital sites for HPV-associated cancer are the cervix, anus, penis, vagina and vulva. The process from HPV infection to cervical cancer has been described in four steps. First, an oncogenic form of HPV enters the epithelium, probably through micro-tears. While most HPV infections are cleared by the immune system, a second critical stage involves HPV establishing a persistent infection that is not cleared. Third, oncogenic HPV integrates its genes into the host cell resulting in chromosomal instability, clonal replication of the infected cell, and the production of intraepithelial lesions. The final step is invasive cancer (50).

Given an identical pathogen and the similarity of tissue (including a transformation zone in the anal canal that is bounded on each side by squamous and columnar epithelium), HPV-induced carcinogenesis leading to cervical cancer is comparable to the process that leads to anal canal cancer (51, 52).

In an adult, the anal canal extends for 2.5 to 5 cm from the anal os (or anal verge), past the dentate line to the rectal mucosa. The dentate line marks the end of the squamous cells and the beginning of the transformation zone where squamous epithelium meets columnar epithelium (53). This region is an

important site for HPV-associated anal cancers (54). Anal cancers can occur either in the perianal region outside of the anal os or in the anal canal; however, HPV is associated with a higher proportion of anal canal cancers than perianal cancers. Therefore, cancers located in increasingly keratinized skin, like the perianal region, are less likely to be associated with oncogenic types of HPV (40).

While most HPV research to date has focused on anogenital disease, epidemiologic research into the association between oncogenic HPV and head and neck cancers has recently increased. Cancers with squamous cell involvement, especially oropharyngeal cancer, are often the focus of this research. Previously thought to be primarily associated with tobacco and alcohol, evidence was produced in 1982 and 1983 for involvement of viruses in oral cancer (55). There is now evidence that HPV is causal in the production of oropharyngeal cancers especially in the tonsilar region (56). Furthermore, sexual behavior has been associated with oropharyngeal cancers, including the lifetime number of vaginal-sex partners (OR, 2.2; 95% CI, 1.2-4.0 for > five lifetime vaginal-sex partners and OR, 3.1; 95% CI, 1.5-6.5 for > 25 lifetime vaginal-sex partners in comparison to zero-five vaginal-sex partners) and oral sex (OR, 3.4; 95% CI, 1.3-8.8 for >= six lifetime oral sex partners in comparison to zero partners) (57).

In the respiratory system, nononcogenic types of HPV typically associated with anogenital warts have also been shown to cause disease. HPV-types 6 and 11 are primarily responsible for a rare disease called recurrent respiratory

papillomatosis (RRP), which is a proliferation of papillomas in the airway to the lung. It is most acute in newborns and likely a result of vertical transmission from mother to child (46).

5. Economic costs for HPV infection and HPV-associated disease

As might be expected from the most common sexually transmitted disease, the economic costs incurred by HPV infection and HPV-associated disease is high. Like HPV epidemiological research, economic studies have focused primarily on the costs incurred for cervical cancer and genital warts with little or no attention paid to other HPV-associated diseases.

Costs for prevention and treatment include direct costs and indirect costs. HPV-associated direct costs include physician services for colposcopies and anoscopies; hospital care for treating cancers; nursing home care and home health care for post-operative cancer patients; and pharmacotherapy for anogenital warts. Indirect costs include lost work due to morbidity and mortality. The direct medical costs associated with anogenital warts in 2004 were conservatively estimated at $200-225 million dollars while the costs of HPV-associated cervical abnormalities were estimated at $4 billion (58). Adding in the estimated costs of other HPV-associated anogenital cancers increased the cost to greater than $5 billion. Indirect costs have not been reported but would at least double the direct costs (58, 59, 60).

B. HPV epidemiology

1. Global distribution of HPV

Piecing together a coherent picture of the global prevalence of HPV in men is difficult due to heterogeneous study methods. Dunne, et al., conducted a systematic search for studies reporting HPV prevalence in men. They identified 40 articles assessing HPV DNA prevalence or seroprevalence in immunocompetent males over age 12 years where the size of the study sample was equal to or exceeded 20 participants. In 27 studies that sampled for HPV DNA at multiple anatomical sites in men, prevalence ranged from 1.3% to 72.9%. A simple majority of these studies reported an HPV prevalence of greater than or equal to 20% (61).

While different study methods and a lack of longitudinal studies make it difficult to develop a global picture of HPV prevalence and disease in men, the geographical distribution of cervical cancer, cervical dysplasia, and HPV prevalence in women is somewhat more clear and reveals strikingly different patterns from region to region. A meta-analysis of 78 studies conducted in Africa, Asia, Europe, North America, Central America, and South America estimated a global cervical HPV prevalence of 10.4% in asymptomatic women; however, that prevalence varies from a high of 31.6% in eastern Africa to a low of 6.2% in southeastern Asia (62). North American, Central American, and South American prevalence was estimated at 11.3%, 20.5%, and 14.3%, respectively. In all regions except Asia, a U-shaped prevalence curve was detected with prevalence highest in

women under the age of 34 years, declining between the ages of 35 and 44, before increasing in older women. In Asia, prevalence continued to decline throughout the lifespan after peaking in women younger than 35 years (62). While other studies find similar age-specific patterns for cervical HPV infection in women (63, 64), one large multinational study calls this pattern into question. Franceschi, et al. found much more diversity in the patterns of age-specific cervical HPV prevalence in different parts of the world (65).

Pooled data from 48 studies reporting HPV genotype-specific prevalence determined that types 16, 18, 31, 58, and 52 were the most common worldwide in asymptomatic women. But, like overall cervical HPV prevalence, type-specific cervical HPV prevalence differed somewhat by region. Type 53 was among the five most common types in North America and Central America (replacing types 58 and 52, respectively). HPV 45 was one of the five most common types in South America, replacing type 52 (62).

Given that the distribution of HPV genotypes differs from region to region (62), it is possible that the distribution of HPV types causing anal cancer also differs by location underscoring the importance of multiregional investigations.

2. Prevention

While HPV types and cervical cancer incidence differs by region, current prevention approaches do not vary with regard to these differences. However, prevention approaches do differ depending on the outcome one is trying to

prevent, either targeting initial infection or other outcomes including lesions and cancer. Prevention also differs by region with regard to the utilization of various strategies. To date, methods to prevent initial infection include vaccines and the modification of sexual behavior including the use of condoms.

The deployment of a preventive vaccine for HPV infection and cervical dysplasia in 2006 reflects important progress in preventing cases of cervical cancer (66). Merck & Co., Inc.'s Gardasil is a quadrivalent vaccine that effectively prevents infection with four HPV types responsible for a majority of cervical dysplasia, cervical cancers, and anogenital warts: HPV types 16, 18, 6, and 11. HPV types 16 and 18 are estimated to cause approximately 70% of cervical cancers and types 6 and 11 are estimated to cause 90% of genital warts worldwide. In a randomized, double-blind clinical trial with women the vaccine reduced the incidence of disease associated with these types by 90% (67). In another randomized, double-blind clinical trial with women, vaccine efficacy was 100% in preventing a variety of HPV-associated outcomes including incident genital warts, genital neoplasia, cervical neoplasia, and cervical cancer (68). A bivalent vaccine designed to prevent HPV 16 and 18 infection is currently under review at the US Food and Drug Administration.

The quadrivalent vaccine is approved for use with women aged 9 to 26, but is not licensed for use with men since there are no data currently available on the vaccine's ability to prevent HPV infection and associated outcomes in men (48); however, male HPV vaccine studies currently underway will determine the

efficacy of the vaccine to prevent HPV infection in males. The vaccine's ultimate utility for men will also depend upon modeling efforts that can provide quantitative insight into the economic and public health impact of the vaccine. One study addressing the issue has determined that a quadrivalent vaccine strategy that vaccinates boys and girls, in addition to catch-up vaccination for persons aged 12 – 24 years, would be as cost-effective as several other currently recommended vaccines (69).

The inclusion of non-cervical HPV-associated diseases like anal cancer in vaccine modeling will also tend to increase the incremental cost effectiveness ratio of an HPV vaccine (69). However, the most accurate modeling of vaccine cost-effectiveness with regard to anal HPV in men requires more natural history data (69, 70) and no such studies of anal HPV in heterosexual men have been published. Indeed, there have been only two studies estimating anal HPV prevalence in heterosexual men (71, 72).

Latex condoms offer a barrier to HPV infection; however, areas of skin that can express HPV, for instance, the scrotum and perianal region, are not covered by condoms. Even so, many studies, but not all, suggest a condom protective effect (73, 74, 75, 76, 77, 78, 79). The effectiveness of condoms as a prevention method for HPV, in addition to other behavioral measures, is also compromised by the highly infectious nature of HPV. As one might expect from the world's most common sexually transmitted disease (62), HPV is easily transmitted, possibly several times easier than other viral sexually transmitted

diseases like HIV or Herpes simplex virus. The median probability of female HPV acquisition per coital act has been estimated at .40 (range .05-1.00) in a study using stochastic computer simulations (78). Given the high prevalence and infectiousness of HPV it is unclear if other modifications to sexual behavior, like reducing the number of partners, would decrease risk for HPV since even one sexual partner carries such a high probability of HPV infection. In one recent study, almost 30% of women acquired cervical and/or genital HPV infection within one year of becoming sexually active with their first and only male sexual partner (80).

Lack of circumcision has been identified in a number of studies as a risk factor for HPV infection (73, 81, 82, 83, 84, 85, 86, 87). Other studies have failed to find a significant association between circumcision and HPV or circumcision and genital warts (27, 88, 89, 90, 91, 92). From a biological perspective, circumcision could help prevent HPV infection on the penis by removing the less keratinized mucosal surfaces of the prepuce that may be more susceptible to HPV infection through micro tears that occur during sexual intercourse (81). However, clinical trials are needed before making any HPV-associated public health recommendations regarding circumcision (93). Even then, any recommendation to remove a portion of the penis for public health purposes must be assessed not only in the context of the relevant science, but also with due consideration given to population-specific cultural values.

3. Interventions

Failing prevention of anogenital HPV infection (a distinct possibility given the high prevalence), the typically decades-long period between infection and invasive cancer provides numerous opportunities for halting the progression of disease.

Cervical Papanicolaou (Pap) tests are investigations of cervical cells to determine if there is evidence of HPV-associated abnormalities. Pap tests are recommended by the United States Preventive Services Task Force (USPSTF) because they can alert a physician to the existence of abnormalities that can almost always be successfully treated. The recommendations suggest that women get Pap tests at least once every three years and that the testing begin within three years of sexual debut or age 21, whichever comes first (94). Pap screening with an abnormal result is typically followed with genotype testing to determine if oncogenic types are involved (95). If oncogenic HPV is involved (or if the Pap test result is LSIL or HSIL) then the patient is referred for colposcopic examination. Potentially precancerous lesions are ablated or surgically removed from the cervix. If precancerous lesions progress to cancer, treatment decisions will be based on tumor size and stage, physical health and age of the woman, and other considerations. Treatment can include the same treatment options as with precancerous lesions, hysterectomy, and/or radiotherapy (96).

While not currently recommended by the USPSTF, some physicians and the New York State Department of Health recommend anal Pap tests for persons

at higher risk of anal cancer including people with HIV and men who have sex with men (51, 97, 98). Anal Pap tests have also been assessed as cost effective if targeted toward HIV-positive and HIV-negative men who have sex with men when performed annually or biannually (99, 100). Anal pap tests are interpreted like cervical pap tests. Abnormal results, either atypical squamous cells of undetermined significance (ASCUS), LSIL, or HSIL, are referred for high-resolution anoscopy (HRA). Lesions identified through HRA are biopsied to assess their cancer potential and then treated (51). Treatment of anal intraepithelial lesions may be more complicated than treatment of cervical intraepithelial lesions, but as with cervical intraepithelial lesions, treatment decisions will be made depending on a variety of factors including lesion size, cancerous potential, and the health of the patient (47).

Finally, interventions for benign genital warts include surgical excision, cryotherapy, and topical agents that can induce tissue necrosis (49).

4. Anal cancer epidemiology

HPV is the primary cause of anal cancer (1, 2); however, the epidemiology of anal HPV and anal cancer, especially in heterosexual men, has received little attention.

A total of 4650 diagnoses of anal carcinoma were expected in the US in 2007 with 1900 of those in men. A total of 690 people were expected to die of anal cancer with 260 of these deaths in men. Other than cervical cancer, anal

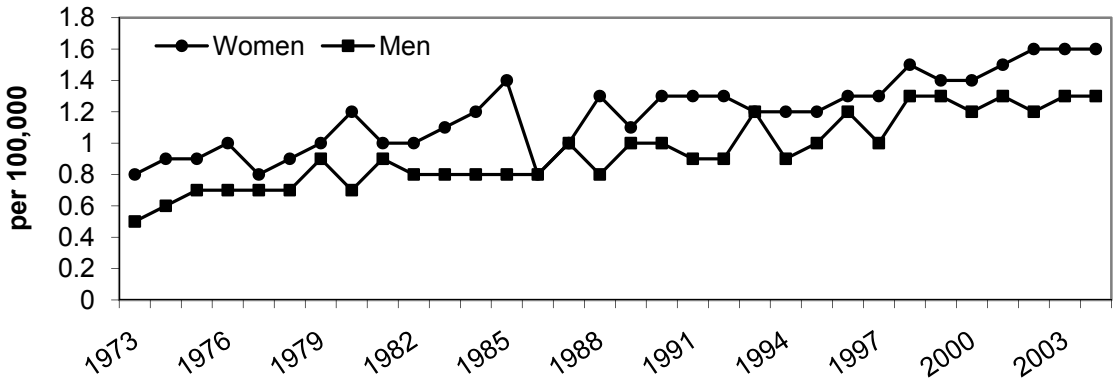
cancer was expected to be the most commonly diagnosed anogenital HPV-associated cancer in the US in 2007 (101). Although not an anogenital cancer, HPV-associated oropharyngeal cancer and oral cavity cancer may be responsible for a higher number of carcinomas each year than anal cancer (102).

Although less common than cervical cancer, the incidence of anal cancer in US men is increasing – 0.5 cases/100,000 in 1974 to 1.3/100,000 in 2004. In the same period cervical cancer incidence decreased (4). Increasing incidence of anal cancer, also noted in Europe (5), is likely due to increased anal disease occurring in immuno-compromised persons and in men who have sex with men (6, 7, 8). Indeed, the risk ratio of observed to expected invasive and *in situ* anal cancers has been reported as 37.9 (95% CI 33.0-43.4) in males with HIV, 59.5 (95% CI 51.5-68.4) in homosexual men with HIV, and 5.9 (95% CI 2.7-11.2) in heterosexual male injection drug users with HIV (103). In men with a history of receptive anal intercourse, the annual incidence of anal cancer in the late 1970's was estimated to be between 12.5 and 36.9/100,000 (104). By comparison, between 2001 and 2005 the annual cervical cancer incidence rate in US women was 8.4/100,000 women (105).

The increasing incidence of anal cancer in the US is occurring among men and women (see Figure 1). According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, the average annual percent change in anal cancer incidence between 1974 and 2004 in

women was 1.8 (95% CI 1.4-2.2). During the same period the annual percent change in anal cancer incidence in men was 2.4 (95% CI 2.1-2.8) (4).

Figure 1. Age-adjusted incidence of malignant, anal cancer in US men and women 1973-2004. Figure created using SEER data (4).



5. Anal HPV prevalence

The epidemiology of anal HPV in heterosexual men is largely unknown. Two studies have reported anal HPV prevalence in asymptomatic men who do not acknowledge sex with other men (71, 72). The first recruited exclusively heterosexual men from a sexually transmitted disease (STD) clinic in Amsterdam in 1994 and the second recruited exclusively heterosexual male partners of women with confirmed HPV in São Paulo, Brazil in 2005. The Amsterdam study estimated an anal HPV prevalence of 1.2% (72) and the São Paulo study estimated an 8% prevalence (71). However, drawing comparisons between these studies is difficult due to different testing methods and study populations. This caveat also applies to the following study synopses due to HPV diagnostics that have become much more sensitive and specific in the last 15 years (10).

Moscicki, et al., in 2003, reported an anal HPV prevalence of 36% in 13-18 year old HIV-negative boys in the US who were selected for study based on high-risk sexual and substance-using behavior; however, that group included boys with same-gender sexual behavior (106).

Anal HPV prevalence can be higher than 50% in other male populations including heterosexual men with HIV (33, 107) and men who have sex with men (30). One study among 22 heterosexual men with HIV in Spain reported an anal HPV prevalence of 68% (107), while another study among 50 male heterosexual injection drug users with HIV in France reported an anal HPV prevalence of 46% (33). Anal HPV prevalence was also high in HIV-negative men who have sex with men with one recent study of 1218 men in four US cities reporting a prevalence of 57% (30).

Regarding anal HPV in bisexual men, one might speculate that their anal HPV prevalence is somewhere between the estimates for heterosexual men and men who have sex with men. Unfortunately, there is very limited information available about bisexual men and anal HPV prevalence. Nielson, et al. estimated an anal HPV prevalence of 24% in a sample of 463 men which included exclusively heterosexual men and men who acknowledged sex with both men and women. The Nielson, et al. prevalence estimate indeed falls between anal HPV prevalence estimates discussed above for men who have sex with men (>50%) and exclusively heterosexual men (<10%). There is also a lack of study of the

genital HPV prevalence of bisexual men. One study has reported a prevalence of 50% in twelve bisexual men recruited at an STD clinic (108).

Anal HPV prevalence has rarely been estimated in community samples of women (32, 109). However, one cohort study enrolled a large sample of women in Hawaii (n=1378) and estimated a 27% baseline prevalence for anal canal HPV in women recruited from health clinics, a health research center, and a health maintenance organization (32). Previously, a study of anal HPV in HIV-positive and HIV-negative women estimated a 42% prevalence in HIV-negative women who were selected into the study based on high risk behavioral characteristics for HIV like injection drug use (109).

The age-specific prevalence of anal HPV in heterosexual men is unknown and may be important for understanding subsequent anal cancer risk. For example, if anal HPV prevalence peaks in heterosexual men at a young age (e.g., < 30 years) and declines rapidly thereafter, then it may be expected that heterosexual men's anal cancer risk would be less than a population whose anal HPV prevalence remains 'steady' throughout the lifespan. One such population is men who have sex with men in whom a high and stable anal HPV prevalence has been reported by Chin-Hong, et al. (30).

In the previously mentioned cohort of women recruited in Hawaii, Hernandez, et al. found no association between age and women who had anal canal HPV in the absence of cervical HPV; however, the same study identified an

inverse association between age and women who had both cervical and anal canal HPV infection (32).

6. Anal HPV natural history

Prevalence is an important measure for understanding the distribution of anal HPV in a population; nonetheless, understanding the risk for its most serious outcome, invasive anal cancer, is the goal. As such, it is critical to learn more about the natural history of anal HPV; however, no such investigations focused on heterosexual men have been reported. Statistics that help describe the natural history of HPV are cumulative incidence, incidence rate, persistence, and clearance of HPV.

The natural history of anal HPV in men who have sex with men has received some attention. Chin-Hong, et al. reported a 61% cumulative incidence of anal HPV in 18 months in 1409 HIV-negative MSM. In HIV-negative MSM with incident anal HPV 16, the same study reported that 74% of the men had persistent infection (defined as two consecutive positive tests spaced six months apart) (110). Two other studies have reported anal HPV incidence measures in MSM with one estimating a 40% cumulative incidence in 12 months in HIV-negative MSM (111) and the second reporting 45 incident cases in 429 HIV-positive and HIV-negative men after 25.5 months of follow up (112).

Recently, the women's Hawaiian cohort reported anal HPV incidence (113). During 1.3 years of follow-up, 303 of 431 women in the study either had

anal HPV at baseline or acquired it. The incidence rate for any new HPV infection was approximately 50/1000 woman-months while the incidence of high risk HPV infection was double the incidence of acquiring low risk HPV types (19.5/1000 vs 8.2/1000 woman-months, respectively) (113).

The study of genital HPV in women has identified the median duration, or time to clearance, of infection as approximately eight months for high risk types and 4.8 months for low risk types (44). Most infections (~90%) will clear within two years (45). Clearance of genital HPV in men has been less studied but was recently estimated at a median of 5.9 months for any type of HPV (114).

Anal HPV persistence was recently estimated in MSM returning for HPV testing every six months. In men with incident infection, HPV 16 and HPV 6 were detected at consecutive visits in 74% and 70% of men, respectively (110). Anorectal HPV persistence was estimated in heterosexual men in one small study of STD clinic patients in Amsterdam (72). Two of 17 men with anal HPV were identified as having “intermediate persistence” which was defined as a positive test for a specific type of HPV at two consecutive visits within one year (72). However, due to its small sample size, high loss to follow up, and less sensitive HPV detection methods, this study did not yield a valid estimate of anal HPV persistence in heterosexual men. Cumulative incidence, incidence rates, persistence and clearance data from nine longitudinal studies of HPV in men are presented in Table 1.

Table 1. Natural history studies of anal, genital, and fingernail HPV in men

Study	Population	Cumulative incidence at 12 months[a]	Incidence rate per 1000 person-months[a]	Persistence at 6 months[a]	Clearance at 6 months[a]
Chin-Hong, et al., 2007 (110)	1409 HIV-negative MSM[b]	Anal HPV AT[b] .41 Anal HPV 6 .07 Anal HPV 11 .03 Anal HPV 16 .09 Anal HPV 18 .04		Anal HPV 16 .74 Anal HPV 6 .70	Anal HPV AT .15
Xi, et al., 1998 (112)	276 HIV-negative MSM 313 HIV-positive MSM		Anal HPV 16[c] .24		
Critchlow,	287 HIV-negative MSM	Anal HPV AT			

Table 1. Natural history studies of anal, genital, and fingernail HPV in men

Study	Population	Cumulative incidence at 12 months[a]	Incidence rate per 1000 person-months[a]	Persistence at 6 months[a]	Clearance at 6 months[a]
et al., 1998 (111)	322 HIV-positive MSM	HIV- .40 HIV+ .54			
Van Doornum, et al., 1994 (72)	48 heterosexual men at STD clinic		Anogenital HPV AT 42.1	Anogenital HPV .03 Genital HPV .15 Anal HPV .06	
Giuliano, et al., 2008 (114)	290 community and college males	Genital HPV AT .29	Genital HPV AT 29.4 Genital HPV 6 2.8 Genital HPV 11		Genital HPV AT .51

Table 1. Natural history studies of anal, genital, and fingernail HPV in men

Study	Population	Cumulative incidence at 12 months[a]	Incidence rate per 1000 person-months[a]	Persistence at 6 months[a]	Clearance at 6 months[a]
			0.5		
			Genital HPV 16		
			4.8		
			Genital HPV 18		
			0.8		
Partridge, et al., 2007 (20)	240 college males[d]	Genital HPV AT			
		.31			
		Genital HPV HRT[b]			
		.24			
		Genital HPV 16			
		.10			
		Genital HPV 18			
		.04			

Table 1. Natural history studies of anal, genital, and fingernail HPV in men

Study	Population	Cumulative incidence at 12 months[a]	Incidence rate per 1000 person-months[a]	Persistence at 6 months[a]	Clearance at 6 months[a]
		Genital HPV MT[b]			
		.18			
		Glans HPV AT			
		.22			
		Glans HPV HRT			
		.16			
		Shaft HPV AT			
		.23			
		Shaft HPV HRT			
		.18			
		Scrotum HPV AT			
		.22			
		Scrotum HPV HRT			

Table 1. Natural history studies of anal, genital, and fingernail HPV in men

Study	Population	Cumulative incidence at 12 months[a]	Incidence rate per 1000 person-months[a]	Persistence at 6 months[a]	Clearance at 6 months[a]
		.17			
		Fingernail HPV AT			
		.16			
		Fingernail HPV HRT			
		.13			
Kjaer, et al., 2005 (115)	388 young conscripts; 374 at 6-8 month follow up	Glans HPV .13		Glans HPV AT .53	
Lajous, et al., 2005 (82)	336 Mexican military men		Genital HPV AT 17.9	Genital HPV AT .06	
de	14 husbands			Urethral HPV	

Table 1. Natural history studies of anal, genital, and fingernail HPV in men

Study	Population	Cumulative incidence at 12 months[a]	Incidence rate per 1000 person-months[a]	Persistence at 6 months[a]	Clearance at 6 months[a]
Sanjose, et al., 2003 (116)				AT .01	
Wikström, et al., 2000(117)	88 men at STD clinic			Penile HPV AT .86	

[a] Denominators for cumulative incidence, incidence rate, persistence, and clearance have been standardized as indicated in the header row. Caution should be exercised with these data since this standardization requires an important assumption: that incidence, persistence, and clearance rates are stable during all follow-up time periods.
[b] MSM, men who have sex with men; AT, any type; HRT, high risk type; MT, multiple types.
[c] Follow up is for incident and prevalent cases.
[d] Sample described as "heterosexually-active males."

Prevalence, incidence, and duration have a simple mathematically relationship (118)

$$\text{Prevalence} \approx \text{Incidence} \times \text{Duration}$$

in circumstances where 1) there is "steady state" population with stable incidence and disease duration, and 2) prevalence is roughly under .10 (118). Given that persistence of HPV infection is analogous to the duration of HPV infection, the equation can be modified to

$$\text{Prevalence} \approx \text{Incidence} \times \text{Persistence}$$

However, given limited epidemiological investigations, it is unclear if the above assumptions hold in the case of anal HPV in heterosexual men. If they do hold, then anal HPV prevalence is a result of the combined effects of its incidence and persistence; thus, incidence and persistence data can provide clues to help determine the underlying processes that may be driving anal HPV prevalence in heterosexual men.

7. Risk factors for anal HPV and anal HPV-associated disease

Anal HPV prevalence, incidence, and persistence are a result of the interplay of host, agent, and environment. As discussed earlier, studies of cervical

HPV and male genital HPV have developed strong evidence for the role of the host's sexual behavior in increasing the risk of HPV infection. Equally compelling are data that indicate the environment, at least with respect to the sexual behavior of the host's partner(s), is also an important feature in understanding risk for HPV (119).

Thirty-one studies have addressed risk factors for anal HPV infection or HPV-associated anal disease (Table 2): nine investigated anal HPV infection, twelve investigated HPV-associated lesions, and 13 investigated risk factors for anal cancer. Most studies with heterosexual men (4/5), men who have sex with men (7/11), and women (5/9) targeted people with HIV.

No studies have reported risk factors for anal HPV infection in asymptomatic heterosexual men. Although one study investigating the association between anal warts and sexual behavior in a small group of heterosexual men and women found no association between anal warts and anodigital insertion in heterosexual men or women (28). Of four studies which assessed factors associated with anal cancer in heterosexual men, three of four identified genital warts as a risk factor (2, 31, 120) and two of four found an increased number of partners associated with anal cancer (1, 2). Cigarette smoking, non-married marital status, anal fissures or fistulas, gonorrhea, and more than twelve episodes of hemorrhoids were also identified as risk factors in heterosexual men (1, 31, 120). Four studies have included heterosexual men with HIV infection (9, 33, 34, 107), but only one has reported risk factors. Piketty et al.

found HIV-related immunological factors and AIDS-defining illnesses associated with anal HPV in 50 heterosexual injection drug users (33).

While the routes by which HPV is able to infect the anal canal are mostly unknown, it clearly occurs in men and women even in the absence of receptive anal intercourse (1, 9, 28, 32, 33, 34). For example, in France, Abramowitz et al. studied HIV-infected heterosexual men, heterosexual women, and HIV-infected men who have sex with men. Of 123 heterosexual men, most of whom were immigrants from Africa, 18 exhibited anal condyloma or anal dysplasia in the absence of any reported receptive anal intercourse. Wilkin et al. reported a 23% prevalence of anal intraepithelial neoplasia in HIV-infected men with no history of receptive anal intercourse (9).

Thus, it seems that the penis is not needed to transport HPV to the anal canal. But just as vaginal intercourse is clearly a very efficient method for transmitting HPV to the cervix, anal intercourse is a very efficient method for transmitting HPV to the anal canal. At least a dozen epidemiological studies have identified receptive anal intercourse as being associated with anal HPV infection or HPV-associated anal disease (1, 2, 9, 30, 31, 34, 104, 111, 113, 121, 122, 123).

Ten studies have assessed risk factors for anal HPV infection, lesions, and/or cancer in men who have sex with men (9, 30, 33, 34, 107, 111, 123, 124, 125, 126). In these studies, the risk factors most commonly found to be associated with one or more of these outcomes in MSM were receptive anal intercourse (9, 30, 31, 34, 111, 123) and an increased lifetime number of sexual partners (2, 9, 33,

111). Declining immune function has also been noted as being strongly associated with anal HPV infection or one of its outcomes (111, 124). Two studies reported a lower age (either under 35 years (124) or under 40 years (9)) as being associated with either anal HPV infection (9, 124) and/or anal lesions (9).

Risk factors for anal HPV in women include a lower age, higher number of lifetime sexual partners, more than five years of oral-contraceptive-pill use, and a current practice of anal sex (32, 113). In women with HIV, multivariate risk factors for anal HPV infection included an age under 36 years, a white race, use of Zidovudine (an anti-retroviral treatment for HIV infection), presence of cervical infection, and decreased immune function (109).

Table 2. Risk factors for anal HPV, anal lesions, and anal cancer by research study in men and women

Risk/protective factors in men and women of any sexual orientation	HPV-associated outcome		
	Anal HPV infection	Anal lesions	Anal cancer
Decreasing age	(9, 109, 113, 124)[a]	(9)	
Race	(109, 113)		
Lower socioeconomic status	(113)		
Urban residence			(127)
Homelessness	(113)		
Higher income (protective)	(113)		
Marital (single, separated or divorced)			(1, 2, 5, 127)
Smoking		(128)	(2, 31, 41, 120)
Declining CD4+ counts	(109, 111, 124)	(9, 33, 34, 121, 126, 128, 129)	
<15 Langerhans cells/mm tissue		(130)	
Current use of antiretroviral therapy (protective)		(9)	
Zidovudine use	(124)		
Renal transplant			(42)

Table 2. Risk factors for anal HPV, anal lesions, and anal cancer by research study in men and women

Risk/protective factors in men and women of any sexual orientation	HPV-associated outcome		
	Anal HPV infection	Anal lesions	Anal cancer
History of anal SIL		(34)	
Increased plasma HIV RNA viral load		(33, 121)	
Previous AIDS-defining event		(33)	
History of cervical SILs		(121, 122)	(1)
Cervical infection	(32, 109)		
History of other anogenital cancers			(131)
History of leukemia/lymphoma			(131)
Subsequent lung, bladder, breast, vulva/vagina, and small intestine cancer			(131)
Past use of hormones	(113)		
Long term oral contraceptive use	(113)		
Alcohol use	(107, 113)		
Infection with a greater number of HPV types		(125)	
History of genital warts		(123)	(1, 2, 31, 120)
History of anal warts	(111, 124)		(1)

Table 2. Risk factors for anal HPV, anal lesions, and anal cancer by research study in men and women

Risk/protective factors in men and women of any sexual orientation	HPV-associated outcome		
	Anal HPV infection	Anal lesions	Anal cancer
History of gonorrhea	(124)		(1, 31)
History of syphilis			(1)
History of Trichomoniasis			(1)
History of genital herpes			(31)
History of labial herpes			(1)
History of Chlamydia			(31)
Hepatitis			(1)
History of anal fissure or fistula			(120)
History of > twelve episodes of hemorrhoids			(120)
History of HIV test			(1)
HIV infection	(111, 124, 129)	(43, 130)	(43)
AIDS diagnosis	(124)		(132)
Use of poppers in previous six months		(125)	
Use of injection drugs in previous six months		(125)	
Age at first sexual intercourse <= 16			(1)

Table 2. Risk factors for anal HPV, anal lesions, and anal cancer by research study in men and women

Risk/protective factors in men and women of any sexual orientation	HPV-associated outcome		
	Anal HPV infection	Anal lesions	Anal cancer
Receptive anal intercourse	(9, 30, 111, 113)	(9, 34, 121, 122, 123)	(1, 2, 31, 104)
Any sex	(111)		
Greater than five partners for anal receptive sex		(125)	
Number of anal intercourse partners			(1)
Increased lifetime number of sexual partners	(111, 113, 124)	(33)	(1, 2)
Increased lifetime number of opposite sex partners			(1, 2)
Increased recent number of sexual partners	(30)		
Recent receptive anal intercourse	(111)		
Frequency of sexual intercourse/month		(34)	
Partners' lifetime number of partners (>= three or unknown or no			(1)

Table 2. Risk factors for anal HPV, anal lesions, and anal cancer by research study in men and women

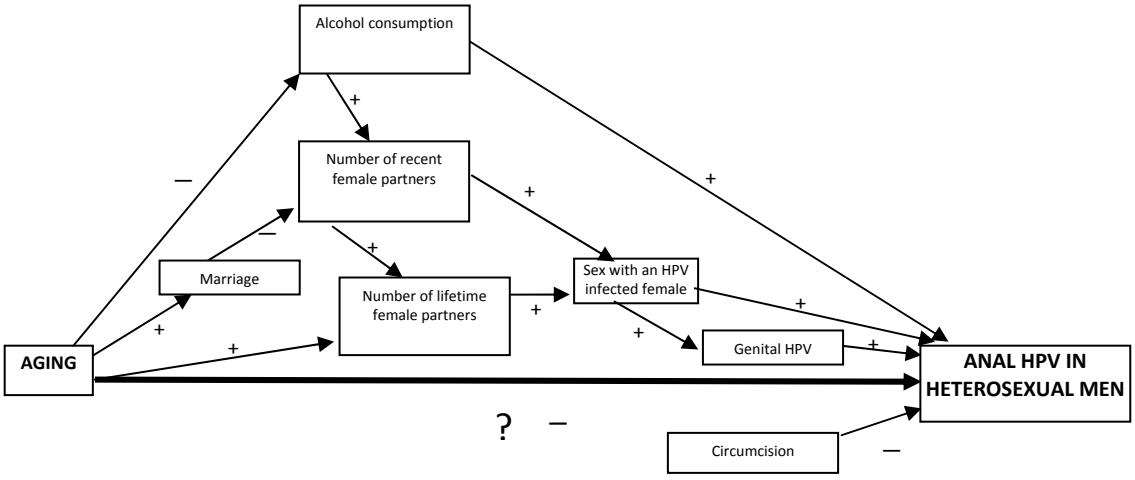
Risk/protective factors in men and women of any sexual orientation	HPV-associated outcome		
	Anal HPV infection	Anal lesions	Anal cancer
current male partner)			
History of STD in partner			(1)
More than four sexual partners before age 18			(1)
Age at first sexual intercourse			(1, 2)
Older age at first receptive intercourse		(125)	
Condom use (risk factor)	(113)		

[a] Numbers refer to the citation number in the present study.

8. Relationship between age and anal HPV among heterosexual men

Given the multiplicity of risk factors for anal HPV infection in men who have sex with men and in women, it seems likely that the relationship between the environment, heterosexual men, and anal HPV is complex. Clarifying these relationships requires a complete account of potential exposures, confounders, and effect modifiers. Using the exposure of age as an example, Figure 2 is a causal diagram presenting a theory of an inverse relationship between age and anal HPV in heterosexual men. The theory is plausible since a lower age has been associated with anal HPV in men who have sex with men, men with HIV, and in women (9, 109, 113, 124). A causal relation is illustrated by an arrow that emanates from a potentially causal variable (e.g., aging) and points to its putative effect (e.g., anal HPV). Positive signs and negative signs mark theorized associations as positive or inverse. The question mark identifies the association of

Figure 2. Diagram proposing a causal relationship between age and anal HPV in heterosexual men



primary interest. For example, the process of aging affects marital status: in the US, a 31 year old man is much more likely to be married than a 21 year old man (133). Marriage, in turn, leads to a reduction in the number of recent female partners; however, the number of recent female sexual partners likely increases the risk of having sex with a woman with HPV which could lead to infection and detection of anal HPV in heterosexual men. Of course, the full story of the relationship between age and anal HPV is much more complicated (e.g., the diagram doesn't depict the role of condoms); however, this diagram also helps to identify potential confounders of the relationship between risk factors and anal HPV. For instance, regarding the relationship between the number of recent female sexual partners and anal HPV, the diagram points to two potential confounders of that relationship: alcohol consumption and age. Conversely, the diagram also indicates that the relationship between age and anal HPV is unconfounded pointing to the bivariate effect measure as being the most valid estimate of their association. Thus the diagram helps support an assessment of the age-specific prevalence of anal HPV among heterosexual men.

9. Genital HPV in men

The presence of genital HPV may help to explain the presence of anal HPV in men (32, 107). When the penis and/or scrotum are the focus of HPV DNA testing in heterosexual men, prevalence estimates range widely, from 9% to 70%, depending on testing method, study population, and the anogenital sampling locations and procedures (26, 71, 72, 84, 108, 134). Investigations of risk factors

have reported inconsistent results for genital HPV risk factors but include younger age, non-white race, Hispanic ethnicity, younger age at sexual debut, lack of a 'steady' sexual partner, single marital status, increased frequency of sex, higher numbers of lifetime and/or recent female sexual partners, lack of circumcision, lack of condom use, smoking, and presence of genital warts (26, 73, 82, 83, 84, 88, 135, 136).

C. A rationale for studying anal HPV in heterosexual men

Given that MSM likely have a much greater burden of HPV-associated anal disease than heterosexual men, why is the study of anal HPV in heterosexual men important? First, it is entirely appropriate that most male anal HPV research to date has targeted men who have sex with men given their increased risk for anal disease. However, it is a concern that healthy heterosexual men comprise a large majority of the male population and that no research regarding anal HPV has targeted them. Also, research indicates that heterosexual men with HIV, even in the absence of receptive anal intercourse, may have a high prevalence of pre-cancerous anal lesions associated with HPV (9). Finally, more clearly understanding the risks associated with anal HPV in heterosexual men may provide important contrasts that help clarify the picture of anal HPV-related morbidity and mortality in other populations.

D. Measurement error

> "One way to formulate the objectives of an epidemiologic study is to view the study as an exercise in measurement. The specific aims then involve the estimation of one of the measures of disease occurrence or effect…The entire process of estimation is in this sense a measurement process (118)."
>
> Kenneth J. Rothman and Sander Greenland

1. Error in sexual behavior surveys

While genotyping tests for HPV have enabled improved detection (137), accurate measurement of exposures leading to anogenital HPV infection lags; however, it is important to know the risk factors associated with anal HPV infection in order to devise strategies that prevent the transmission and sequelae of HPV. Data describing sexual behaviors are usually collected through self-report; however, there is concern that study participants' self-reported sexual behaviors may not be valid; that is, they may not reflect reality (137, 138, 139, 140).

The heterogeneous results for genital HPV risk factors described earlier may be due, in part, to measurement error. The measurement of factors associated with anal cancers and anal HPV relies on self-reported data that is compromised by a number of sources of measurement error including the social

desirability of acknowledging behaviors discouraged by society (141, 142). This issue is common to sexual behavior research, and is one limitation in reports recording human sexual behavior (133, 143).

Misclassification is the result of information bias (144); thus, the misclassification of sexual behavior can bias HPV investigations. One specific concern of the present study is the possibility of exposure misclassification of sexual orientation, a kind of information bias that may decrease internal validity and therefore cast doubt on conclusions regarding prevalence of HPV. Such misclassification may lead to erroneous estimates of the prevalence of anal HPV in heterosexual men if some men labeled heterosexual are behaviorally bisexual or homosexual.

Of course it is also possible that other measures of sexual behavior will be biased including number of sexual partners, frequency of recent sexual behavior, and use of condoms. Misclassification in these areas would tend to bias exposure/outcome effect estimates that help explain causal mechanisms that result in HPV at the anus in heterosexual men.

The quantitative effects of bias can come in two forms: differential or non-differential (144). If the rate of sexual behavior misclassification is the same for both cases and non-cases, then non-differential misclassification bias has occurred. This would tend to drive estimates of effect toward the null (as long as the misclassification is not dependent on other errors) (118). If, however, the misclassification of sexual behavior is greater for cases (or non-cases), then the

result is differential misclassification bias. For example, if cases are less likely to disclose same-gender sexual behavior and also are more likely to have anal HPV infection, then prevalence estimates and exposure effect estimates will be differentially biased.

There are numerous opportunities for measurement error that result in misclassification. For sexual behavior surveys they can be classified into two major types: the requirements, or demands, of the recall assignment and the sociological context of the survey. In self-administered questionnaires, literacy, requisite skip patterns, length of the instrument, and memory burden are all demands of the recall task that can introduce measurement error into a study. Each of these demands can be more finely enumerated. For instance, the burden on memory of recalling one's sexual behaviors is further influenced by the length of the recall period, the fineness of detail one is requested to recall, and whether or not the target behavior is common or rare (145).

The other major type of measurement error common to sexual behavior questionnaires, the sociological context of the survey, can influence a participant to invoke a strategy that manipulates the image the participant wants to portray. This image then can be consistent with, or vary to some degree from, a putative "truth." The degree the image varies from the truth is a measure of what is often called self-presentation bias (146). For example, in an effort to present an image that conveys elevated sexual competence, a male participant might report a greater number of sexual partners than is accurate. Or, in an effort to avoid

shame, a participant might report higher levels of condom use if he or she perceives condom use to be normative.

The control of measurement error requires a diverse set of solutions. While measurement error that occurs due to the demands of the task may be more under the control of the researcher (e.g., questionnaire length, required recall period), measurement error due to social context is less concrete and less amenable to correction by study design. In the previous example of misclassification of same-gender sexual behavior, divergence of the participant's reported sexual behavior from reality also represents self-presentation bias and may result from a complex interplay between societal expectations and individual personality. These circumstances are unlikely to be controlled by any action of the researcher. Furthermore, the level of stigma attached to same-gender sex changes; it is not uniform among cultures prevalent in North America, let alone the rest of the world. For instance, a Caucasian university student may perceive stigma regarding same-gender sex very differently than a working class African American man. Likewise, cultural values and meanings are sensitive to social context (147). For example, the Latino culture values of 'respeto' and 'simpatía' may lead Latino people to report more socially acceptable behaviors on questionnaires (148).

As such, culture is likely to add complexity to interpretations of results that are vulnerable to sexual behavior misclassification. One potential consequence is greater bias in the effect measures that estimate the association

between culture (as reflected in race, ethnicity, socioeconomic status, sexual orientation, etc.) and anal HPV.

2. Effect of mode of instrument

Different modes of data collection are likely to produce different amounts of measurement error due to their varying demands on the participant and their varying levels of susceptibility to the social context. In general, face-to-face interviews, where a trained interviewer asks questions of the participant, is perceived to require fewer demands upon the participant (145). For example, the participant does not need to know how to read and does not have to navigate skip patterns. Furthermore, the interviewer can help explain words or concepts that may be unfamiliar to the participant. Importantly, an interviewer can request further explanation when the participant reports behavioral inconsistencies. While there may be fewer logistical demands on the participant in a face-to-face interview, the biasing potential of social context is reinforced by the inclusion of a human interviewer; thus, measurement error can increase due to a participant's perceived need to manage his image before another human being. A participant may also have the perception of reduced confidentiality in a face-to-face interview (145).

While the self-administered questionnaire (SAQ) depends more upon the skills of the participant (e.g., to be able to comprehend questions or to follow skip patterns), it may attenuate measurement error introduced by the social context.

Some studies have found that self-administered instruments, either of the paper and pencil variety or computer-assisted self-interview, reduce measurement error and tend to produce reports of higher frequencies of sensitive sexual and drug using behaviors than do face-to-face interview methods (149, 150, 151, 152, 153, 154, 155). It is thought that higher frequencies of sexual behaviors, particularly stigmatized behaviors, reflect greater validity since adults are more likely to underreport such behaviors (140). Likewise, lower frequencies of normative behaviors like condom use are usually assumed to be more valid (140).

Computer-assisted self-interview (CASI) combines positive features of both face-to-face interviews and SAQs, while adding a limited number of negative features. CASI reduces the demand on the participant by automating skip patterns. CASI can also contain "pop-up" features that provide definitions of unfamiliar terms. Its audio version, audio-CASI, reads the question to the participant to reduce error caused by illiteracy. Like face-to-face interviewing, CASI can query the participant if the computer algorithm detects inconsistencies in the participant's responses, or if the participant provides responses that are outside the realm of reality (for example, a birth date in the future). Like SAQs, CASI may also decrease measurement error due to social context by increasing the participant's perception of confidentiality and by decreasing self-presentation bias (156, 157, 158, 159). A disadvantage of CASI in comparison to SAQ is the increased cost although it may be cost effective if sample size reaches a desired

level (160). In addition, populations not familiar with computers may be made more uncomfortable by CASI technology (161, 162, 163).

A study design using a daily or weekly diary requests that the participant record his sexual behavior (either on paper or online) proximal to its occurrence. This method increases participant burden but may also increase the accuracy of reporting behaviors by reducing memory-related errors. Diary methods have also been criticized as reactive in that the act of recording sexual behavior may affect the kinds or amounts of sexual behavior of the participant (145).

Direct observation of human sexual behavior, especially sexual intercourse, is sometimes employed in research although the conditions for such observations may require a manufactured environment or laboratory which begs the question of generalizability of findings or ecological validity – the extent to which the results of a laboratory experiment can be duplicated in a more natural setting (164).

However, almost invariably, the modes of sexual behavior data collection rely on self-reports. Thus, the validity of the measurements cannot be directly assessed. Indirect methods to validate self-reported sexual behavior include the collection of biological samples for assessment of sexually transmitted diseases (165, 166, 167) and the use of secondary data collection methods like the concurrent use of SAQ and diary methods (168, 169, 170). In the case of collecting biological samples, concordance between sexual behavior and disease can be diminished by any number of factors including the fact that risky sexual behavior

often does not result in contraction of an STD. Collection of the same sexual behavior data using two different measurement instruments like a SAQ and a diary may help provide some evidence of validity (169, 171, 172) but since self-reports are still the basis of each collection method, measurement error can still enter the study through all the methods previously discussed.

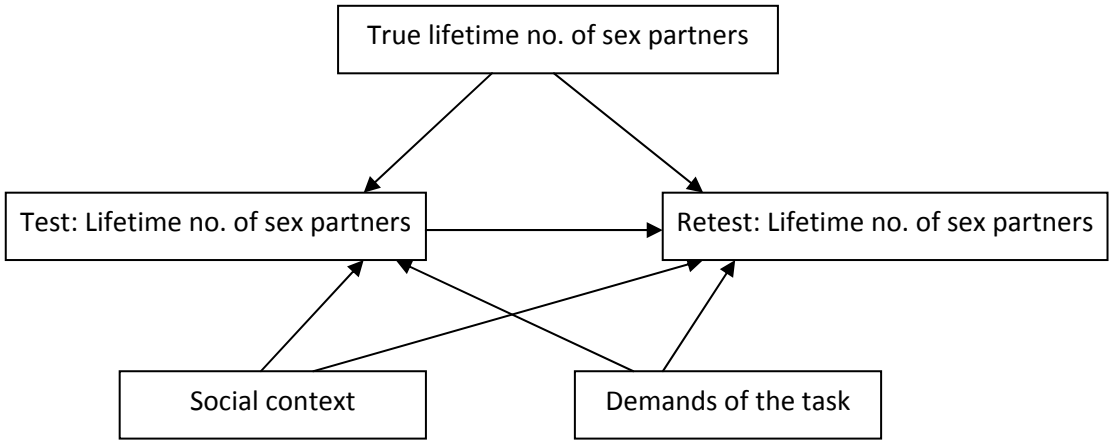
3. Assessing reliability through test-retest studies

Due to the existence of potential measurement error from a variety of different sources, the validity of any study relying on self-report has to be considered. Unfortunately, the lack of validity in such studies cannot be studied directly. Instead, repeated self-reported measures of a sexual behavior can be collected to expose inconsistent responses that may point to measurement error and a lack of validity (11, 173, 174, 175, 176, 177). While concordance between repeated measurements cannot vouch for validity, at least non-concordance can sometimes alert the researcher to a problem with measurement. In other words, reliability is necessary for validity, but not sufficient (176).

From a more theoretical perspective, we can say that perfect reliability is indeed a test for validity if the only common cause for identical answers on test and retest is the truth (178). This idea can be explored further through the lens of a causal diagram. Figure 3 illustrates the association between answers on test and retest to the question, “In your life, what is the number of women with whom you have had sexual intercourse?” The diagram illustrates four possible sources for

the association between test and retest. First, the test and retest are associated due to cause and effect. The researcher would hope that identical answers on the test and retest do not depend on the initial test; for example, it is hoped that the participant does not answer the question on the retest by simply remembering his answer on the test. Rather, the researcher hopes the association is due to the

Figure 3. Causal diagram of relationships between test and retest



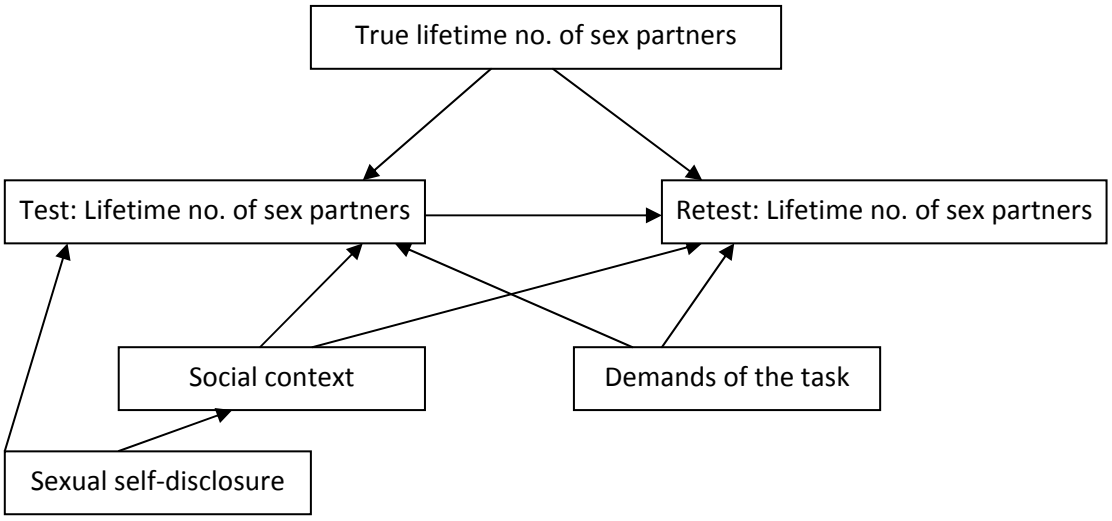
second possible cause: the reporting of truth by the participant on both test and retest. Unfortunately there are two other possible sources for the association, both of which harm the validity of the self-report data. The other two possible common causes for identical answers on test and retest are the 'Social context' and 'Demands of the [survey] task' (145). In the diagram, 'Social context' and 'Demands of the task' are creating an unwanted relationship between test and retest. The question then is, "How can the contribution of 'Social context' and 'Demands of the task' on the test and retest association be lessened so that the

effect of Truth is the only effect that remains?" One practical approach might involve using a computer-assisted test that automatically skips to the correct questions based on participant input. This solution lessens the demands on the participant to adhere to skip patterns (179). Shortening the test would also lessen the time demands on the participant. As demands on the participant are reduced, this potential source of association between test and retest loses power allowing the Truth cause to account for more of the association we see between test and retest.

The researcher may find it harder to manipulate the 'Social context' since its contribution differs from locale to locale and since it emanates from cultural values that may be entrenched or even unknown to the researcher. Nevertheless, the goal for the researcher is to try to lessen the power of all common causes of concordance between test and retest with the exception of the concordance caused by the reporting of accurate and 'true' information. For example, the involvement of 'Social context' in the test-retest association can be lessened by creating a less judgmental atmosphere so the participant will be less concerned about disapproval for sexual behaviors she may disclose. One way to do that is to remove the interviewer from the situation; that is, allow the participant to divulge answers on a self-administered questionnaire rather than a face-to-face interview. By eliminating a human interviewer, this tactic is literally removing some of the 'Social context' in the test-retest situation. Such a tactic is known to produce less socially desirable answers by the participant (145). Another option

that would lessen the association caused by 'Social context' is to quantify its contribution to the test-retest association and then adjust for it. Catania has developed a scale that addresses the participant's comfort with disclosing sexual behavior in a research setting. The instrument is short and has been psychometrically tested for validity (140). By measuring a participant's comfort with sexual self-disclosure, a researcher could then use it to lessen the contribution of 'Social context' (see Figure 4). This tactic may also be helpful

Figure 4. Causal diagram of relationships between test and retest while adjusting for comfort with sexual self-disclosure



when using a questionnaire in multiple cultures where there may be different levels of comfort with sexual self-disclosure.

4. Empirical test-retest studies

Banking on their ability to uncover validity problems (although not to prove validity), at least 30 test-retest studies using a variety of survey methods have measured the reliability of sexual behavior items in a number of populations (see Table 3). Of these, eight test-retest studies have focused on sexual behavior SAQs (11, 173, 180, 181, 182, 183, 184, 185). With the exception of one study from Germany with a sample of 23 men (173), these studies have targeted adolescents or women. In addition to gender differences, the expression of self-presentation bias and other sources of measurement error may also differ by age. For example, the novelty of sexual behavior for adolescents may be more salient which likely leads to better recall (186). Also, a generally higher number of lifetime sexual partners for adults, compared to adolescents, may make recall of these greater numbers more difficult and thus lead to less reliable measures (174, 181, 187). Test-retest reliability studies of SAQs that collect sexual behavior data from community samples of adult men may provide new insight into the validity of these instruments.

On a broader scale, comparisons of sexual behavior by country may be helpful for programs that attempt to deliver large scale prevention programs for STDs; however, if sexual behavior measures are to be used cross-nationally, then the measures should produce reliable data for each locale. Unfortunately, studies assessing the cross-national reliability of a sexual behavior CASI are absent from the literature. CASI, and its audio version audio-CASI, have been shown in

population-based studies and randomized experiments to improve sexual behavior data quality (152, 154, 188, 189, 190); however, it is not clear that computer-assisted self-interview survey methods will increase the reliability of sexual behavior survey methods in all situations (161, 162, 171, 190, 191, 192, 193, 194, 195). Diverse cultural traditions and expectations, especially with regard to human sexuality, may limit CASI's ability to support reliable data collection. A multinational comparison of CASI's test-retest reliability would provide insight into the utility of cross-national comparisons of human sexual behavior that use this technology for data collection. While there are studies comparing CASI (or audio-CASI) with other survey methods like SAQ or face-to-face interviews, there are few studies reporting the test-retest reliability of this method for a sexual behavior questionnaire (150, 151, 196).

When low reliability items are found in sexual behavior questionnaires, it may also be useful to understand characteristics, demographics or otherwise, that are associated with these items; however, predictors of lower test-retest reliability for specific sexual behavior items have only occasionally been reported in the literature (11, 151, 197). Likewise, nonresponse to questionnaire items, or refusal rates, may also involve image management. Only one study has assessed predictors of nonresponse to questionnaire items (198).

Finally, sexual behavior studies often limit their reporting of reliability to sexual behaviors and do not report on the reliability of demographic characteristics and non-sexual behaviors collected by the same instrument. A

comparison of reliability between sexual behaviors and non-sexual behaviors (some of which may be less associated with image management) may provide further insight into measurement error, including presentation bias issues.

Table 3. Reliability studies using the same survey method at test and retest

Study		Test-retest design		Sample characteristics			
Author	Year	Survey method(s)	Test interval, days[a]	Sex	Adult/ adolescent	Target population	Sample size
Wolford (199)	2008	ACASI[b]	6.5	male/female	adult	Severely mentally ill	53
Müller (173)	2007	SAQ[b]	16.0	male/female	adult	Community	46
Sieving, et al. (183)	2005	SAQ	9.6	female	adolescent	Reproductive health clinics	152
Krawczyk, et al. (196)	2003	ACASI	3.0	male/female	adult	People with HIV	69
Brener, et al. (180)	2002	SAQ	15.6	male/female	adolescent	Students: high schools	4619
Durant, et al. (181)	2002	SAQ	7.0	female	adult	Students: college	185
Schlect, et al. (11)	2001	SAQ, FTF[b]	45.0 - 1800.0[c]	female	adult	Population-based/clinics	14,775
St. Lawrence, et al. (184)	1999	SAQ	14.0	female	adult	Clinics serving low income people	30

Table 3. Reliability studies using the same survey method at test and retest

Study		Test-retest design		Sample characteristics			
Author	Year	Survey method(s)	Test interval, days[a]	Sex	Adult/ adolescent	Target population	Sample size
Kalichman, et al. (182)	1997	SAQ	14.0	female	adult	Housing projects/social service agencies	51
Taylor, et al. (185)	1994	SAQ	30.0	female	adult	Women in a current sexual relationship	269
Romer, et al. (150)	1997	ACASI	10.5	male/female	adolescent	Children in public housing	34
Williams, et al. (151)	2000	FTF, ACASI	2.5	male/female	adult	Drug users: heroin or cocaine	392
Schrimshaw, et al. (176)	2006	FTF	17.0	male/female	adolescent	GLB[b] (age 14-21) recruited form GLB organizations	64
Hearn, et al. (200)	2003	FTF	22.0	female	adolescent	Community: low income	50

Table 3. Reliability studies using the same survey method at test and retest

Study		Test-retest design		Sample characteristics			
Author	Year	Survey method(s)	Test interval, days[a]	Sex	Adult/ adolescent	Target population	Sample size
						neighborhoods	
Petry (201)	2001	FTF	30.0	male/female	adult	Drug treatment	84
Sohler, et al. (202)	2000	FTF	10.5	male	adult	Treatment for mental health: homeless	39
Carballo-Dieguez, et al. (175)	1999	FTF	7.0	male	adult	Gay organizations/media	27
Van Doynhoven, et al. (174)	1999	FTF	14.0	male/female	adult	STD[b] clinic attenders	288
De Irala, et al. (203)	1996	FTF	14.0	male/female	adult	Drug treatment	246
Mahler, et al. (204)	1995	FTF	17.0	male/female	adult	Drug treatment for	58

Table 3. Reliability studies using the same survey method at test and retest

Study		Test-retest design		Sample characteristics			
Author	Year	Survey method(s)	Test interval, days[a]	Sex	Adult/ adolescent	Target population	Sample size
						alcoholism	
Needle, et al. (197)	1995	FTF	2.0	male/female	adult	Drug users: IDU[b] and other drugs	196
Dowling-Guyer, et al. (205)	1994	FTF	2.0	male/female	adult	Drug users: IDU or cocaine/opioid	225
McElrath, et al. (206)	1994	FTF	180.0	male/female	adult	Drug treatment for IDUs	366
Rohan, et al. (177)	1994	FTF	147.0	female	adult	Students: college	74
Fabricant, et al. (207)	1993	FTF	1.0	male/female	adult	Community: households in Sierra Leone	1156
McKinnon, et al.	1993	FTF	34.0	male/female	adult	Treatment for mental health	48

Table 3. Reliability studies using the same survey method at test and retest

Study		Test-retest design		Sample characteristics			
Author	Year	Survey method(s)	Test interval, days[a]	Sex	Adult/ adolescent	Target population	Sample ize
(208)							
Darke, et al. (209)	1991	FTF	7.0	male/female	adult	Drug users: current and past opioid users	64
McLaws, et al. (169)	1990	FTF	2.5	male	adult	Sex workers recruited from brothels in Sydney	30
Coates, et al. (210)	1986	FTF	3.0	male	adult	MSM[b] recruited from gay organizations	26
Carey, et al. (211)	2001	TLFB[b]	5.0	male/female	adult	Outpatient mental health patients	66
Wienhardt, et al.	1998	TLFB	7.0	male/female	adult	Students: college	58

Table 3. Reliability studies using the same survey method at test and retest

Study		Test-retest design		Sample characteristics			
Author	Year	Survey method(s)	Test interval, days[a]	Sex	Adult/ adolescent	Target population	Sample size
(212)							

[a] When only a test-retest range is provided in a study, it is averaged to facilitate study-by-study comparisons.
[b] SAQ=self-administered questionnaire; ACASI=audio computer-assisted self-interview; FTF=face-to-face; TLFB=timeline followback; GLB=gay, lesbian, and bisexual; STD=sexually transmitted disease; IDU=injection drug users; MSM=men who have sex with men.
[c] Comprises six studies with six different test-retest intervals.

E. Summary of introduction

Little is known about anal HPV in men, especially in heterosexual men. Against this backdrop of scarce data, the incidence of anal cancer has almost tripled in the last three decades. While knowledge about anal HPV in MSM has advanced in the last decade – important advances given the increased rate of anal cancer in MSM – the much greater numbers of heterosexual men and lack of prevalence and risk factor data about anal HPV in heterosexual men exposes a critical research gap. The research described in this dissertation will fill important gaps in knowledge about anal HPV in heterosexual men by 1) assessing the reliability of a self-administered questionnaire used in the collection of anal HPV exposure data with a US sample of men; 2) assessing the prevalence of and risk factors for anal HPV in a domestic sample of heterosexual men; and 3) assessing the reliability of a computer-assisted self-interview used in the collection of exposure data from men recruited into a multinational study of anogenital HPV. The knowledge gained from this research will provide a stronger foundation for future studies that seek to develop preventive measures, including vaccines, which prevent anal HPV infection, screening that can identify men at increased risk for anal cancer, and educational interventions that can reduce the risk for anal HPV infection and its consequences.

III. PRESENT STUDY

The current section reviews the methods and results of this dissertation research. Following these accounts are conclusions and directions for future research generated by the present study.

The methods and results are presented within the following conceptual framework. Research related to the prevalence of and risk factors for anal human papillomavirus is at the heart of this dissertation; however, these results are dependent upon self-reported data that should accurately represent the characteristics and behaviors of the study population. Accordingly, the quality of these data should be assessed in order to better understand the role of measurement error in prevalence and risk factor estimates; therefore, a study was conducted to assess the test-retest reliability of the self-administered questionnaire used in the cross-sectional anal HPV prevalence study. The methods and results of this reliability study are presented first. The longitudinal study from which this reliability study draws its data was funded by the Arizona Disease Control and Research Commission. Therefore, this test-retest study is hereafter referred to as the ADCRC reliability study.

Next, the methods and results of the prevalence and risk factors paper are presented (hereafter called the anal HPV prevalence study). The results of this phase of the dissertation, in turn, led to additional questions about anal HPV in heterosexual men and the need for replicate studies in order to confirm or refute the prevalence and risk factor findings.

To field follow-up anal HPV studies, the author has secured funding from the National Institutes of Health (NIH) and from industry to conduct ancillary anal HPV studies to an ongoing NIH longitudinal study called the Human Papillomavirus in Men (HIM) Study. These ancillary studies are discussed in the future directions section and are made possible by the existence of the HIM Study's archived anal canal specimens collected by Dr. Anna Giuliano and her team at the Moffitt Cancer Center and Research Institute. In addition to the archived specimens, demographic and behavioral data from the men who donated the specimens were collected as part of the HIM Study. Unlike the questionnaire assessed in the ADCRC reliability study, these data were collected with a different survey method and from a cross-national sample of men. As such, the test-retest reliability of the instrument used in the HIM study was assessed in preparation for the impending follow-up studies of anal HPV in men. The methods and results of this second test-retest reliability study (hereafter called the HIM reliability study) are presented at the end of the current section. Since the methods of this second test-retest reliability study are similar to the methods of the ADCRC reliability study, they are presented in a slightly more abbreviated form.

A. The ADCRC reliability study

1. Methods

The methods for this study encompass study design and recruitment, participant procedures, questionnaire description, sample description, and statistical analyses.

i. Study design and recruitment

Men were recruited between September, 2003 and May, 2005 to a longitudinal study of the natural history of genital HPV. Men were enrolled if they met eligibility criteria that included an age of 18 to 44 years, a residence in southern Arizona, no prior penile or anal cancers or genital warts, a willingness to comply with a total of four visits over 18 months, and no plans to relocate.

Recruitment was conducted in Tucson, Arizona at a variety of community locales through flyers targeting the University of Arizona campus, advertisements in local newspapers and on radio, direct mail advertisements, and face-to-face recruitment at the STD clinic of the Pima County Health Department. Participants were offered a nominal monetary incentive for their participation. The incentive increased in value at subsequent study visits to minimize participant drop out. All men consented to participation in the study using forms and protocols approved by the Institutional Review Board of the University of Arizona. Details of recruitment and study design have also been described elsewhere (114).

ii. Participant procedures

Men expressing interest in participating in the study received an appointment to come to the clinic for an initial visit. At this run-in visit, those who consented to the longitudinal study experienced all participant activities to help them determine whether they wanted to remain in the longitudinal study which would require their participation for an additional 18 months.

Participants completed a paper and pencil 86-item self-administered questionnaire and a study clinician collected exfoliated skin cells at penile and scrotal sites for HPV testing. Men were then scheduled for the baseline visit approximately two weeks later (*M* = 21.5 days, *SD* = 23.8, median = 16 days, range 9-292 days) at which time they completed the same self-administered questionnaire again.

The exfoliated skin cell samples were subjected to DNA detection by polymerase chain reaction and genotyping. Men received their first HPV test results at their follow-up visit, approximately six months later. The testing of samples for HPV in this longitudinal study was similar to the procedures used in the anal HPV prevalence study; therefore, details regarding the testing process are included below in the Methods section for that study.

iii. Questionnaire description

The questionnaire contained 86 items with 16 demographic questions, seven alcohol use questions, eight tobacco use questions, and 55 sexual behavior questions. The questionnaire had previously been used to assess sexual behavior in women (213) and had been adapted for and pretested with men.

The sexual behavior items assessed history of sexually transmitted diseases; circumcision; incidence and frequency of penetrative sexual behaviors (vaginal, anal, and oral sex) with women and men; age at first intercourse; number of female and male partners; frequency of condom use with vaginal and anal sex; incidence and frequency of sex with 'steady' and other partners; time since last vaginal sex and anal sex; and history of paying for sex. Participants were asked to recall the frequency of substance use and sexual behaviors for varying periods of time including the last month, the last three months, and lifetime.

iv. Sample description

A total of 1140 men were assessed for inclusion in the study either after contacting study staff or after being approached at the STD clinic. Six-hundred eighteen men met eligibility criteria and 379 of these men completed a run-in questionnaire. A total of 334 of these returned to complete a baseline questionnaire and were included in the reliability study. A comparison of study participants and those who did not return for the baseline visit found no

statistically significant differences with regard to demographic, tobacco use, sexual health history, or sexual behavior variables.

Men who attended both the run-in visit and the baseline visit had a mean age of 30.2 years (*SD* = 8.1). A majority identified as white (75.9%) while 19.5% reported a Hispanic ethnicity (Table I, Appendix A).

v. Statistical analyses

A subset of items from the questionnaire was selected for assessment of reliability with preference given to items where reliability coefficients would not be biased by the test-retest interval. For example, while the questionnaire required recall of behaviors over several time periods, items with a one-month recall period were not assessed because the time interval between test and retest (*M*=21.5 days) would have led the participant to recall sexual behavior for largely different time periods.

A total of 40 variables were assessed including 28 categorical, four ordinal, and eight discrete variables. Demographic, tobacco use, and sexual behavior variables were included in the assessment. In addition, a three-category variable for number of days between the test and retest was created (1 – 14 days, 14 – 30 days, or > 30 days) to estimate how a lengthening interval might affect reliability coefficients.

All statistical analyses were conducted using SAS (version 9.2, SAS Institute Inc., Cary, NC, USA). Refusal rates for each questionnaire item were

calculated. A refusal was recorded if a participant chose the refusal option on any particular item or if the participant declined to answer an item that was not precluded by a skip pattern. If a participant responded to a question that should have been skipped because of skip instructions, the response was not used in calculating refusal rates or reliability coefficients.

For categorical variables, the kappa statistic (κ) was calculated. Unlike percent agreement, κ identifies the level of agreement after correcting for chance agreement (214). Benchmarks for interpreting κ values followed Landis and Koch (215):

Kappa statistic	Strength of Agreement
<0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost perfect

Since the κ statistic can be unstable in situations where there are a small number of cases (216), reliability was not assessed for binary variables with a case total of less than five (145).

For ordinal variables a weighted κ statistic (217) was calculated in order to distinguish between levels of disagreement. For instance, in responding to a question about the frequency of condom use with five possible responses, if a subject chose the adjacent categories of "more than half the time" and "half the time" on run-in and baseline, respectively, simple κ would identify zero agreement between the two responses; however, weighted κ would give credit for the partial agreement.

Discrete variables were assessed using the intraclass correlation coefficient (ICC). Measuring an individual's response to a questionnaire at two time points, as with the current study, involves two variables that share metrics and variance; therefore, an *intra*class correlation coefficient is indicated rather than, for example, an *inter*class correlation coefficient like the Pearson product-moment correlation coefficient (218). The ICC is rooted in analysis of variance and is defined by the ratio of the between-person variance and the total variance. The total variance is the sum of the between and within-person variance. Subjects with high consistency on test-retest scores will have small within-person variance compared to between-person variance. In such situations, the ICC will be closer to 1.0 (219). All ICCs created from skewed variables were transformed using Fisher's z transformation before calculating confidence intervals (220). Confidence intervals (CI) were then transformed back to the original scale. Outliers were assessed using scatter plots and none were considered highly influential.

SAS 9.2 does not have built in procedures for calculating either ICCs or Fisher *z* transformations with confidence interval calculations. Therefore, a freely available SAS macro was located on the Internet for calculation of ICCs. The quality of the macro was tested using raw data and ICC calculations published in Shrout and Fleiss, 1979 (221). Testing of the macro with the published data produced the identical answers derived by Shrout and Fleiss. Next, the author wrote a macro to conform to formulas provided by Rosner, 2000 (220) for Fisher *z* transformations with calculation of confidence interval calculations. Testing of the macro produced the identical answers derived by Rosner.

Logistic regression was performed to identify predictors of unreliable reporting for lifetime number of female sexual partners. This variable was chosen because studies have identified lifetime number of sexual partners as particularly susceptible to measurement error (11, 174) and because it has been strongly associated with an increased risk for HPV and other sexually transmitted diseases (27). A dichotomous variable was created to delineate unreliable vs. reliable reporting. Unreliable reporting was defined as a difference between test and retest of five or more partners. The cut point identifying unreliable reporting was intended to highlight discrepancies that could more seriously bias estimates of effect. For example, because men who have fewer than approximately five lifetime female sexual partners may be at lower risk for genital HPV infection (27, 84), a discrepancy of five or more partners on test and retest could bias estimates of the association between lifetime number of sexual partners and HPV infection.

Bivariate associations were computed between this dependent variable and ten potential predictors of unreliable reporting (age, race, ethnicity, marital status, education, income, country of birth, number of years since first intercourse, lifetime number of female sexual partners, and length of test-retest interval). A liklihood ratio test with a p value of less than .20 identified candidate variables for multivariate regression. Independent predictors of unreliable reporting for the dependent variable were identified using a backwards selection process. Potential confounders were identified by their association with both the dependent and independent variable and by their ability to substantially modify the odds ratio (OR). Finally, goodness-of-fit for the final model was assessed using the Hosmer-Lemeshow test.

2. Results

Item refusal rates were generally below 5% with the exception of income, country of residence, length of residence in the US, and one sexual behavior question. The sexual behavior question asked about the frequency of sexual intercourse with women in the past three months (refusal rate 6.5% on test and 7.8% on retest).

Reliability was substantial or almost perfect for demographic variables (Table II, Appendix A). Of these, household income per month was the least reliable (weighted κ = .74). Most of the misclassification on income involved

participants' switching between adjacent income categories. κ was over .90 for all tobacco-use items.

Most sexual behavior items also had almost perfect reliability. Less reliable were questions asking the participant to report the health conditions of their sexual partners. For example, κ was .67 for an item asking the participant if he had ever had a sex partner with a sexually transmitted disease. Stable κ statistics for two additional variables (ever diagnosed with genital warts and ever diagnosed with syphilis) could not be calculated because there were too few positive responses. Kappa tables for selected variables are included in Tables 4 – 9 of this section.

Table 4. Participant responses for race at run-in and baseline of the ADCRC questionnaire

	Race at baseline						
Race at run-in	White	Black	Asian	AI/AN*	Other	DK*	Total
White	176	0	0	0	11	0	187
Black	0	11	0	0	0	0	11
Asian	0	0	6	0	0	0	6
AI/AN	0	0	0	8	0	0	8
Other	4	0	0	0	21	0	25
DK	1	0	0	0	0	1	2
Total	181	11	6	8	32	1	239

Simple $\kappa = 0.83$

*AI/AN, American Indian/Alaskan Native; DK, Don't Know

Table 5. Participant responses for ethnicity at run-in and baseline of the ADCRC questionnaire

	Ethnicity at baseline		
Ethnicity at run-in	Yes	No	Total
Yes	63	0	63
No	2	257	259
Total	65	257	322

Simple $\kappa = 0.98$

Table 6. Participant responses for gross household income per month at run-in and baseline of the ADCRC questionnaire

	Income at baseline				
Income at run-in	< $1500	$1500 - $3999	>= $4000	Don't Know	Total
< $1500	107	18	1	5	131
$1500 - $3999	9	95	2	1	107
>= $4000	3	7	27	0	37
Don't Know	4	1	3	18	26
Total	123	121	33	24	301

Weighted $\kappa = 0.74$

Table 7. Participant responses for ever diagnosed with an STD at run-in and baseline of the ADCRC questionnaire

	Ever STD at baseline			
Ever STD at run-in	Yes	No	Don't Know	Total
Yes	72	5	0	77
No	8	236	2	246
Don't Know	0	3	4	7
Total	80	244	6	330

Simple $\kappa = 0.86$

Table 8. Participant responses for ever had sex partner with an STD at run-in and baseline of the ADCRC questionnaire

	Ever had partner with STD at baseline			
Ever had partner with STD at run-in	Yes	No	Don't Know	Total
Yes	115	12	13	140
No	6	87	11	104
Don't Know	10	19	58	87
Total	131	118	82	331

Simple $\kappa = 0.67$

Table 9. Participant responses for ever had vaginal sex at run-in and baseline of the ADCRC questionnaire

	Ever had vaginal sex at baseline		
Ever had vaginal sex at run-in	Yes	No	Total
Yes	309	1	310
No	0	21	21
Total	309	22	331
	Simple κ = 0.98		

Table 10. Participant responses for ever had sex with a man at run-in and baseline of the ADCRC questionnaire

	Ever had sex with a man at baseline		
Ever had sex with a man at run-in	Yes	No	Total
Yes	64	6	70
No	0	247	247
Total	64	253	317
	Simple κ = 0.94		

Scatter plots were constructed for discrete variables in order to visualize the dispersion of data and to assess outliers. A wider dispersion of data points from the diagonal indicates less agreement between run-in and baseline. Selected

scatter plots are reproduced in Figures 5 – 7. When outliers were apparent in the scatter plot (e.g., Figure 7), a sensitivity analysis was conducted whereby the potentially influential outlier was removed and the ICC was recalculated. These analyses identified no outliers that substantially modified the ICC.

Figure 5. Scatter plot for years smoking cigarettes: run-in vs. baseline

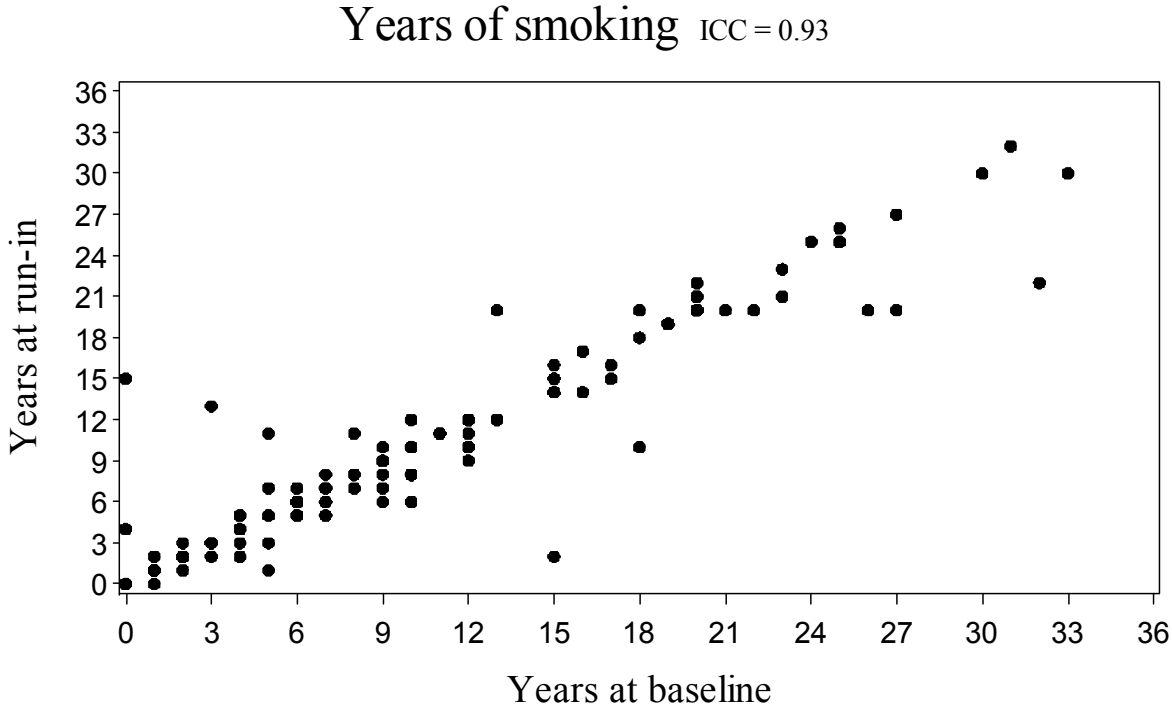


Figure 6. Scatter plot for age at first sexual intercourse: run-in vs. baseline

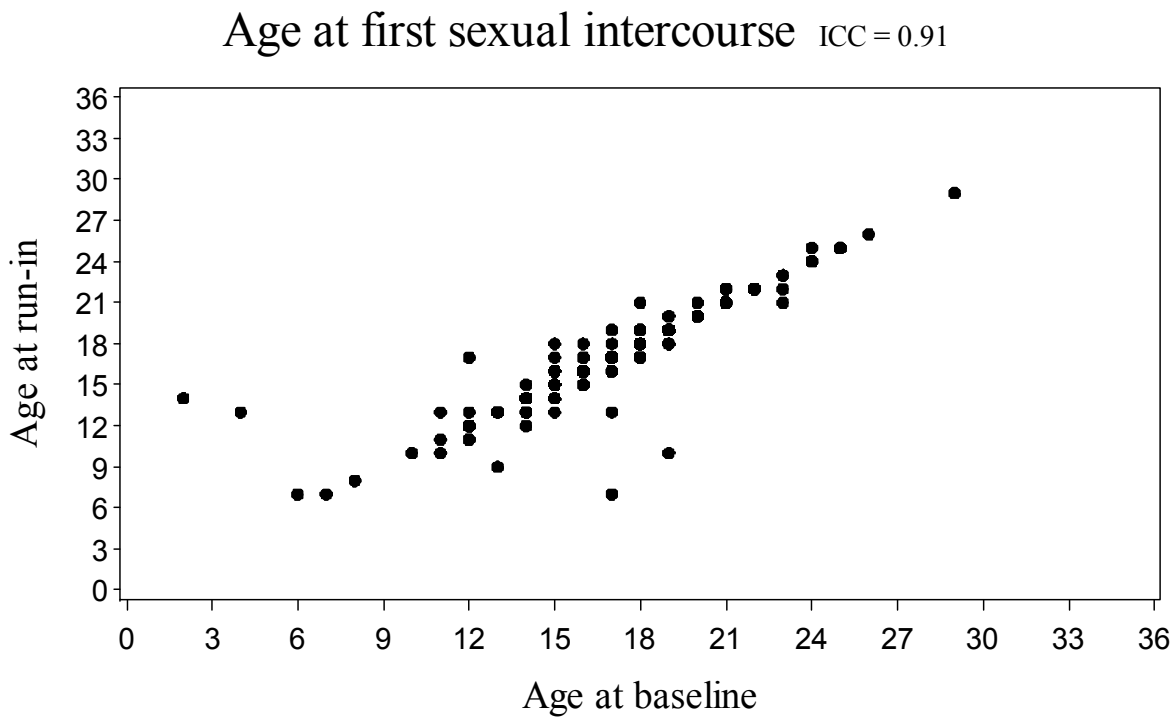
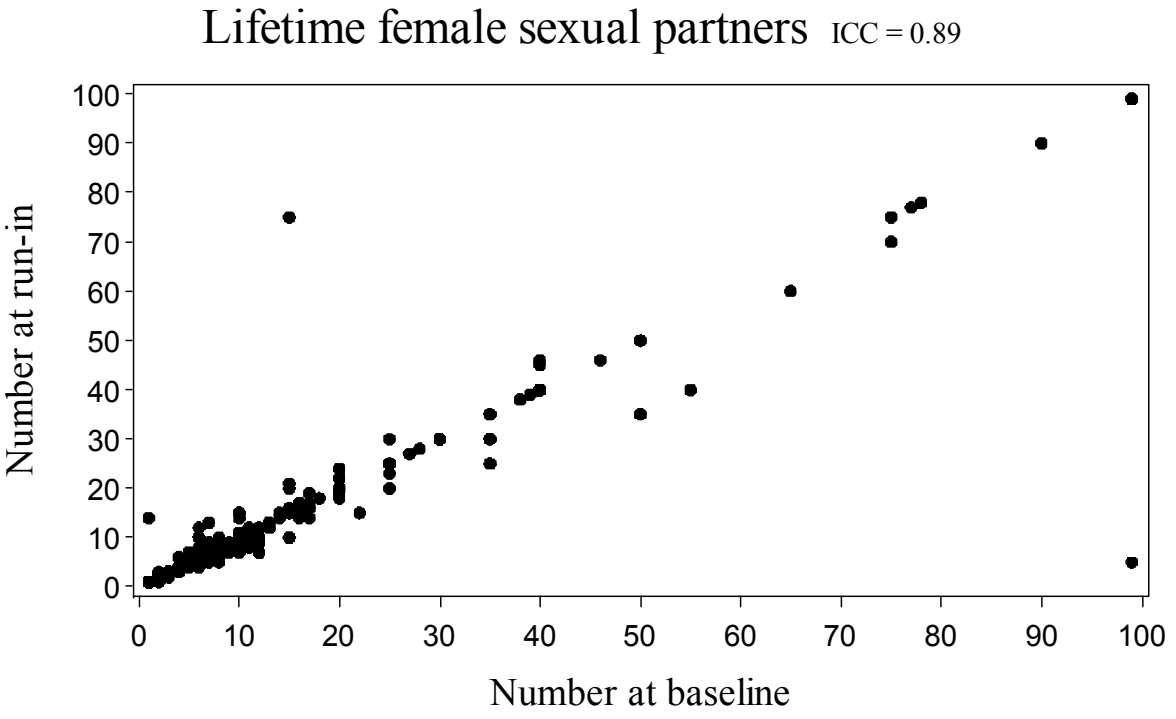


Figure 7. Scatter plot for lifetime number of female sexual partners: run-in vs baseline



Lifetime number of female sexual partners was assessed to identify major predictors of unreliable reporting when comparing answers provided at the run-in and baseline visit. In bivariate analysis (Table III, Appendix A), variables associated with unreliable reporting between test and retest were an older age (OR, 1.13; 95% CI, 1.07–1.20), black race (OR, 4.34; 95% CI, 1.03–18.23) compared with white race, increasing years since first intercourse (OR, 1.12; 95% CI, 1.07–1.18), and an increasing lifetime number of female sexual partners (OR, 1.03; 95% CI, 1.02–1.05).

In multivariate analysis (Table IV, Appendix A), older age (OR, 1.12; 95% CI, 1.06–1.20), and lifetime number of female sex partners (OR, 1.02; 95% CI, 1.01–1.04) were independent predictors of unreliable reporting. Sixteen or more years of education (compared with 12–15 years of education) was inversely associated (OR, 0.33; 95% CI, 0.13–0.88) with unreliable reporting. Holding lifetime number of female partners constant at the sample mean of 15.0, there was a 2% probability that a 25-year-old with 16 or more years of education would be unreliable on test and retest for lifetime number of female partners. There was a 10% probability that a 40-year-old with 16 or more years of education would provide unreliable answers on this item. There was a 25% probability that a 40-year-old man with a high school education would provide unreliable answers on his lifetime number of female sexual partners.

The final model fit the data well (Hosmer-Lemeshow p = 0.43) and no confounders of the association between the independent and dependent variables were identified.

B. The anal HPV prevalence study

The methods for this study encompass study design and recruitment, participant procedures, questionnaire description, exfoliated cell sample diagnostics, sample description, and statistical analyses.

1. Methods

i. Study design and recruitment

Men were recruited from 2003 to 2006 to a cross-sectional study, in Tucson, Arizona, and Tampa, Florida. Men must have acknowledged sexual intercourse with a woman within the past year. Participants were between 18 and 40 years old, had no current STD diagnosis, no pain during urination nor penile discharge, and acknowledged no history of genital warts, anal cancer, or penile cancer. Recruitment was supported by flyers posted on college and university campuses, newspaper advertisements, radio, direct mail, and face-to-face enrollment at an STD clinic. All participants consented to the study protocol which was approved by University of Arizona, University of South Florida, Centers for Disease Control and Prevention, and United States Department of Defense human subjects protection committees.

ii. Participant procedures

Men were instructed not to have sex for 24 hours before they were sampled for HPV to avoid detection of incidental HPV from a partner. Men were also instructed not to bathe the day of the sampling to avoid washing away HPV DNA expressed on the surface of the skin.

Using a different saline-wetted Dacron swab for each anatomical site, clinicians sampled six anogenital sites from each of the men: urethra, coronal sulcus/glans penis, penile shaft (including prepuce if present), scrotum, perianal region, and anal canal.

For the urethral sampling, the swab was inserted 2 cm into the urethra and then rotated as it was withdrawn. For penile and scrotal sampling, separate Dacron swabs were rubbed over the entire surface of each (including separate swabs for the glans penis/coronal sulcus and penile shaft). The prepuce, if present, was sampled with the shaft.

For the perianal region and anal canal, the clinician asked the men to bend forward, grab their buttocks and then pull them apart gently. Any visible fecal material was first removed with a cotton pad. A wetted swab was then rubbed over the perianal skin in the area surrounding the anal verge but no more than two centimeters away of the anal verge. With another saline-wetted swab, the lower anal canal between the anal verge and the dentate line was sampled by inserting the swab, rotating, and withdrawing. The perianal and anal canal sampling were added to the study after 58 men had already completed the study.

In addition, participants self-collected a semen sample for analysis. The urethral and semen sampling were discontinued in the third year of the study because the proportions of HPV-positive samples from these sites were much lower than for other sites.

Two clinicians completed all sampling of the men in the current study. Each clinician was trained in sampling techniques which included how to avoid contamination of the sampling sites. The clinicians also drew blood and examined the anal region and genitals for lesions, abrasions, discharges, or other abnormalities. Lesions and warts were sampled with a wet Dacron swab and their locations were recorded.

To preserve DNA for HPV analyses, the clinician placed each wet Dacron swab into its own vial with Digene Specimen Transport Medium™ (STM) and then immediately refrigerated the samples at 4°C. Samples were then transferred to a –70°C freezer until HPV testing was conducted.

iii. Questionnaire description

Participants completed a self-administered 51-item written questionnaire that included demographic, alcohol and tobacco use, sexual health history, and sexual behavior questions. Approximately halfway through recruitment, eleven questions dealing with same-gender sexual behavior were added to this instrument which was then identical to the instrument assessed for reliability in the ADCRC reliability study discussed previously.

iv. Exfoliated cell sample diagnostics

All exfoliated cell samples were analyzed for HPV DNA and β-globin. β-globin is a gene that virtually always occurs in human cells and, as such, serves as an indication that the Dacron swab which was rubbed against the skin collected an adequate number of cells. DNA was extracted from the samples using the QIAamp DNA Mini Kit (Quigen) according to manufacturer's instructions. To identify HPV DNA, laboratory staff used the polymerase chain reaction (PCR) consensus primer system (PGMY 09/11) to amplify a fragment of the HPV L1 gene. The presence of HPV in each specimen was tested by amplifying 5µl of the DNA extracts with the PGMY 09/11 L1 consensus primer system(10) and Ampli*Taq* Gold polymerase (Perkin-Elmer, Foster City, CA). Each 50 µl amplification contained 1X PCR Buffer II; 2.5 mM MgCl2; 200µM (each) dCTP, dGTP, and dATP; 600µM dUTP; 7.5 U of AmplTaq Gold; 1µM of PGMY09; 1µM PGMY11; 2.5 nM of B_PC04; 2.5 nM of B_GH20; and 5µl of the template. For eventual inclusion of uracil-N-glycosylase to prevent product carryover, dTTP was replaced with dUTP. To determine specimen adequacy, the GH20/PC04 human β-globin target was co-amplified using the B_GH20 and B_PC04 primers along with HPV consensus primer amplification. To ensure accuracy and prevent possible contamination, for every PCR plate a negative control (H_2O) and a positive control (DNA from CaSki cells) was run. Samples were amplified using Perkin-Elmer GeneAmp PCR System 9700.

HPV genotyping was then conducted on all samples using the reverse line blot method (222). DNA probes labeled with biotin detected 37 HPV types: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51-56, 58, 59, 61, 62, 64, 66-73, 81-84, IS39, and CP6108. A sample was considered positive if either the PCR or genotyping tests detected HPV DNA. Oncogenic HPV types were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 (15). A sample positive by PCR but without positive genotyping for any of the 37 types was labeled as having "unclassified" HPV. β-globin positivity at the anal canal and perianal region were 95.5% and 90.5%, respectively.

v. Sample description

Within the total study population of 463 men, 253 participants completed the expanded questionnaire which included questions about same-gender sex. Of these, 29 men (11.6%) acknowledged anal and/or oral sex with another man while another two men either refused to answer questions about same-gender sex or left the questions blank. The remaining 222 men who denied lifetime anal and/or oral sex with men were the participants included in the analysis. Tests of proportion were used to assess differences in sociodemographic factors between the current study population and the men excluded from analysis.

vi. Statistical analyses

We combined testing results from the anal canal and perianal region and then created a binary outcome variable that indicated either the presence or absence of any anal HPV DNA, regardless of the presence of genital, urethral and seminal HPV (Table 11). The case group consisted of men with anal HPV (at anal canal and/or perianal region) and the non-case group consisted of men who did not have anal HPV but who may have had infection at a genital site or in semen. Therefore, the anal HPV non-case group consisted of both genital HPV positive and HPV negative men.

Table 11. Dependent variables in anal HPV prevalence study

Variable	Variable type
Any anal HPV	dichotomous
Oncogenic anal HPV	dichotomous
Nononcogenic anal HPV	dichotomous
Unclassified anal HPV	dichotomous

Any participant positive for any one of 13 oncogenic HPV types, regardless of the presence of other HPV DNA, was considered positive for oncogenic anal HPV. Any participant positive for a nononcogenic HPV, regardless of the presence of other HPV DNA, was considered positive for nononcogenic anal HPV.

Detection of HPV DNA on PCR but not genotyping constituted a positive result for “unclassified” HPV. A high proportion of men in this study had “unclassified” infection at anal sites (7.7%); however, these unclassified types

may have included types not thought to be sexually transmitted or may have been false-positive results of PCR testing. To lessen the potential for misclassification, the analysis of factors associated with anal HPV was restricted to men with HPV detected by genotyping, thus reducing the study population from 222 to 198 men.

Forty-four independent variables were assessed for their association with the dependent variables (Table 12).

Table 12. Independent variables in anal HPV prevalence study

Variable	Variable type
Age	categorical
Race/ethnicity	categorical
Years of education	ordinal
Marital status	categorical
Household income per month	continuous
Work status	dichotomous
Alcohol use	categorical
Ever used tobacco	dichotomous
Smoked at least 100 cigarettes	dichotomous
Age starting smoking cigarettes	discrete
Pack-years of tobacco use	continuous
Number of cigarettes smoked currently	categorical
Age at first sexual intercourse	discrete
Ever STD diagnosis	dichotomous
Ever had sex partner with an STD	dichotomous
Ever had sex partner with an abnormal Pap smear	dichotomous
Ever had sex partner with genital warts	dichotomous
Genital warts diagnosis (study clinician diagnosed)	dichotomous
Ever diagnosed with herpes	dichotomous
Ever diagnosed with Chlamydia	dichotomous

Table 12. Independent variables in anal HPV prevalence study

Variable	Variable type
Ever diagnosed with gonorrhea	dichotomous
Ever diagnosed with syphilis	dichotomous
Ever had sex with a man	dichotomous
Lifetime number of female sexual partners	discrete
Number of different female sexual partners in past three months	discrete
Number of new female sexual partners in past three months	discrete
Frequency of sexual intercourse with females in past one month	discrete
Frequency of sexual intercourse with females in past three months	discrete
Ever had vaginal sex	dichotomous
Ever had oral sex	dichotomous
Ever had anal sex	dichotomous
Last partner was a new sex partner	dichotomous
Last sex was with 'steady' partner	dichotomous
Circumcision (self-report)	dichotomous
Circumcision (clinician-report)	dichotomous
Condom use at last vaginal sex	dichotomous
Condom use at last anal sex	dichotomous
Condom use for vaginal sex in past three months	ordinal

Table 12. Independent variables in anal HPV prevalence study

Variable	Variable type
Condom use for anal sex in past three months	ordinal
Condom use with partners other than 'steady' in past three months	ordinal
Use of a condom at first sex with 'steady'	dichotomous
Genital HPV (by genotyping)	dichotomous
City of residence	dichotomous

ORs and 95% CIs were calculated by bivariate and multivariate logistic regression. Variables with statistically significant univariate associations with anal HPV ($p < .05$) and variables with a p value of less than .20 on a likelihood ratio test were initially included in modeling. Independent risk factors for anal HPV were identified using a backwards-elimination logistic regression with robust variances. Variables with a $p > .10$ on a Wald test were individually removed until a final set of risk factors remained. Previously rejected variables using the Wald test were again assessed for significance ($p < .10$) in the final model.

Rejected variables were also assessed for their potential role as confounders in the traditional manner; that is, variables associated with both the independent and dependent variable, that also modified the odds ratio by more than 10%, were included in the final model.

Multivariate analyses were adjusted by time of laboratory analysis due to a trend of increasing prevalence observed over the first half of the laboratory analysis period. The trend was attributed to improvements in laboratory methods. Data were analyzed using Intercooled Stata 9.2 for Windows (College Station, Texas, USA) and SAS 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

2. Results

Table 1, Appendix B, presents sociodemographic data of the 222 men included in this analysis in comparison with the men who were part of the parent study but excluded for this analysis. Men were excluded if they had not been asked questions about same-gender sex, if they acknowledged same-gender sex, or if they refused to answer questions about same-gender sex. Seven factors were statistically different between the current analysis and the men excluded from the current analysis: residence, race/ethnicity, marital status, lifetime number of female sexual partners, circumcision, smoking status and level of smoking.

Seventy-two percent of the men were between the ages of 18 and 29 years, 60% identified as white race, 18% as Hispanic, and most men were single, divorced, or separated (80%). None of the men acknowledged HIV infection and none had visible warts or lesions at anal sites. Participants reported having sexual intercourse with a median of one woman in the previous three months and a lifetime median of nine women.

Table 2, Appendix B, presents HPV type distribution by anatomical site. Prevalence at the anal canal and perianal region was 16.6% (n = 36) and 21.3% (n = 45), respectively, while overall anal HPV prevalence was 24.8% (n = 55). The prevalence of any oncogenic HPV type at an anal site was 5.9% (n = 13), and the prevalence of any nononcogenic type was 13.1% (n = 29). Regarding the anal canal specifically, twelve of 36 (33.3%) men with HPV had an oncogenic HPV type detected. The most commonly detected HPV types at anal sites were types 68 and CP6108.

Thirty-nine of 140 men (27.9%) under age 30 had anal HPV, while only eight of 58 men (13.8%) 30 years of age and over had anal HPV (OR, 2.41; 95% CI, 1.05-5.55). When prevalence is viewed by age group, men in their twenties had the highest prevalence (Figure 8).

Figure 8. Age-specific prevalence of anal HPV in 222 heterosexual men

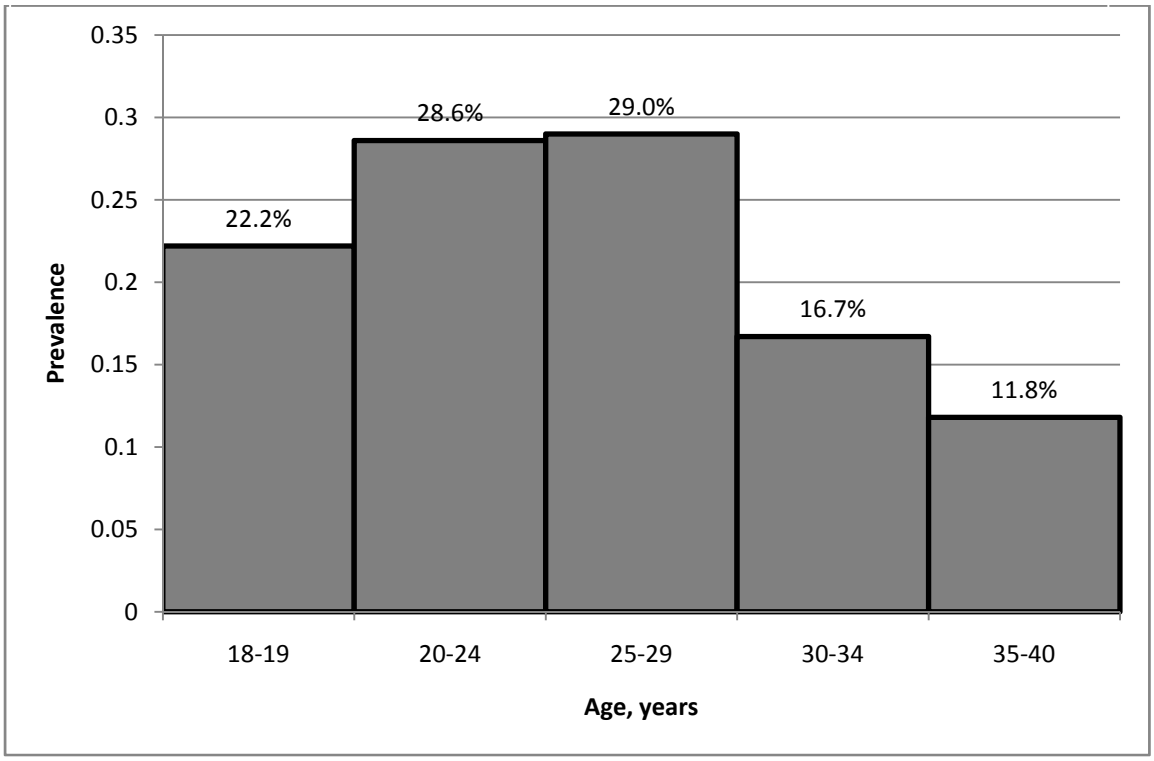


Figure 1, Appendix B, presents the distribution of oncogenic, nononcogenic, and unclassified HPV among men with HPV DNA detected only at anal sites (n = 16) compared to men with HPV DNA detected only at genital sites (n = 95). Type 68 was the most commonly found type at both anal and genital sites with six men having this type at both sites. One man had five HPV types detected at both anal and genital sites.

Factors associated with anal HPV in bivariate analyses (Table 3, Appendix B) were a younger age (in comparison to 30-40 years: OR, 2.41; 95% CI, 1.05-5.55 for 18-29 years), an increased number of lifetime female sexual partners (in comparison to 1-5 partners: OR, 2.65; 95% CI, 1.03-6.84 for 11-20 partners),

frequency of sex with females in the last month of 2-4 times (in comparison to 0-1 times: OR, 3.20; 95% CI, 1.01-10.17), and the presence of genital HPV as confirmed by genotyping (in comparison to no genital HPV: OR, 2.15; 95% CI, 1.03-4.46).

In multivariate analyses (Table 4, Appendix B), a larger number of lifetime female sexual partners (in comparison to 1-5 partners: OR, 3.66; 95% CI, 1.06-12.62 for 11-20 partners) and higher frequency of sex with females in the last month (in comparison to 0-1 times per month: OR, 3.89; 95% CI, 1.03-14.63 for 2-4 times per month) were independently associated with anal HPV.

C. The HIM reliability study

1. Methods

The methods for this study encompass study design and recruitment, sample description, participant procedures, questionnaire description, test-retest interval, and statistical analyses.

i. Study design and recruitment

The data for the HIM reliability study come from the Human Papillomavirus in Men (HIM) Study, an ongoing NIH-funded study. The HIM Study is a prospective natural history study recruiting a multinational group of 3750 participants (223).

Men were recruited in Mexico (Cuernavaca), Brazil (São Paulo), and the US (Tampa) beginning in March, 2005. Men were enrolled if they were between

the ages of 18 and 70 years; resided in the targeted recruitment areas; had no prior anal cancer, penile cancer or genital warts; no current STD diagnosis including HIV; no history of imprisonment, homelessness, or drug treatment in the prior six months; and were willing to comply with visits every six months for four years.

Men were recruited in a different manner at each study site. In Mexico, men were recruited through the largest health plan in the state of Morelos. In Brazil, men were recruited from the largest clinic in São Paulo that tests for HIV and STDs. In the US, men were recruited from the University of South Florida campus in Tampa and the general community. Participants received a nominal monetary incentive to join the study. All enrolled participants consented to the HIM Study protocol which was approved by human subjects protection committees of the University of South Florida, National Institute of Public Health of Mexico, and the Ludwig Institute for Cancer Research, Brazil. Details of study recruitment and design have also been described elsewhere (223, 224).

ii. Sample description

The first 1069 men to complete their run-in and baseline visits were the participants in the current test-retest reliability study. They had a mean age of 31.5 years (*SD* = 10.5); however, age varied by study site with the median age of participants in Brazil and Mexico (33 years for both countries) approximately ten years older than participants recruited in the US (median 23 years). As expected,

the racial and ethnic characteristics of the sample also varied by study site. About one-half of the combined sample reported a non-white race (50.8%) while 41.4% reported a Hispanic ethnicity. Also noteworthy is that the Brazil participants reported a higher median number of female sexual partners during the lifetime (10 partners) than the participants in Mexico (5 partners) or the US (6 partners). Other population characteristics are provided in Table 1, Appendix C.

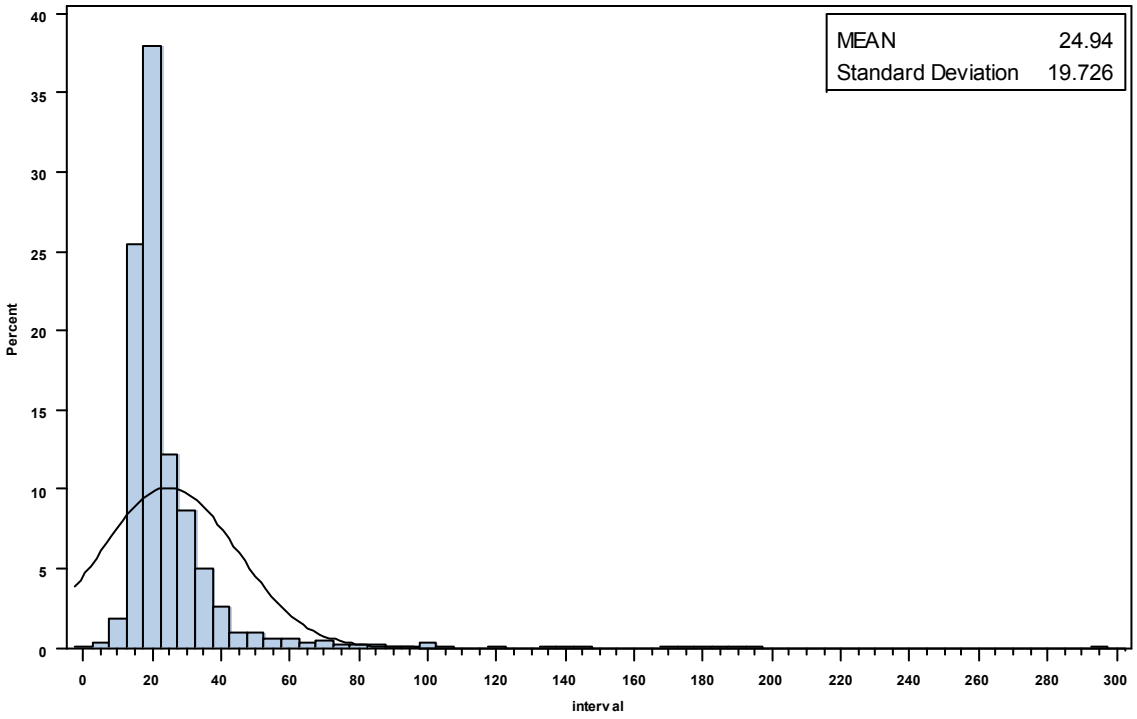
iii. Participant procedures

Men expressing interest in participating in the study received an appointment to come to the clinic for a first visit. At this run-in visit, men who consented to the research protocol experienced all of its aspects to help them determine if they wanted to remain in the longitudinal study which would require their participation for an additional four years.

After receiving instruction in how to use the computer-assisted self-interview, participants completed the interview in private. For participants who could not use the CASI, staff provided a self-administered paper questionnaire, or alternatively, a face-to-face interview. The CASI was written in the primary language of the region and elicited information about participant demographics, substance use, sexual health history, and sexual behaviors implicated in the transmission of HPV. Data from CASI were stored on hard disks at each clinic site, backed-up nightly and transmitted to a central database at the H. Lee Moffitt Cancer Center on a weekly basis.

After completing the CASI, men were sampled at anogenital sites for HPV. Men were then scheduled for a follow-up visit which was completed approximately three weeks later (median = 21 days) in which they again completed an identical CASI (Figure 9). Men did not receive their first HPV test results until six months later at the subsequent clinical visit.

Figure 9. Test-retest interval (in days) of participants in the HIM study



iv. Questionnaire description

With non-threatening questions placed at the beginning, the interview contained 88 items with eight demographic questions, eight alcohol use questions, nine tobacco use questions, 18 sexual health history questions, and 45 sexual behavior questions. The interview was based on the self-administered

questionnaire used in the ADCRC reliability study and used questions with virtually identical wording.

To create the computer-assisted self-interview for each country, the interview was developed, piloted, translated, back-translated, organized for skip patterns, and then programmed for a Windows®-based computer. Participants' sexual health was assessed with questions about their history of STD infections, the existence of a current sexual partner, and circumcision status. Participants were also asked about the sexual health history of their partners. The sexual behavior items assessed incidence and frequency of penetrative sexual behaviors (vaginal, anal, and oral sex) with women and men; age at first intercourse; number of female and male partners; frequency of condom use for vaginal and anal sex; incidence and frequency of sex with 'steady' and other partners; time since last vaginal sex and anal sex; and history of paying for sex. Participants were asked to recall the frequency of substance use and sexual behaviors for varying periods of time including the last month, the last three months, and lifetime. The sexual behavior items included questions that parallel the core indicators recommended by UNAIDS for monitoring a population's risk profile for HIV (225).

v. Test-retest interval

Differences in the test-retest interval by study site could impact reliability coefficients since the participants would be reporting behaviors for somewhat

different periods of time. For example, some participants reporting the number of new female partners in the past three months would be expected to report different numbers of partners at test and retest if, in fact, they had new sexual partners during the test-retest interval. While the participant in such an example would be accurately reporting his number of partners, his answers would be identified as inconsistent and result in a decreased reliability coefficient. Furthermore, if the interval between test and retest was different for each study site, the comparison of reliability coefficients by study site would have to account for this difference. In fact, there was a lack of congruity in the median time between test-retest interviews across study sites with median intervals in days of 21, 25, and 16 days for Brazil, Mexico, and the US, respectively. A Kruskal-Wallis test confirmed a statistically significant difference in test-retest interval by site ($X^2 = 315.5$, $df = 2$, $p < .0001$). Differences in the test-retest interval across study sites were used to help interpret differences in reliability by study site.

vi. Statistical analyses

A subset of items from the interview was selected for assessment of reliability with preference given to items where reliability coefficients would be less biased by the test-retest interval. Specifically, items requiring recall for time periods of less than three months were excluded. A total of 38 variables were assessed including 25 categorical, four ordinal, and nine discrete variables. Variables were 14 sexual health history variables and 24 sexual behavior

variables. Refusal rates for each interview item were calculated. A refusal was defined as the choice of the refusal option on any particular item.

For each interview item, reliability coefficients were calculated for the combined sample and for each of the three study sites. Combined sample coefficients were calculated by averaging study site coefficients after weighting by the inverse of the variance (226). Reliability coefficients were also calculated for each item by age (< 30 years vs ≥ 30 years) and by lifetime number of female sexual partners (≤ the median of seven partners vs > seven).

For categorical variables, κ was calculated. Benchmarks for interpreting κ values followed Landis and Koch (215) as in the ADCRC reliability study. Because the κ statistic can be unstable in situations where there are sparse data (216), coefficients were not computed for variables where the number of cases or non-cases was less than five (145). For ordinal variables a weighted κ statistic was calculated (217) in order to distinguish between levels of disagreement. Discrete variables were assessed using the intraclass correlation coefficient (ICC) (218). All ICCs created using non-normal variables were transformed using Fisher's z transformation before calculating confidence intervals (220). Confidence intervals were then transformed back to the original scale.

Outliers in the bivariate distributions of each discrete variable were assessed using scatter plots. Upon initial analysis, extreme outliers were identified in two discrete variables. For lifetime number of female sexual partners, one participant reported a value of 11,111,109,632 partners on both run-

in and baseline interviews. For age at first sexual intercourse with women, one participant reported a value of 1993 on run-in. Each was removed before any ICCs were calculated for these variables.

2. Results

With exceptions for skip patterns, participants at each study site answered virtually all of the 38 questions under study. For example, 19 variables, including all sexual health history variables, had overall and study site-specific refusal rates under 1% (data not shown). For the total sample, refusal rates for questions about sexual behaviors (e.g., vaginal sex, oral sex, and age at first sexual intercourse) were generally 5.0% or lower except for lifetime number of female sexual partners (6.0% on test and retest, respectively) and frequency of condom use for paid vaginal or anal intercourse (11.8% on both run-in and baseline) (Table 2, Appendix C).

When refusal rates were averaged by study site, Mexico participants were the least likely to refuse to answer questions (1.0% on both run-in and baseline) and Brazil participants were the most likely to refuse to answer (2.4% and 2.5% on run-in and baseline, respectively). For example, on the baseline questionnaire, 12.6% of Brazilian men refused to report their lifetime number of female sexual partners compared with 1.9% of Mexican men, and 4.0% of US men. Brazilian participants had higher refusal rates than either Mexican or US participants for 14 of 19 sexual behavior variables in Table 2, Appendix C.

κ and weighted κ reliability coefficients for each study site and the combined sample were almost perfect ($\kappa \geq 0.81$) or substantial ($\kappa = 0.61 – 0.80$) for all questions (Table 3, Appendix C). The categorical questions with lower, but still substantial, κ coefficients, asked men if they had ever been diagnosed with HIV and if they had ever paid a man for sex ($\kappa = 0.68$ for both questions in the combined sample). Stable κ and weighted κ statistics for two variables (ever diagnosed with syphilis and the frequency of condom use for paid vaginal or anal sex) could not be calculated for any of the three study sites because there were too few cases or non-cases. In Tables 13-21, κ tables are produced for selected variables. Unless otherwise noted, the κ statistic is calculated from the average of the study site κ statistics after weighting by the inverse of the variance for each statistic. κ statistics calculated from the total sample without weighting by individual study sites are noted. This occurred, for example, when a study site statistic could not be calculated due to a low number of cases or non-cases.

Table 13. Participant responses for ever paid a woman for sex at run-in and baseline of the HIM interview

	Ever paid a woman for sex at baseline		
Ever paid a woman for sex at run-in	Yes	No	Total
Yes	58	1	59
No	0	21	21
Total	58	22	80
	Simple $\kappa = 0.97$*		

*κ calculated from total sample without weighting.

Table 14. Participant responses for circumcision at run-in and baseline of the HIM interview

	Circumcision at baseline			
Circumcision at run-in	Yes	No	Don't Know	Total
Yes	444	3	2	449
No	6	580	7	593
Don't Know	0	3	22	25
Total	450	586	31	1067
	Simple $\kappa = 0.96$			

Table 15. Participant responses for ever had vaginal sex at run-in and baseline of the HIM interview

	Ever had vaginal sex at baseline		
Ever had vaginal sex at run-in	Yes	No	Total
Yes	960	4	964
No	2	44	46
Total	962	48	1010
	Simple κ = 0.93*		

*κ calculated from total sample without weighting.

Table 16. Participant responses for ever had sex with a man at run-in and baseline of the HIM interview

	Ever had sex with a man at baseline		
Ever had sex with a man at run-in	Yes	No	Total
Yes	179	10	189
No	10	804	814
Total	189	814	1003
	Simple κ = 0.94		

Table 17. Participant responses for ever paid a man for sex at run-in and baseline of the HIM interview

	Ever paid a man for sex at baseline		
Ever paid a man for sex at run-in	Yes	No	Total
Yes	12	5	17
No	5	196	201
Total	17	201	218
	Simple $\kappa = 0.68$*		

*κ calculated from total sample without weighting.

Table 18. Participant responses for ever diagnosed with HIV at run-in and baseline of the HIM interview

	Ever diagnosed with HIV at baseline			
Ever diagnosed with HIV at run-in	Yes	No	Don't Know	Total
Yes	9	5	0	14
No	2	1009	11	1022
Don't Know	1	9	22	32
Total	12	1023	33	1068
	Simple $\kappa = 0.68$*			

*κ calculated from total sample without weighting.

Table 19. Participant responses for ever diagnosed with genital warts at run-in and baseline of the HIM interview

	Ever genital warts at baseline			
Ever genital warts at run-in	Yes	No	Don't Know	Total
Yes	21	4	1	26
No	3	1002	7	1012
Don't Know	0	10	20	30
Total	24	1016	28	1068

Simple $\kappa = 0.76$*

*κ calculated from total sample without weighting.

Table 20. Participant responses for ever had vaginal, anal, or oral sex at run-in and baseline of the HIM interview

	Ever had vaginal, anal, or oral sex at baseline		
Ever had vaginal, anal, or oral sex at run-in	Yes	No	Total
Yes	958	15	973
No	19	65	84
Total	977	80	1057

Simple $\kappa = 0.78$

Table 21. Participant responses for ever diagnosed with Chlamydia at run-in and baseline of the HIM interview

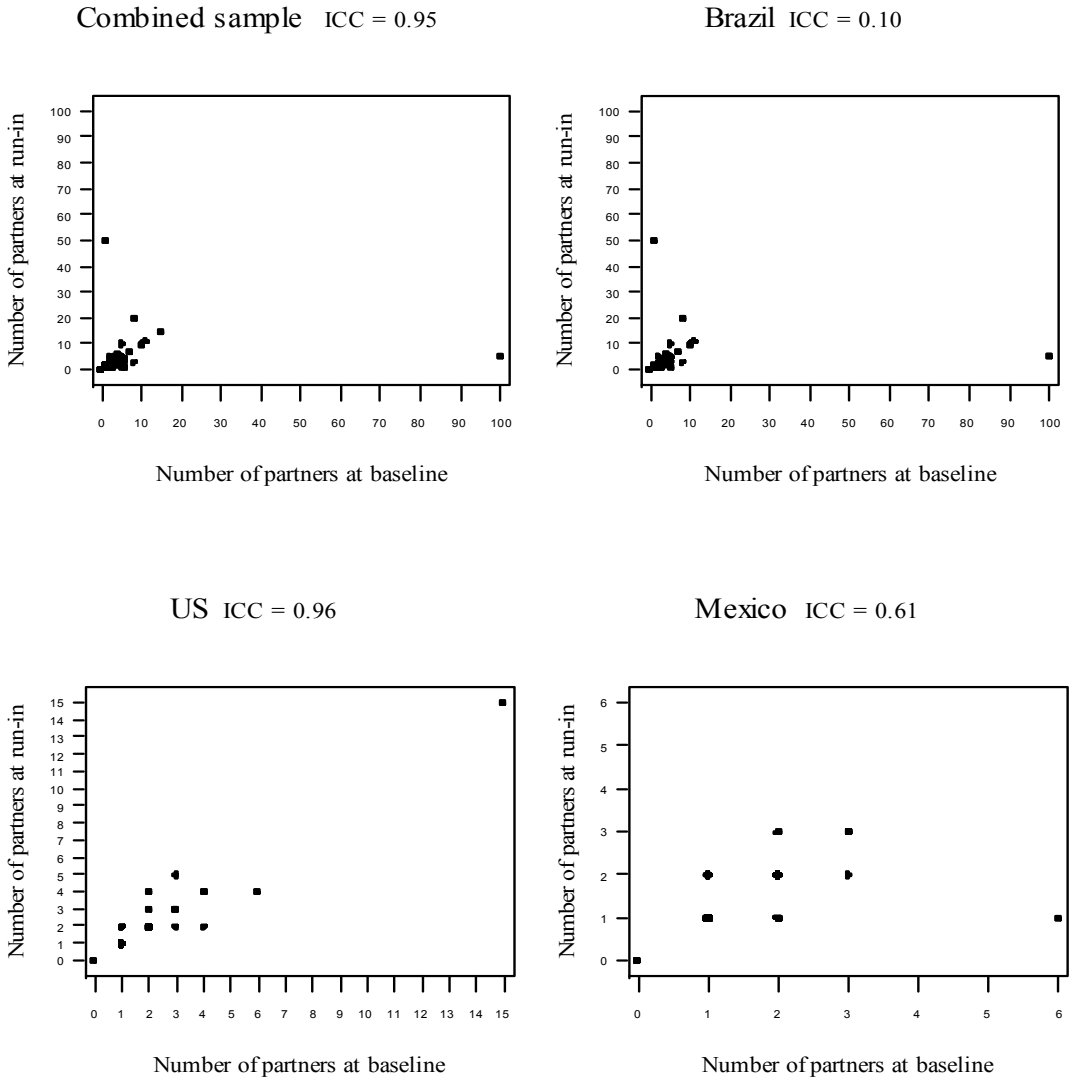
	Ever diagnosed with Chlamydia at baseline			
Ever Chlamydia at run-in	Yes	No	Don't Know	Total
Yes	20	4	0	24
No	4	996	6	1006
Don't Know	0	12	27	39
Total	24	1012	33	1069
	Simple $\kappa = 0.77$*			

*κ calculated from total sample without weighting.

Combined sample, Mexico, and US ICC scores for all discrete variables were ≥ 0.86 except for the Mexico ICC for the variable number of sex partners other than the 'steady' partner (ICC = 0.61). ICC scores in Brazil dropped for three items asking men to report their number of sexual partners; specifically, the items asked for the lifetime number of male anal sex partners (ICC = 0.50), the number of different female sexual partners in the past three months (ICC = 0.58), and the number of sexual partners in the past three months other than a 'steady' sexual partner (ICC = 0.10). Scatter plots identified a small number of extreme outliers in the bivariate distributions of all three variables. For the variable number of sexual partners in past three months other than a 'steady' partner, one

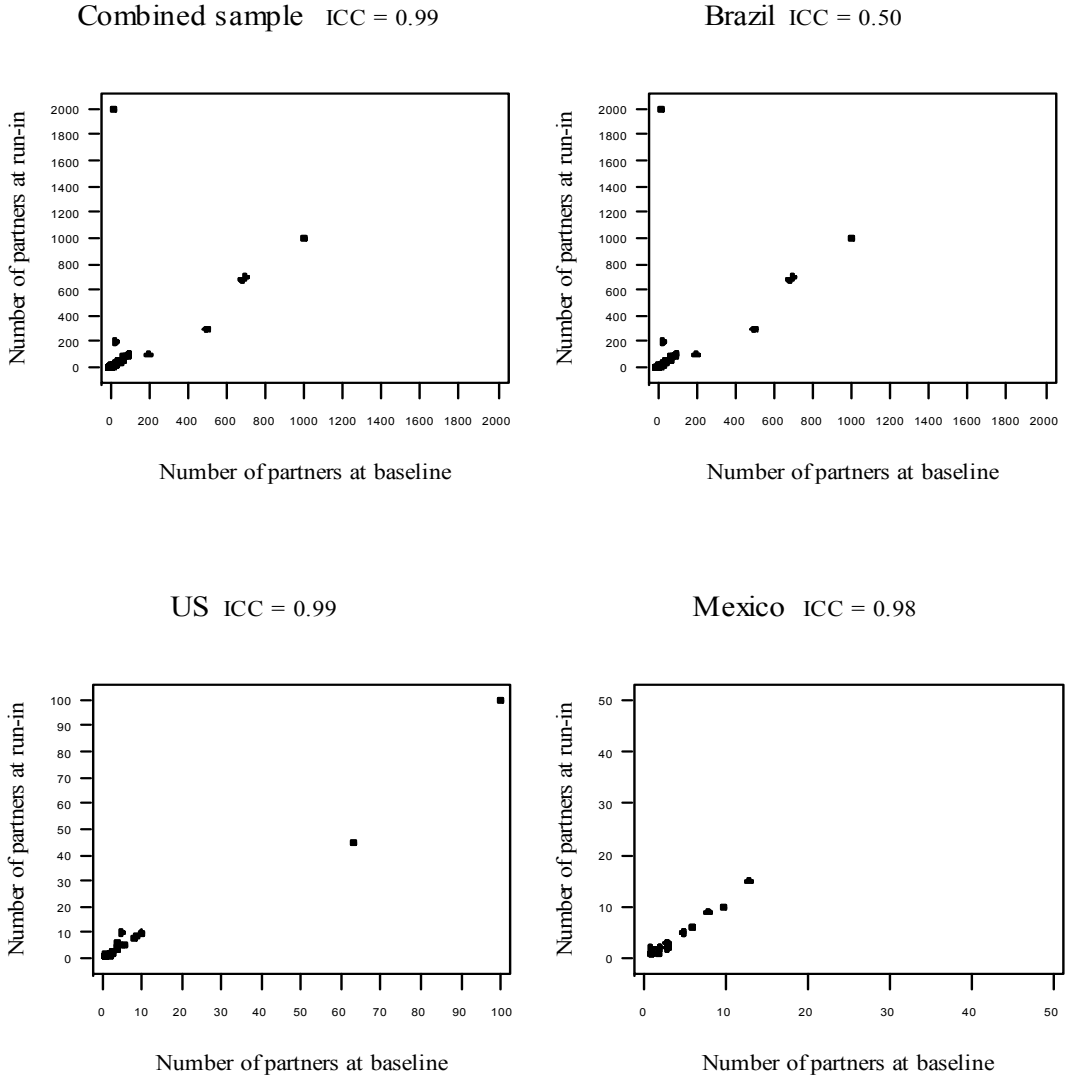
outlier was identified in the Mexico scatter plot while two outliers were identified in the Brazil scatter plot (Figure 10). When the one outlying participant in the Mexico sample was removed, the Mexico ICC increased from 0.61 to 0.84. When the two outlying participants in the Brazil sample were removed, the Brazil ICC increased from 0.10 to 0.79. For lifetime number of male anal sex partners, one outlier was identified in the Brazil scatter plot: a number of partners of 2000 at run-in and 20 at baseline (Figure 11). When this participant was removed from the data set, the ICC for Brazil increased from 0.50 to 0.99. For the variable number of different female sexual partners in the past three months, one outlier (100 partners at run-in and 30 partners at baseline) was identified in the Brazil scatter plot (Figure 12). When the outlier was removed, it resulted in the Brazil ICC increasing from 0.58 to 0.92. Scatter plots for two additional variables with high combined sample ICCs, age at first sexual intercourse with women (ICC = 0.91) (Figure 13) and lifetime number of female sexual partners (ICC = 0.94) (Figure 14) are included for comparison.

Figure 10. Scatter plots for number of sexual partners in past three months other than 'steady' sexual partner: run-in vs baseline for combined sample, Brazil, Mexico, and US



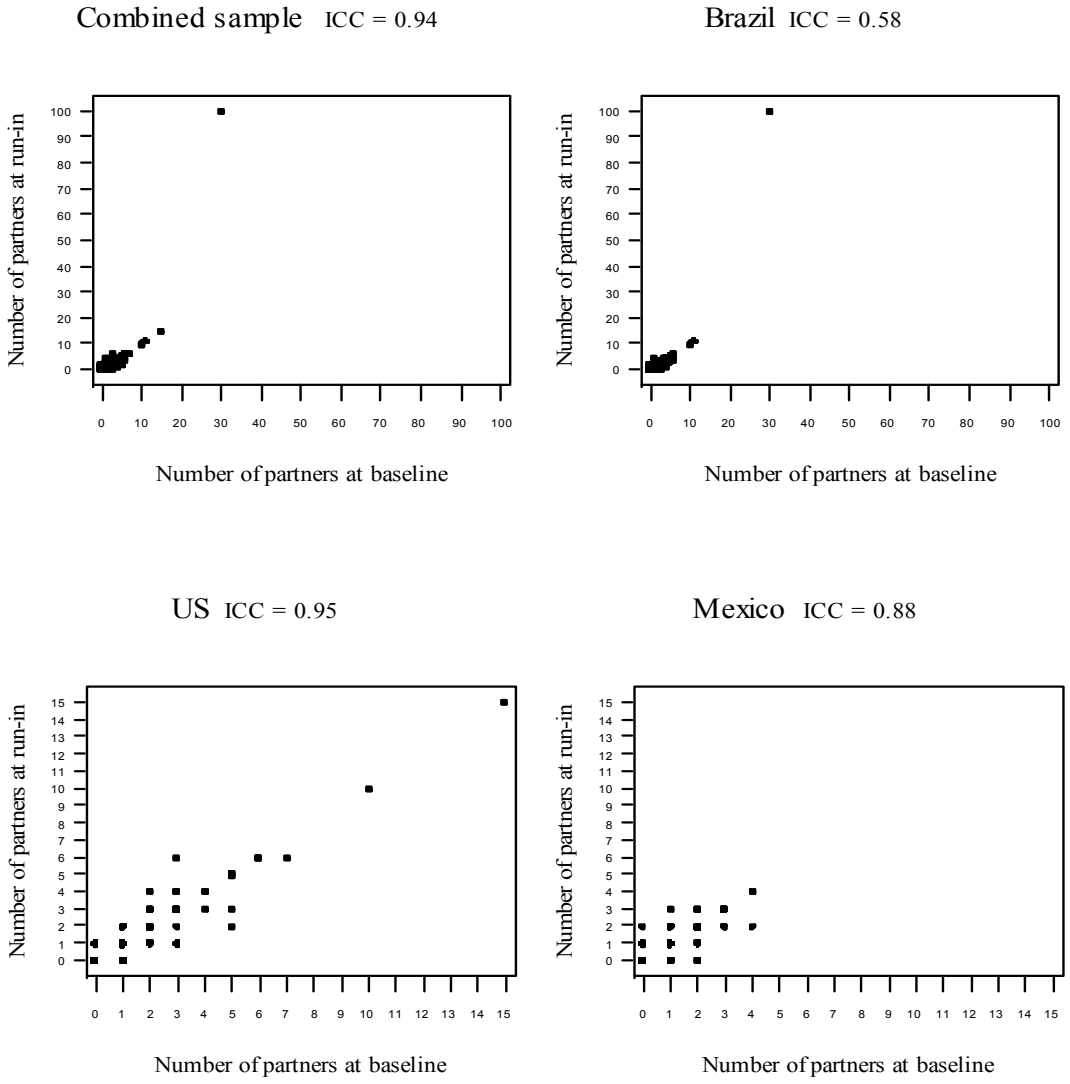
Note: Axes for study sites have different scales. Data points may represent more than one participant.

Figure 11. Scatter plots for lifetime number of male anal sex partners: run-in vs baseline for combined sample, Brazil, Mexico, and US



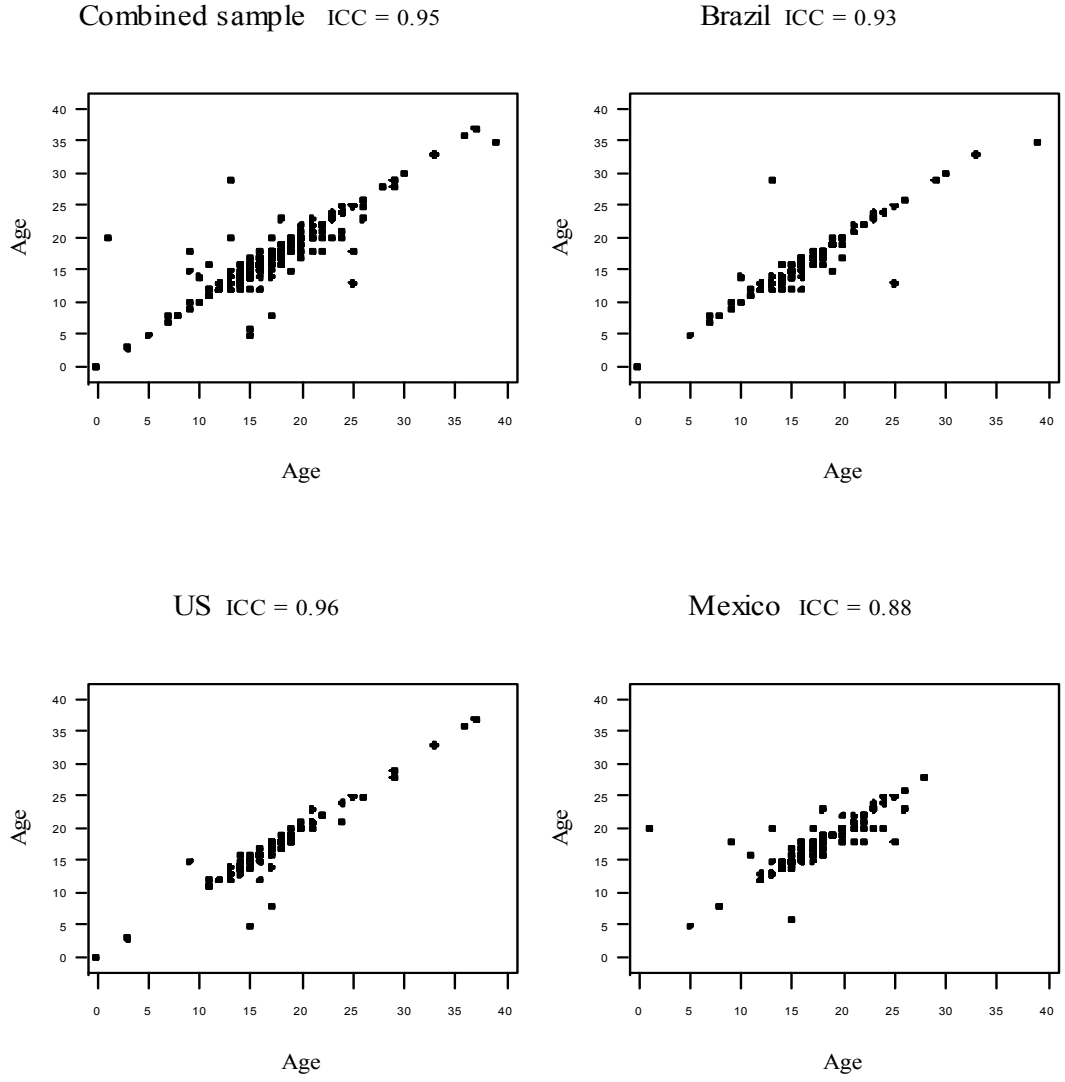
Note: Axes for study sites have different scales depending on the range of observations in the plot. Data points may represent more than one participant.

Figure 12. Scatter plots for number of different female sexual partners in the past three months: run-in vs baseline for combined sample, Brazil, Mexico, and US



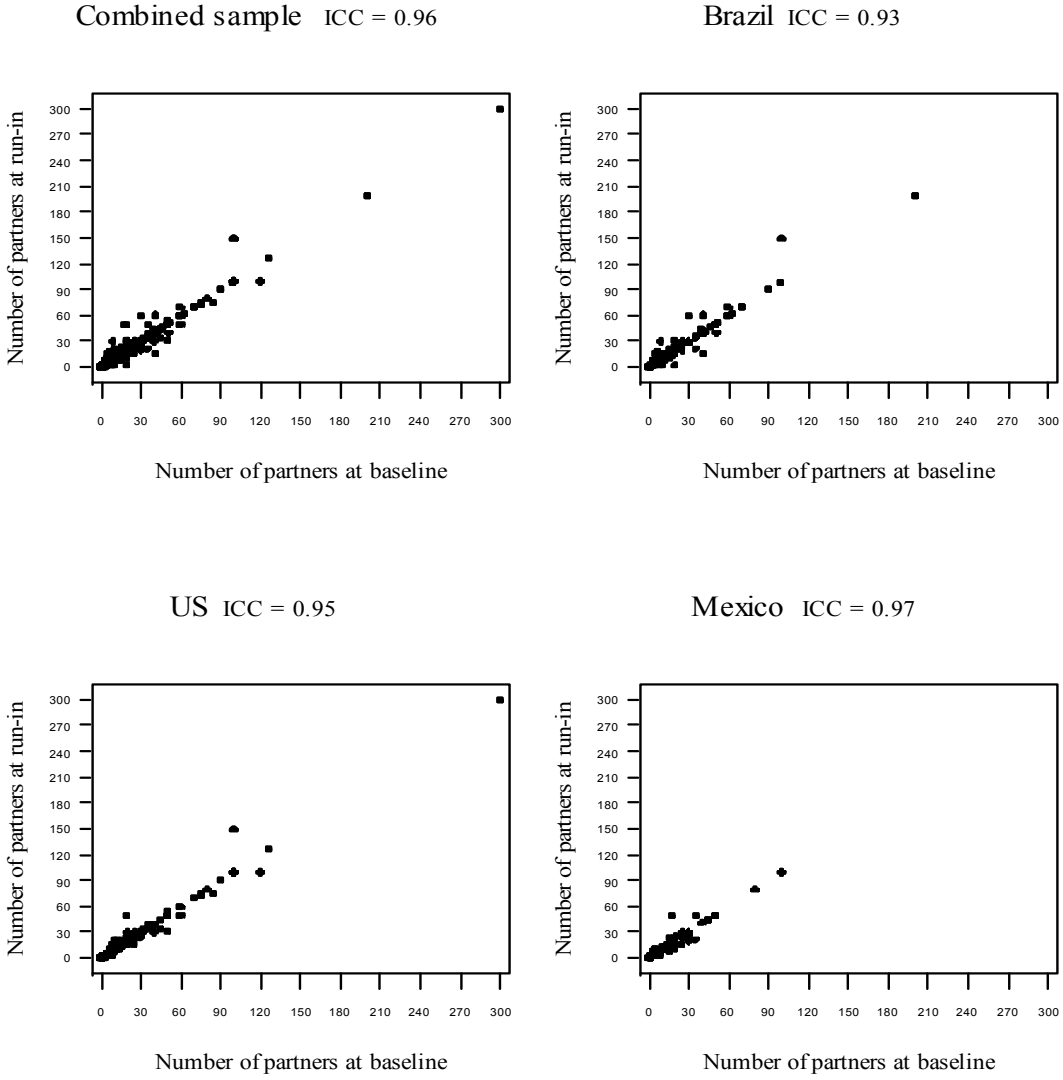
Note: Axes for study sites have different scales. To facilitate viewing the bivariate distribution, the observation 11,111,109,632, was removed from the overall and Brazil plot. Data points may represent more than one participant.

Figure 13. Scatter plots for age at first sex with females: run-in vs baseline for combined sample, Brazil, Mexico, and US



Note: An extreme outlier, 1993, was removed to allow adequate visualization of the bivariate distribution. Data points typically represent more than one participant.

Figure 14. Scatter plots for lifetime number of female sexual partners: run-in vs baseline for combined sample, Brazil, Mexico, and US



Note: In order to adequately visualize the bivariate distribution, observations of greater than or equal to 300 partners have been truncated. Data points typically represent more than one participant.

In the US sample, all reliability coefficients were 0.76 or higher. In Mexico, all were 0.61 or higher. In Brazil, three questions had coefficients lower than 0.61. These are the three discrete variables discussed above.

Of 38 questions assessed, in 25 it was possible to calculate a reliability coefficient for each study site due to a sufficient number of cases and non-cases. For eight of these 25 questions there was a difference of more than ten percentage points within at least one pair of the three study site reliability coefficients (Table 3, Appendix C). For example, an ICC of 0.71 and 0.85 for Brazil and the US, respectively, involves a difference of 14 percentage points between these two coefficients for the question asking about any lifetime diagnosis of hepatitis C. Of the eight questions generating differences in coefficients of more than ten points, five questions had study site coefficients that differed between eleven and 20 percentage points (as in the previous example) and three questions had study site coefficients that differed between study sites by more than 20 percentage points. These are the same three discrete variables detailed above where certain study site reliability coefficients were highly influenced by a few extreme outliers.

When κ and weighted κ coefficients were calculated by age (< 30 years vs ≥ 30 years), all categorical and ordinal items had substantial or almost perfect reliability regardless of age (Table 4, Appendix C). All discrete variables had ICC scores ≥ 0.85 with the exception of the same three discrete variables discussed above: the lifetime number of male anal sex partners (ICC = 0.50 for an age ≥ 30

years), the number of different female sexual partners in the past three months (ICC = 0.60 for an age ≥ 30 years), and the number of sexual partners in the past three months other than a 'steady' sexual partner (ICC = 0.12 for an age ≥ 30 years). In these three variables, the lower reliability was traced to the same outliers identified above who were all participants aged 32 to 44 years.

Reliability coefficients were also calculated by lifetime number of female sexual partners (Table 4, Appendix C). Men who had both above and below the median number of seven partners had substantial or almost perfect reliability coefficients for all categorical and ordinal variables except two: ever had vaginal, anal or oral sex (κ = 0.39 for > seven partners); and ever paid a man for sex (κ = 0.54 for ≤ seven partners). Two discrete variables also showed lower reliability: lifetime number of male anal sex partners (ICC = 0.50 for ≤ seven partners) and number of sex partners in the past three months other than a 'steady' sex partner (ICC = 0.29 for > seven partners).

IV. DISSERTATION CONCLUSIONS AND FUTURE DIRECTIONS

A. Dissertation conclusions

This study is the largest to examine anal HPV prevalence in men who do not acknowledge oral or anal sex with other men and the first to investigate factors associated with anal HPV in asymptomatic heterosexual men. Anal HPV prevalence in this study was 24.8% which suggests that HPV is a common anal infection in sexually active heterosexual men who have no visible anal warts or lesions. This finding parallels research indicating that anal HPV is also common among sexually active women (32). Among men in this study with anal HPV, 33.3% harbored an oncogenic HPV type.

While anal HPV prevalence can be higher than 50% in some male populations including heterosexual men with HIV (33, 107) and men who have sex with men (30), none of the men in the current study acknowledged HIV infection and none acknowledged lifetime sex with other men. There were 29 men, excluded from the current analysis, who acknowledged lifetime oral or anal sex with another man. Interestingly, these men had a prevalence of anal HPV comparable to that of men who did not acknowledge sex with another man (20.7% vs 24.8%; $p = 0.63$).

It is possible that we may have misclassified some of the men's sexual behavior. Same-gender sexual behavior remains a highly socially stigmatized behavior, and some men avoid acknowledging it (143). If we incorrectly classified bisexual men as men who only have sex with women, then heterosexual anal HPV prevalence may be lower. However, the ADCRC reliability study, which used a

similar study sample and the same questionnaire, identified high reliability for most sexual behavior items including the question that asked men if they had ever had sex with another man (κ = 0.94). Even so, it seems plausible that a man intent on concealing a history of sex with men may invoke a strategy to remember his answers to such questions. Errors due to untruthfulness result in dependent misclassification because the degree of misclassification of one measurement depends on the degree of misclassification of the other measurement. Such a situation will lead to a correlation of errors for the two measurements and bias the reliability coefficient upwards. It reminds us that highly reliable data cannot be assumed to also be valid.

While it is possible that the κ for ever had sex with another man was inflated by dependent misclassification, it is also possible that κ was attenuated, for example, if a participant decided to conceal same-gender sex on the test but then answered truthfully on retest.

The test-retest reliability result for the question about same-gender sex mirrors the reliability findings for most of the other sexual behavior questions in the ADCRC reliability study. Indeed, reliability was generally equivalent for sexual behavior questions and for non-sexual behavior questions that may be less susceptible to self-presentation bias, e.g., birth date and marital status. Reliability dropped somewhat, but was still substantial, for items that asked about oral sex, payment for sex with males, use of a condom at first sex with a 'steady' sex partner, and the health of the men's sexual partners (for example, partners'

histories of STDs or abnormal Pap smears). These overall findings of high reliability are consistent with other test-retest reliability studies with populations of women and adolescents completing sexual behavior questionnaires (180, 183, 227).

We might also question the results of the anal HPV prevalence study if a large proportion of men refused to answer sexual behavior questions; however, in general, only a small minority of men chose this option. For example, for the question about same-gender sex, ~1% of men on both test and retest chose to refuse to answer the question. This rate of refusal was indicative of that found with most other sexual behavior questions in the ADCRC reliability study. Low nonresponse to sexual behavior items has been previously observed (228); however, explicit refusals to answer a question should be considered only a subset of the total amount of refused questionnaire items. Some men may have felt more comfortable with answering a question falsely and less comfortable with skipping a question or checking the refuse option (140).

If measurement error is not the chief reason for our unexpected results regarding a high anal HPV prevalence in heterosexual men, what are the other possible reasons for this finding? The anal HPV prevalence reported in this study may be higher than in two previous studies (71, 72) due to 1) differences in sampling technique, 2) genotyping of samples regardless of PCR HPV results, and 3) genotyping of 37 HPV types detectable in the assay (229). Van Doornum, et al. tested 85 men from a sexually transmitted disease clinic who acknowledged

sex only with women and found 1.2% positive for anal HPV (72). That team detected DNA using a four primer PCR system that detected five HPV types. Nicolau, et al., using hybrid capture technology detecting 18 HPV types, reported an 8% anal canal HPV prevalence in 50 Brazilian men who were heterosexual partners of women with confirmed HPV infection (71). These assays that detect five and 18 HPV genotypes would be expected to yield a lower prevalence estimate than an assay that detects 37 HPV types. On the other hand, given the composition of the samples in these two published studies, the current study's general community sample may not help explain the higher anal HPV prevalence in the present study.

The factors associated with anal HPV in this analysis are similar to factors previously identified for genital HPV in prior publications (26, 83, 84, 136, 229). We found that lifetime number of female sexual partners and frequency of sexual intercourse with women in the past month were independently associated with anal HPV while lack of circumcision was marginally associated with anal HPV. Also, in the ADCRC reliability study, both lifetime number of female sexual partners and circumcision had high reliability (ICC = 0.89 and κ = 0.93); therefore, it seems unlikely that substantial misclassification explains these results.

While lifetime number of female sexual partners had high test-retest reliability in the ADCRC reliability study, there was enough discordance between participants' answers on test and retest to allow an investigation of the predictors

of unreliable reporting. Increasing age and a greater lifetime number of female sexual partners were independent predictors of unreliable reporting while 16 or more years of education was inversely associated with unreliable reporting of lifetime number of female partners.

Increasing measurement error on questionnaires in association with fewer years of education has been seen in prior research (11). In addition, our finding among mostly heterosexual men that a higher lifetime number of female sexual partners led to unreliable reporting of those partners echoes prior research among women and gay men where higher frequency behaviors were also associated with increased measurement error (181, 187). Our definition of unreliable reporting, a difference between test and retest of five or more partners, may be appropriate given the ADCRC participants' mean of 15.0 lifetime female sexual partners. A lower cut point would have labeled more participants as inconsistent even though the actual difference between test and retest was small and would have little impact on estimates of effect. Also, for men who actually increased their lifetime number of sexual partners between test and retest, a lower cutpoint would label more of these men as unreliable even though they may have reported their behavior accurately. Conversely, allowing for a greater amount of inconsistency before labeling the difference as indicative of unreliable reporting may have been too low a standard for reliability.

The two variables of age and lifetime number of sexual partners were moderately correlated in the ADCRC reliability study (Spearman $r = 0.39$; $p <$

.0001) as one would expect given that the lifetime number of sexual partners cannot decrease as age increases. Given this correlation, one practical use of this knowledge may be to support memory recall of lifetime number of sexual partners in men over a certain age, for example, using Timeline Followback methods which tether the recall of behaviors to specific events in a participant's life (211).

The third factor we found associated with anal HPV in the prevalence and risk factor analysis, frequency of sexual intercourse in the prior month, is noteworthy for the inconsistency in the association. In multivariate analysis, the risk associated with this behavior was limited to men who acknowledged a frequency of sex of 2-4 times a month. Conversely, men who acknowledged the highest frequency of sex in the last month, five or more episodes of sex, were not at increased risk for anal HPV. In contrast, Baldwin, et al., reported a dose-response relationship between sexual frequency in the past three months and HPV (OR, 3.65; 95% CI, 1.49–8.97 for a frequency of vaginal and/or anal intercourse of >30 in the past three months in comparison to a frequency of 0-5) (73). The reason for the lack of a dose-response relationship in the present study is unclear although one explanation is that heterosexual men who have the most sex are more likely to be in a monogamous relationship and therefore less likely to have exposure to HPV.

Since the reporting of frequency of sexual intercourse has been noted as potentially unreliable in some previous research (174), it is possible that our

results for this factor are primarily due to measurement error. Unfortunately, frequency of sexual intercourse in the prior month could not be assessed in the ADCRC reliability study. Items measuring recall for shorter time periods, like frequency of sexual intercourse in the prior month, were not assessed to minimize potential bias due to the test-retest interval (mean 21.5 days, median 16 days). Given the lack of test-retest reliability testing, measurement error cannot be assessed in this item.

This reliability study could have been improved upon by the use of a retest that explicitly referenced the same time period as the original test. Such a measure may have reduced bias introduced by the temporal offset of the test-retest interval. However, such a measure would have required construction of a different baseline questionnaire which then would have been inappropriate for the longitudinal nature of the larger study.

The ADCRC reliability study, while establishing high reliability for the self-administered questionnaire, has limitations. For example, the interval between test and retest also could have promoted bias if the period was short enough to allow the recall of prior answers (230); however such explanations have been disputed as a significant source of bias (231). In addition, this reliability study's test-retest interval is a common span of time that may balance the competing goals of limiting recall of prior answers while providing a largely overlapping reference period for both test and retest questions (232). Also, a test-retest interval variable was created and no statistically significant association was found

between interval length and the reliability of the lifetime number of female sexual partners item (p = 0.31, data not shown). Other researchers have also found the number of partners reported on test and retest was unaffected by the recall interval (206).

Another limitation is that, compared with non-volunteers, men who volunteered for the current study dealing with sexual behaviors may be less likely to be evasive about reporting their sexual behaviors. That is, men who returned for the baseline retest, which indicated their desire to commit to the 18-month longitudinal study, may be more committed to providing high quality data, leading to higher reliability; thus, the study may not be generalizable to a general population of non-volunteers.

While our assessment of risk factors for anal HPV may have used reliable data, the question of how HPV was transmitted to the anal region in these men is still unclear. One possibility is that there may be other unmeasured factors associated with anal HPV infection. Our questionnaire gathered data about penetrative sexual practices implicated in HPV transmission between men and women: vaginal, anal, and oral intercourse; however, none of these behaviors are seemingly able to transmit HPV to the anal region of a man who acknowledges sex only with women. Our questionnaire did not ask about other sexual behaviors such as self-initiated or partner-initiated anal massage, or anodigital insertion. Of note, one study has reported an association between non-penetrative sex (finger-vulvar, penile-vulvar, and oral-penile) and genital HPV in female virgins (74). In

addition to sexual behaviors involving the perianal region or anal canal, non-sexual behaviors may also help explain anal HPV prevalence in heterosexual men. Four studies suggest HPV transmission via hand carriage (19, 20, 21) and objects (233) may be possible.

If HPV DNA can be transmitted by fingers or objects, then self-transference from the penis or scrotum to perianal region or anal canal may occur as a result of sexual or non-sexual behaviors. This explanation requires that male genital infection lie in the causal pathway between the risk factors we measured and anal HPV. Accordingly, it is possible that this investigation identified risk factors associated with genital HPV in addition to anal HPV. Indeed, genital and anal HPV DNA were associated in these men in univariate analysis; however, type-specific concordance between genital HPV and anal HPV was not perfect. The lack of complete concordance may be due to a number of reasons; for example, it is possible that the natural history of HPV, including duration of infection, is different at the genitals and anus. It is also possible that HPV types have a different tropism for tissues specific to the anal canal vs the male genitals.

It is unlikely these results are due to study-related contamination with inadvertent transfer of HPV DNA from either genital to anal sites or from perianal region to the anal canal since rigorous sampling methods were used by study clinicians.

With regard to the prevalence study, the study population was self-selected which could affect the kind of men who enrolled. Some may have avoided the study while others may have been attracted to it because of concerns about STDs. While participant self-selection may limit generalizability, the men in the prevalence study came from diverse community settings which may make the results more representative.

Additional limitations to the prevalence study include its sample size. It was not powered to detect risk factors for HPV at specific anatomical sites like the perianal region or the anal canal.

Finally, the sub-sample of men selected for this analysis differed from the excluded men on seven different factors: residence, race/ethnicity, marital status, lifetime number of female sexual partners, circumcision, smoking status and level of smoking. Since recruitment occurred in Tampa and Tucson, variation in geography and recruitment practices may explain some differences in these variables (234, 235). However, the prevalence of anal HPV in the excluded men (22.8%) was comparable to the prevalence in the included men. This result makes it less likely that exclusionary characteristics affected the results.

The HIM reliability study documents the successful transformation of the ADCRC self-administered paper and pencil survey for US men into a different method, CASI, for a multinational group of men.

In the HIM reliability study, 1069 men in Brazil, Mexico and the US were asked the same sexual health history and sexual behavior questions at run-in and

baseline using CASI. The reliability coefficients for almost all of the 38 assessed questions were > 0.60. However, three discrete variables were of concern: the lifetime number of male anal sex partners, the number of different female partners in the past three months, and the number of sex partners in the past three months other than a 'steady' partner.

The poorer reliability in these variables is due to the presence of outliers identified in scatter plots. For lifetime number of male anal sex partners and number of different female sexual partners in the past three months, an extreme outlier in each variable was identified in the Brazil sample. When these observations were removed, the Brazilian ICC of each of these variables increased to ≥ 0.92. For the third discrete variable, number of sex partners in the past three months other than a 'steady' partner, three outliers were identified: two in Brazil and one in Mexico. When these observations were removed, the ICC increased from 0.10 to 0.79 for Brazil and from 0.61 to 0.84 for Mexico.

The influence of the four participants responsible for these outliers (three in Brazil and one in Mexico) was also apparent when reliability coefficients were stratified for men < 30 years old and those ≥ 30 years old. These outlying participants were all older than age 30 years. Therefore, while reliability coefficients for all questions completed by the younger men were ≥ 0.71, older men's reliability suffered for the same three discrete variables discussed above: lifetime number of male anal sex partners (ICC = 0.50), the number of different female partners in the past three months (ICC = 0.60), and the number of sex

partners in the past three months other than a 'steady' partner (ICC = 0.12). When the four outlying participants were once again removed, the ICC of the three variables increased to ≥ 0.89.

When stratified by the median lifetime number of female sexual partners, these outliers also distorted the reliability coefficients for two discrete variables: lifetime number of male anal sex partners (ICC = 0.50 for men with ≤ 7 female sexual partners) and number of sex partners in the past three months other than a 'steady' partner (ICC = 0.29 for men with > 7 female sexual partners). After removal of the same Brazilian outlier identified above in the variable for lifetime number of male anal sex partners, the ICC score increased from 0.50 to 0.99. After removing the same three outliers identified above (two Brazilian and one Mexican) for number of sex partners in the past three months other than a 'steady' partner, the ICC increased from 0.29 to 0.85.

During subsequent calculation of reliability coefficients stratified by the median lifetime number of female sexual partners, lower reliability was also identified in two categorical variables: ever had vaginal, anal, or oral sex (κ = 0.39 for men with > seven partners) and ever paid a man for sex (κ = 0.54 for men with ≤ seven partners). Seven of 441 men with greater than the median number of sexual partners reported at run-in that they had never had anal, vaginal, or oral sex. In addition to inviting concern about validity, this small number of cases may have contributed to instability in the κ coefficient. Likewise, only six men with fewer than seven partners at baseline acknowledged ever

paying a man for sex, possibly lending instability to the κ coefficient. During the design of this study, we were aware that a small number of cases could create instability in the κ coefficient; therefore, we decided to not report coefficients where the number of cases or non-cases was less than five. Future investigations may wish to consider increasing this minimum requirement for number of cases or non-cases.

It is possible that sparse data for reporting certain sex behaviors was a result of cultural stigmatization attached to these behaviors (236), for example, paying a man for sex. Or, the sparse data may simply reflect a lack of behavioral heterogeneity in the population.

The existence of outliers in this study could have occurred for a variety of reasons. First, a conspicuous difference in answers on test and retest for number of sex partners may have occurred because the true number of partners was different at test and retest (140).

Second, it is possible that the reliability of reporting casual sex partners may differ among the samples due to different levels of cultural stigmatization attached to these behaviors (236). For example, the Brazilian men recruited in a clinic may be less likely to want to reveal their number of different female sex partners in comparison with men primarily recruited from a university (US) or men recruited from a health plan (Mexico).

Third, reliability scores may also have suffered in Brazil if the survey was less culturally competent for Brazilian men than for Mexican or US men. The

questionnaire from which the HIM Study's CASI was created was developed in the Southwest US near the Mexican border. It is possible that the genesis of the questionnaire in the US-Mexico border region lent itself to an instrument that was somewhat more culturally competent with US and Mexican participants and less so with Brazilian participants.

Reliability may also have been affected by the number of days between test and retest. The US study site had the lowest median interval (16 days) while the Mexico site had the highest median interval (25 days); however, this potential cause for different reliability by site seems unlikely because reliability coefficients for the Mexican men were, in general, comparable to the US men. Also, reliability coefficients for discrete variables showed no declining pattern as the number of days between test and retest increased (data not shown). A large test-retest interval also does not seem responsible for the extremely discrepant outliers discussed above since each of these four participants had test-retest intervals of ≤ 22 days.

Finally, measurement error may have differed in the three sites as a result of differing levels of exposure to computer technology. Not only was there a higher median age in Brazil, but also a higher percentage of Brazil participants were over the age of 45 years compared with Mexico and the US (14.8%, 6.1%, and 7.7% respectively). It is possible these older men in Brazil had less exposure to computers which may have lead to less comfort with the technology and

therefore increased measurement error, a phenomenon reported elsewhere (161, 162, 237).

However, even with the above potential threats to reliability noted, it is important to remember that, absent the small number of extreme outliers and presence of sparse data in two questions, virtually all coefficients indicate the HIM Study instrument reported these men's sexual behavior in a highly reliable manner. This result with a CASI instrument may be due, in part, to the fact that in all countries, participants were primarily educated men living in an urban setting. In collecting data on abortions from Mexican women, Lara, et al. found audio-CASI more appropriate for urban and educated participants than for rural residents in Mexico (237). Our findings are also in accord with two studies of audio-CASI in Brazil. Simões and colleagues compared audio-CASI with a face-to-face interview and found that audio-CASI was not only acceptable to men recruited at a health clinic, but that it also elicited more reports of sensitive sexual behaviors (153, 189).

To our knowledge, no studies have reported test-retest reliability for a sexual behavior survey delivered with CASI; however, three reliability studies with adults have reported results for audio-CASI (151, 196, 199). For a variety of reasons, these studies are difficult to compare with the current study. First, the studies use a different survey method. Also, two of the studies had a shorter test-retest interval (i.e., three days or less) inviting concern about participants recalling answers from the initial interview (151, 196). Two of the three audio-

CASI studies reported composite reliability scores reflecting groups of questions instead of individual reliability scores for each interview item (196, 199). It is difficult to compare composite measures of reliability with the item-specific coefficients of the current study. In addition, unlike the three audio-CASI studies, the HIM reliability study recruited men from a variety of community settings in three countries.

We are aware of one other cross-national test-retest reliability study of sexual behavior measures. Schlect, et al. assessed the reliability of data collected in face-to-face interviews and by self-administered questionnaires using a pooled dataset from six studies. That study found women in diverse cultures could report age at first sexual intercourse with high reliability (ICC = 0.68 – 0.97); however, reliability suffered substantially, and differed considerably by study site, when the women reported their lifetime number of sexual partners (ICC = 0.08 – 0.94). In contrast, the current study found almost perfect reliability for this question across all three study sites. These heterogeneous results may be due to important methodological differences between the two studies. Schlect, et al. assessed the reliability of a pooled dataset comprised of data from separate and distinct studies that not only had different survey methods and study protocols, but also different and lengthy test-retest intervals (i.e., six weeks to five years). The current study may be more suited for a cross-national reliability study since each study site used identical protocols and had more homogenous test-retest intervals. Of course, differences in the reliability findings of the two studies may

also be due to the different survey methods being assessed (CASI vs. face-to-face interview or self-administered questionnaire).

Refusal rates in the HIM reliability study, as in the ADCRC reliability study, were generally low which has been found previously with surveys of human sexuality (190, 238). All sexual health history questions had refusal rates of less than 1% while overall refusal rates for some sexual behavior items were higher. Lifetime number of female sexual partners was refused by 4.0% of US respondents on test and retest. While comparative rates are not available for Brazil and Mexico, these rates are comparable to the 6.1% refusal rate reported in the US for the General Social Survey of the National Opinion Research Center for the number of sexual partners in the last twelve months (239). In contrast, the Brazilian men's rate of refusal for the lifetime number of female sexual partners question was 11.7% and 12.6% on run-in and baseline, respectively. The difference between the US and Brazilian men may be due to the targeted recruitment for Brazilian men in an STD clinic vs US men at a university. Higher refusal rates from participants using audio-CASI in an STD clinic in comparison with a face-to-face interview have been reported previously (240). Also, a 2006 Brazilian study noted higher refusal rates for audio-CASI in a health facility in Rio de Janeiro. The authors speculated that study participants had an expectation of more personal service in a health facility and therefore were more likely to refuse questions posed by a computer (153).

The highest refusal rate (11.8% on both run-in and baseline) was for a question asking about the frequency of condom use for paid vaginal or anal sex; however, these proportions may be misleading since only 17 participants in the study answered this question (primarily because of skip patterns). Also noteworthy is that items requiring the participant to provide a numeral, as opposed to a nominal answer, were approximately twice as likely to be refused in Brazil and Mexico compared to the US where numerical items and nominal items were refused at about the same rate (data not shown).

The HIM reliability study has several limitations, some of which are similar to limitations in the ADCRC reliability study. In addition, due to the targeted recruitment in each country, the results should not be generalized to the rest of the population in each country.

In summary, with few exceptions, we found very high reliability using the same computer-assisted self-interview instrument in three culturally and linguistically different countries. While not guaranteeing validity, these results indicate that, for the current instrument, data collection with CASI from men in diverse settings may result in reliable sexual behavior data for most questions. However, caution is still warranted especially regarding the potential loss of reliability for questions requiring numerical responses.

For future studies of anal HPV in heterosexual men, the HIM reliability study results suggest that

1) while most studies do not have the luxury of repeated measures, when they are available they should be used to identify measures with lower reliability. One can then exercise more caution when using these measures for effect estimation and in interpreting results.
2) repeated measurements provide an opportunity for the identification of participants whose reporting of data is unreliable and therefore invalid. Investigators can then assess the impact of these individuals on estimates of effect.
3) due to the constant presence of measurement error, investigators should take steps to attenuate it. For example, Timeline Followback methods that attempt to support memory recall might be employed when collecting higher frequency sexual behavior data or sexual behavior data from older men. Also, efforts should be made to minimize error measurement through the use of methods that decrease the demands of the survey task (e.g., CASI) and that decrease social desirability bias. For example, methods that may limit self-presentation bias include added privacy for the survey taker and self-administered questionnaires (either paper and pencil or computer-assisted) that use non-judgmental language.

Finally, future reliability studies in diverse communities might be improved by collecting data about the level of social desirability bias that may be

operating in each community. This information could be used to help control for social desirability bias when comparing cross-cultural sexual behavior data. These data may be relatively easily collected by the use of short instruments that quantify a participant's comfort with sexual self-disclosure (241).

B. Future directions

This study is an important first examination of anal HPV prevalence in a community sample of asymptomatic heterosexual men. We do not believe these data should be used to change clinical practice at this time; however, further research is needed that characterizes anal HPV infection in other populations of men who acknowledge sex only with women. It is also the first examination to assess risk factors for anal HPV in asymptomatic heterosexual men. However, clearly understanding the full complement of risk factors for anal HPV in heterosexual men will require more study.

Future studies are needed in three areas: confirmation of the age-specific prevalence of anal HPV in community samples of heterosexual men, investigation into the routes of transmission of anal HPV in heterosexual men, and longitudinal studies of the natural history of anal HPV in heterosexual men.

Our finding of a prevalence of almost 25% in heterosexual men needs to be corroborated. It is a surprising result that begs similar observations in other samples of men. The results also suggest the possibility of a lower anal HPV prevalence for heterosexual men in their 30's as compared with younger men.

Conversely, Chin-Hong, et al. reported a stable age-specific anal HPV prevalence pattern in MSM (30). If such a trend of decreasing age-specific prevalence in heterosexual men is confirmed in future studies, it could be due to a number of reasons including a lack of persistence of anal HPV in older heterosexual men or different sexual behavior for younger vs. older men.

Future studies should also collect sexual and non-sexual exposure information that may clarify routes of transmission to the perianal region and anal canal. A recent study offers additional evidence that HPV is often transmitted by the hands (21). If such a transmission route is a significant contributor to anal HPV prevalence in men, then behavioral approaches to preventing HPV infection at this anatomical site become more complicated while vaccine-related approaches seemingly make more sense.

Finally, just as longitudinal studies played a critical role in development of preventive vaccines for cervical cancer, longitudinal studies are now needed to elucidate the natural history of anal HPV infection in both younger men and older men to help inform questions about the applicability of vaccines for them. Furthermore, in men who do not have receptive anal intercourse, natural history studies will help us understand the relationship between incident genital HPV and anal HPV infection which may be important for understanding the risk for anal HPV and anal HPV-associated disease in men (93).

The author has secured funding from the National Cancer Institute and from industry to follow up this prevalence study by investigating anal HPV in

men recruited for the HIM Study. Currently secured funding will allow an anal HPV prevalence and risk factor study with this larger sample of men that is multinational, and a six month incidence and persistence study with the same sample. Successful completion of these ancillary studies to the HIM Study will provide much needed information to help determine prevention strategies for HPV infection at the anus, in addition to its consequences like anal dysplasia and anal cancer. This greater understanding of anal HPV and its consequences may also support a greater awareness of the distribution of sexually transmitted disease in sexually diverse groups of men.

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APPENDIX A – ADCRC RELIABILITY STUDY

Running head: RELIABILITY IN A SEXUAL BEHAVIOR QUESTIONNAIRE

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Test-retest reliability and predictors of unreliable reporting in a sexual behavior questionnaire for US men

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Abstract

Accurate knowledge about sexual behaviors is important for the development of prevention strategies targeting sexually transmitted diseases; however, there have been few studies assessing the reliability of questionnaires designed for community samples of adult men. A test-retest reliability study was conducted on a questionnaire completed by 334 men who had been recruited in Tucson, Arizona, for a longitudinal study of human papillomavirus. Reliability coefficients and refusal rates were calculated for 38 non-sexual and sexual behavior questionnaire items. Predictors of unreliable reporting for lifetime number of female sexual partners were also assessed. Refusal rates were generally low with slightly higher refusal rates for questions related to immigration, income, the frequency of sexual intercourse with women, lifetime number of female sexual partners, condom use, and the lifetime number of male anal sex partners. Kappa and intraclass correlation coefficients were substantial or almost perfect for all non-sexual and sexual behavior items. Reliability dropped somewhat for items that asked about oral sex, payment for sex, and the men's knowledge of their sexual partners' health including abnormal Pap tests and prior STDs. Age and lifetime number of female sexual partners were independent predictors of unreliable reporting while years of education was inversely associated with unreliable reporting. These findings among a community sample of adult men are consistent with other test-retest reliability studies with women and adolescents.

KEY WORDS: reliability; test-retest; sexual behavior; questionnaires; adult men

INTRODUCTION

Knowledge about the sexual behaviors of men informs the design of strategies that prevent the transmission and sequelae of sexually transmitted diseases. Data describing sexual behaviors are usually collected through self-report; however, there is concern that study participants' self-reported sexual behaviors may not be valid (Catania, Gibson, Chitwood, & Coates, 1990; Franco, 1997; Potterat, Phillips, & Muth, 1987; Stoneburner, Chiasson, Solomon, & Rosenthal, 1986) due to several sources of measurement error including the demands of the recall task and the sociological context of the survey (Schroder, Carey, & Vanable, 2003). For example, self-presentation bias – the result of a participant's effort to manage information in order to shape his or her image (Catania, 1999) – is a threat to validity if the participant's image diverges from reality.

Unfortunately, the validity of sexual behavior measurements is difficult or impossible to assess due to cultural taboos that disapprove of the direct observation of human sexual behavior. Lacking a direct assessment of validity, studies often collect data through repeated self-reported measures of a sexual behavior to expose unreliable or inconsistent responses that may point to measurement error and, therefore, a lack of validity (Carballo-Dieguez, Remien, Dolezal, & Wagner, 1999; Müller, 2007; Rohan, McLaughlin, & Harnish, 1994; Schlecht, et al., 2001; Schrimshaw, Rosario, Meyer-Bahlburg, & Scharf-Matlick, 2006; Van Duynhoven, Nagelkerke, & Van de Laar, 1999).

Test-retest studies have measured the reliability of sexual behavior items in a variety of populations (Brener, et al., 2002; Kalichman, Kelly, & Stevenson, 1997; Schrimshaw, et al., 2006; Sohler, Colson, Meyer-Bahlburg, & Susser, 2000; Taylor, Rosen, & Leiblum, 1994). Some studies find that self-administered instruments, either of the paper and pencil variety or computer assisted, reduce measurement error and tend to produce reports of higher frequencies of sensitive sexual and drug using behaviors than do face-to-face interview methods (Boekeloo, et al., 1994; Des Jarlais, et al., 1999; Le, Blum, Magnani, Hewett, & Do, 2006; Romer, et al., 1997; Simoes, Bastos, Moreira, Lynch, & Metzger, 2006a; Turner, et al., 1998; Williams, et al., 2000). It is thought that higher frequencies of sexual behaviors, particularly stigmatized behaviors, reflect greater validity since adults are more likely to underreport such behaviors (Catania, et al., 1990).

Eight test-retest studies of self-administered sexual behavior questionnaires (SAQ) have been published (Brener, et al., 2002; Durant & Carey, 2002; Kalichman, et al., 1997; Müller, 2007; Schlecht, et al., 2001; Sieving, et al., 2005; St Lawrence, et al., 1999; Taylor, et al., 1994). With the exception of one study from Germany that included 23 men (Müller, 2007), these studies have assessed the reliability for questionnaires designed for either adolescents or women. However, the expression of measurement error may differ by age, sex, or other population characteristics. For example, the novelty of sexual behavior for adolescents may lead to better recall (Tourangeau, 2000) than would occur

among older, more experienced males. Also, a generally higher cumulative number of sexual partners for adults, as opposed to adolescents, may make recall of these larger numbers more difficult and thus lead to less reliable measures (Downey, Ryan, Roffman, & Kulich, 1995; Durant & Carey, 2002; Van Duynhoven, et al., 1999).

When low reliability items are found in sexual behavior questionnaires, it may also be useful to understand characteristics, demographics or otherwise, that are associated with less reliable items; however, predictors of lower test-retest reliability for specific sexual behavior items have only occasionally been reported in the literature (Morrison-Beedy, Carey, & Tu, 2006; Needle, et al., 1995; Schlecht, et al., 2001; Williams, et al., 2000). Likewise, nonresponse to questionnaire items, or refusal to answer specific questions, also increases measurement error. In the one study that assessed predictors of nonresponse to questionnaire items (Catania, McDermott, & Pollack, 1986), non-responders were more likely than responders to feel threatened by questions about their sexuality, and to have less sexual experience and knowledge.

Finally, studies often limit their reporting of reliability to sexual behaviors and do not report the reliability of demographic characteristics and non-sexual behaviors collected by the same instrument. A comparison of the reliability of responses to questions about sexual behaviors and non-sexual behaviors (some of which may be less associated with image management) may provide further insight into presentation bias.

The objective of the present study was to assess the test-retest reliability of a wide range of sexual and nonsexual items on a self-administered questionnaire delivered to a community sample of 334 men in Tucson, Arizona. The study also sought to assess predictors of unreliable reporting for lifetime number of female sexual partners – a sexual behavior that is important for better understanding the transmission of sexually transmitted diseases.

METHOD

Participants

Men were recruited between September, 2003, and May, 2005, to a longitudinal study of the natural history of genital human papillomavirus (HPV). Men were enrolled if they met eligibility criteria that included an age of 18 to 44 years, a residence in southern Arizona, no prior penile or anal cancers or genital warts, a willingness to comply with a total of four visits over 18 months, and no plans to relocate within the next two years.

Recruitment was conducted at a variety of community locales through flyers targeting a large university campus, advertisements in local newspapers and on radio, direct mail advertisements, and face-to-face recruitment at a public sexually transmitted disease clinic. Participants were offered a nominal monetary incentive for their participation. All men consented to participation in the study using forms and protocols approved by the Institutional Review Board of the University of Arizona. Additional details of recruitment and study design have

been described elsewhere (Giuliano, et al., 2008). Men were included in the reliability study if they attended both the run-in visit and the baseline visit approximately two weeks later.

Participants attending both visits had a mean age of 30.2 years (*SD* = 8.1). A majority identified as white (75.9%) while 19.5% reported a Hispanic ethnicity. Table I includes additional characteristics of the study population and refusal rates.

Procedure

Men expressing interest in participating in the study received an appointment to come to the clinic for an initial visit. At this run-in visit, those who consented to the study experienced all participant activities to help them determine whether they wanted to remain in the longitudinal study which would require their participation for an additional 18 months. Participants completed a paper and pencil 86-item self-administered questionnaire, and a study clinician collected exfoliated skin cells at external genital sites for HPV testing. Men were then scheduled for the baseline visit approximately two weeks later (*M* = 21.5 days, *SD* = 23.8, median = 16 days, range 9-292 days), at which time they completed the same self-administered questionnaire again. Men received their first HPV test results at their follow-up visit, approximately six months later.

Of 379 men who completed a run-in questionnaire, 334 returned to complete a baseline questionnaire and were included in the reliability study. A comparison

of study participants and those who did not return for the baseline visit found no statistically significant differences with regard to demographic variables, tobacco use, or sexual behavior variables.

Measures

Substance Use and Sexual Behaviors

The questionnaire contained 86 items with 16 demographic questions, seven alcohol use questions, eight tobacco use questions, and 55 sexual behavior questions. The questionnaire had previously been used to assess sexual behavior in women (Giuliano, et al., 2002) and had been adapted for and pretested with men.

The sexual behavior items assessed history of sexually transmitted diseases; circumcision; incidence and frequency of penetrative sexual behaviors (vaginal, anal, and oral sex) with women and men; age at first intercourse; number of female and male partners; frequency of condom use with vaginal and anal sex; incidence and frequency of sex with 'steady' and other partners; time since last vaginal sex and anal sex; and history of paying for sex. Participants were asked to recall the frequency of substance use and sexual behaviors for varying periods of time including the last month, the last three months, and lifetime.

Data Analysis

A subset of items from the questionnaire was selected for assessment of reliability with preference given to items where reliability coefficients would not be biased by the test-retest interval. For example, while the questionnaire required recall of behaviors over several time periods, items with a one-month recall period were not assessed because the time interval between test and retest (M=21.5 days) would have led the participant to recall sexual behavior for largely different time periods. A total of 40 variables were assessed including 28 categorical, four ordinal, and eight discrete variables. Demographic, tobacco use, and sexual behavior variables were included in the assessment. In addition, a three-category variable for number of days between the test and retest was created (1 – 14 days, 14 – 30 days, or > 30 days) to estimate how a lengthening interval might affect reliability coefficients.

Refusal rates for each questionnaire item were calculated. A refusal was recorded if a participant chose the refusal option on any particular item or if the participant declined to answer an item that was not precluded by a skip pattern. If a participant responded to a question that should have been skipped because of skip instructions, the response was not used in calculating refusal rates or reliability coefficients.

For categorical variables, the kappa statistic (κ) was calculated. Unlike percent agreement, κ identifies the level of agreement after correcting for chance agreement (Cohen, 1960). Benchmarks for interpreting κ values followed Landis

and Koch (Landis & Koch, 1977). Since the κ statistic can be unstable in situations where there are a small number of cases (Maclure & Willett, 1987), reliability was not assessed for binary variables with a case total of less than five (Schroder, et al., 2003).

For ordinal variables a weighted κ statistic was calculated (Cicchetti & Allison, 1971) in order to distinguish between levels of disagreement. For instance, in responding to a question about the frequency of condom use with five possible responses, if a subject chooses the adjacent categories of "more than half the time" and "half the time" on run-in and baseline, respectively, simple κ will identify zero agreement between the two responses; however, weighted κ will give credit for the partial agreement.

Discrete variables were assessed using the intraclass correlation coefficient (ICC) (McGraw & Wong, 1996). All ICCs created from skewed variables were transformed using Fisher's z transformation before calculating confidence intervals (Rosner, 2000). Confidence intervals were then transformed back to the original scale. Outliers were assessed using scatter plots and none were considered highly influential.

Logistic regression was performed to identify predictors of unreliable reporting for lifetime number of female sexual partners. This variable was chosen because studies have identified lifetime number of sexual partners as particularly susceptible to measurement error (Schlecht, et al., 2001; Van Duynhoven, et al., 1999) and because it has been strongly associated with an increased risk for HPV

and other sexually transmitted diseases (Nielson, et al., 2007; Nyitray, et al., 2008). A dichotomous variable was created to delineate unreliable vs. reliable. Unreliable reporting was defined as a difference between test and retest of five or more partners. The cut point identifying unreliable reporting was intended to highlight discrepancies that could more seriously bias estimates of effect. For example, because men who have fewer than approximately five lifetime female sexual partners may be at lower risk for genital HPV infection (Nielson, et al., 2007; Vaccarella, et al., 2006), a discrepancy of five or more partners on test and retest could bias estimates of the effect of lifetime number of sexual partners on HPV infection. Bivariate associations were computed between this dependent variable and ten potential predictors of unreliable reporting (age, race, ethnicity, marital status, education, income, country of birth, number of years since first intercourse, lifetime number of female sexual partners, and length of test-retest interval). A liklihood ratio test with a *p* value of less than .20 identified candidate variables for multivariate regression. Independent predictors of unreliable reporting collected at the baseline visit were identified using a backwards selection process. Potential confounders were identified by their association with both the dependent and independent variable and by their ability to substantially modify the independent variable odds ratio. Finally, goodness-of-fit for the final model was assessed using the Hosmer-Lemeshow test.

RESULTS

Item refusal rates were generally below 5% with the exception of income, country of residence, length of residence in the US, and three sexual behavior questions. The sexual behavior questions asked about the lifetime number of female sexual partners (refusal rate 3.7% on test and 7.0% on retest), the frequency of sexual intercourse with women in the past three months (refusal rate 6.5% on test and 7.8% on retest), and the lifetime number of male anal sex partners (refusal rate 5.5% on test and 14.7% on retest).

Test-retest reliability for 38 items in the sexual behavior questionnaire is presented in Table II. Reliability was substantial or almost perfect for demographic variables. Of these, household income per month was the least reliable (weighted κ = .74). Most of the misclassification on income involved participants' switching between adjacent income categories. κ was over .90 for all tobacco-use items.

Most sexual behavior items also had almost perfect reliability. Less reliable (but still substantially reliable) were questions asking the participant to report the health conditions of their sexual partners. For example, κ was .67 for an item asking the participant if he had ever had a sex partner with a sexually transmitted disease. Stable κ statistics for two additional variables (ever diagnosed with genital warts and ever diagnosed with syphilis) could not be calculated because there were too few positive responses.

In bivariate analyses (Table III), variables associated with unreliable reporting of lifetime number of female sexual partners were older age (OR, 1.13; 95% CI, 1.07–1.20), race (OR, 4.34; 95% CI, 1.03–18.23 for black race compared with white race), an increasing number of years since first intercourse (OR, 1.12; 95% CI, 1.07–1.18), and an increasing lifetime number of female sex partners (OR, 1.03; 95% CI, 1.02–1.05).

In multivariate analyses (Table IV), older age (OR, 1.12; 95% CI, 1.06–1.20) and lifetime number of female sexual partners (OR, 1.02; 95% CI, 1.01–1.04) were independent predictors of unreliable reporting. Also, 16 or more years of education, compared with 12–15 years of education, was inversely associated with unreliable reporting (OR, 0.33; 95% CI, 0.13–0.88). Holding lifetime number of female partners constant at the sample mean of 15.0, there was a 2% probability that a 25 year old with 16 or more years of education would be unreliable on test and retest for lifetime number of female partners. In contrast, there was a 10% probability that a 40 year old with 16 or more years of education would provide unreliable answers on this item. There would be a 25% probability that a 40 year old man with a high school education would provide unreliable answers on his lifetime number of female sexual partners.

The final model fit the data well (Hosmer-Lemeshow $p = 0.43$) and no confounders of the association between the independent and dependent variables were identified.

DISCUSSION

The 334 men in this study, recruited from the general community, provided consistent answers to most demographic, tobacco use, and sexual behavior questions on both test and retest. The sexual behavior items were generally as reliable as the demographic items. Reliability dropped somewhat for items that asked about oral sex, payment for sex with males, the use of a condom at first sex with 'steady', and the health of the men's sexual partners (for example, partners' histories of STDs or abnormal Pap smears). The study's overall findings are consistent with other test-retest reliability studies with populations of women and adolescents that also found generally high reliability for sexual behavior questionnaires (Brener, et al., 2002; Durant & Carey, 2000; Sieving, et al., 2005).

While men in this study were explicitly given permission to refuse to answer items on the questionnaire, with a few exceptions, most men completed all the questions. This is consistent with observations from other studies (Peterson & Catania, 1997). Items with higher nonresponse in the current study included questions related to immigration. Persons not born in the US were asked how long they had lived in the US. A total of 8.3% (2/24) on test and 12.5% (3/24) on retest refused to answer the question. Also, 6.0% (20/334) of persons on the retest refused to report in which country they had lived most of their lives. The refusal rates on this item and the previous item may be due, in part, to participants who perceive a more threatening climate for immigrants in the US. An item asking about income was refused by 5.4% and 8.4% of participants on

the test and retest, respectively. The perceived threat associated with divulging income information has been documented previously (Peterson & Catania, 1997).

Regarding higher refusal rates for sexual behavior items, 6.5% and 7.8% of participants on test and retest refused to report the frequency with which they had sexual intercourse with women in the previous three months. The previously mentioned high refusal rate for condom use with anal sex may be due to the lack of a nearby skip pattern for men who had not performed anal sex or any recent anal sex. Finally, on test and retest, 5.5% (4/73) and 14.7% (10/68) of men acknowledging sex with other men did not report the lifetime number of male anal sex partners. Since this item came near the end of the 86 item questionnaire, it is possible that participant fatigue led to the higher refusal rates. Refusal rates should be considered only a subset of the total amount of refused questionnaire items. Some men may have felt more comfortable with answering a question falsely and less comfortable with skipping a question or checking the refuse option (Catania, et al., 1990).

Increasing age and a greater lifetime number of female sexual partners were independent predictors of unreliable reporting while 16 or more years of education was associated with reliable reporting for lifetime number of female partners. Increasing measurement error on questionnaires in association with lower educational attainment has been seen in prior research (Schlecht, et al., 2001) as has an age effect that degrades consistency between test and retest for lifetime number of sex partners (Downey, et al., 1995; Durant & Carey, 2002; Van

Duynhoven, et al., 1999). It is also possible that the effect of increasing age is simply requiring the older person to remember more years of sexual activity which likely limits reliability due to memory failure (Fenton, Johnson, McManus, & Erens, 2001; Kauth, St Lawrence, & Kelly, 1991; Lagarde, Enel, & Pison, 1995; Tourangeau, 2000). The present study's finding among mostly heterosexual men that a higher lifetime number of female sexual partners was associated with more unreliable reporting of those partners echoes prior research among women and gay men where higher frequency behaviors were also associated with increased measurement error (Downey, et al., 1995; Durant & Carey, 2002; Morrison-Beedy, et al., 2006). Our definition of unreliable reporting, a difference between test and retest of five or more partners, may be appropriate given the participants' mean of 15.0 lifetime female sexual partners. A lower cut point would have labeled more participants as inconsistent even though the actual difference between test and retest was small and would have little impact on estimates of effect. Also, for men who actually increased their lifetime number of sexual partners between test and retest, a lower cutpoint would label more of these men as unreliable even though they may have reported their behavior accurately. Conversely, allowing for a greater amount of inconsistency before labeling the difference as indicative of unreliable reporting may have been too low a standard for reliability.

We chose to assess the predictors of unreliable reporting of lifetime number of female sexual partners because number of sexual partners is a risk factor that is

strongly associated with HPV infection in men and therefore plays a crucial role in determining risk for anogenital HPV in men. Initially we also planned to assess predictors of unreliable reporting for a history of sex with men and for age at first sexual intercourse – two variables that are also important in determining risk for anogenital HPV; however, only lifetime number of female sexual partners generated a large enough number of discordant answers between test and retest to allow creation of a binary variable (unreliable vs reliable) with adequate cell sizes.

The two variables of age and lifetime number of sexual partners were moderately correlated (Spearman $r = 0.39$; $p < .0001$) as one would expect given that the lifetime number of sexual partners cannot decrease as age increases. Given this correlation, one practical use of this knowledge may be to support memory recall of lifetime number of sexual partners in men over a certain age, for example, using Timeline Followback methods (Carey, Carey, Maisto, Gordon, & Weinhardt, 2001).

Due to the time interval between test and retest (mean 21.5 days, median 16 days), participants were asked to recall their sexual behavior for slightly different time periods. For example, the reliability of the item, “In the past 3 months, how many times did you have sexual intercourse with a woman?” may be expected to decline if the frequency of the men’s sexual behavior changed during the test-retest interval in comparison to the three months prior to the test. To minimize potential bias caused by the test-retest interval, items measuring recall for time

periods of one month were not assessed. Also, a test-retest interval variable was created and no statistically significant association was found between interval length and the reliability of reporting on lifetime number of female sexual partners (p = 0.31, data not shown). Other researchers have also found the number of partners reported on test and retest was unaffected by the recall interval (McElrath, Chitwood, Griffin, & Comerford, 1994).

The interval between test and retest also could have promoted bias if the period was short enough to allow the recall of prior answers (Nunnally, 1978); however such explanations have been disputed as a significant source of bias (McKelvie, 1992). In addition, this study's test-retest interval is a common span of time in test-retest studies that may balance the competing goals of limiting recall of prior answers while providing a largely overlapping reference period for both test and retest questions (Wiederman, 2002). Even so, it seems plausible, for example, that a man intent on concealing a history of sex with men may have invoked a strategy to remember his answers to such questions. Errors due to untruthfulness result in dependent misclassification because the degree of misclassification of one measurement depends on the degree of misclassification of the other measurement. Such a situation will lead to a correlation of errors for the two measurements and bias the reliability coefficient upwards. It also reminds us that highly reliable data cannot be assumed to also be valid. Alternatively, a participant may have decided to conceal a behavior on the test

but then decided to answer truthfully on retest which would have attenuated the reliability coefficient.

The reliability coefficients we calculated may be inflated because, compared with non-volunteers, men who volunteered for the current study dealing with sexual behaviors may be less likely to be evasive about reporting their sexual behaviors. That is, men who returned for the baseline retest, which indicated their desire to commit to the 18-month longitudinal study, may be more committed to providing high quality data, leading to higher reliability; thus, the study may not be generalizable to a general population of non-volunteers.

Finally, the Landis and Koch categories that label levels of reliability as 'almost perfect,' 'substantial,' etc. are subjective (Landis & Koch, 1977); however, they are useful for discussions that compare reliability coefficients.

This study could have been improved upon by the use of a retest that explicitly referenced the same time period as the original test. Such a measure may have reduced bias introduced by the temporal offset of the test-retest interval. However, such a measure would have required construction of a different baseline questionnaire which then would have been inappropriate for the longitudinal nature of the larger study.

As computer technology becomes more commonplace, it seems likely that computer-assisted self-interview technology will increasingly become the survey method of choice; however, it is not clear that CASI survey methods increase the reliability of sexual behavior survey methods in all situations (Jaya, Hindin, &

Ahmed, 2008; Jennings, Lucenko, Malow, & Devieux, 2002; Jobe, Pratt, Tourangeau, Baldwin, & Rasinski, 1997; Johnson, et al., 2001; Le, et al., 2006; Metzger, et al., 2000; Morrison-Beedy, et al., 2006; Simoes, Bastos, Moreira, Lynch, & Metzger, 2006b; Turner, et al., 1998; Van den Brakel, Vis-Visschers, & Schmeets, 2006). While there are studies comparing CASI (or audio-CASI) with other survey methods like SAQ or face-to-face interviews, we are aware of few studies reporting the test-retest reliability of this method for a sexual behavior questionnaire (Krawczyk, et al., 2003; Romer, et al., 1997; Williams, et al., 2000; Wolford, et al., 2008). Since none of these studies have assessed reliability in a general community sample of adults, future research should assess the level of test-retest reliability obtainable by CASI for sexual behavior data collected from general populations.

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Table I. Characteristics of study participants (n = 334)

Variable[a]	*N*	%
Age, years		
Mean=30.2 ± 8.1 (18-44)	331	-
Refuse[b]	3	0.9
Race[c]		
White	224	75.9
Black	12	4.1
American Indian/Alaskan Native	8	2.7
Asian	6	2.0
Other	36	12.2
Don't Know	1	0.3
Refuse	8	2.7
Ethnicity		
Hispanic	65	19.5
Non-Hispanic	263	78.7
Refuse	6	1.7
Marital status		
Single, never married	208	62.3
Married	46	13.8
Cohabitating	33	9.9
Divorced/widowed	38	11.4

Table I. Characteristics of study participants (n = 334)

Variable[a]	*N*	%
Refuse	8	2.4
Education, years		
Less than 12	20	6.0
12-15	174	52.1
More than 15	136	40.7
Refuse	4	1.2
Household income, monthly		
Less than $1500	124	37.1
$1500-$3999	121	36.2
More than $4000	35	10.5
Don't Know	26	7.8
Refuse	28	8.4
Age at first sexual intercourse		
Under 15 years	45	14.0
16-17 years	136	42.2
18-19 years	86	26.7
20-29 years	45	14.0
Refuse	10	3.1
Lifetime number of female sexual partners		
Mean=15.0 ± 19.6 (1-99)	291	-

Table I. Characteristics of study participants (n = 334)

Variable[a]	*N*	%
Refuse	22	7.0
Ever had sex with a man		
Yes	70	21.7
No	249	77.1
Refuse	4	1.2

[a] At baseline.

[b] Refuse is defined as participants who left the question blank or chose the refuse option, and who were not otherwise precluded from refusing due to a skip pattern.

[c] Numbers do not add to 334 due to skip patterns.

Table II. Kappa and intraclass correlation coefficients by questionnaire item

Variable	*N*[a]	κ[b] or ICC[c]	95% CI[d]
Demographics			
Race	239	.83	.75– .91
Ethnicity	322	.98	.95– 1.00
Country of birth	330	.97	.92– 1.00
Years lived in the U.S. if not born in the U.S.	20	.99	.97– 1.00
Country of residence for most of life	302	1.00	-
Birth date	330	.95	.93– .96
Marital status	320	.93	.89– .97
Years of education[e]	329	.92	.89– .96
Household income per month[e]	301	.74	.68– .81
Tobacco use			
Ever used tobacco	322	.90	.85– .95
Smoked at least 100 cigarettes	204	.99	.97– 1.00
Age started smoking cigarettes	130	.91	.87– .93
Years of smoking cigarettes	126	.93	.91– .95
Sexual health history			
Ever diagnosed with a sexually transmitted disease	330	.86	.80– .92
Ever diagnosed with genital herpes	324	.88	.74– 1.00
Ever diagnosed with Chlamydia	324	.88	.80– .97

Table II. Kappa and intraclass correlation coefficients by questionnaire item

Variable	*N*[a]	κ[b] or ICC[c]	95% CI[d]
Ever diagnosed with gonorrhea	323	.81	.63– .99
Ever diagnosed with non-gonococcal urethritis	324	.82	.74– .91
Ever diagnosed with hepatitis B	322	.80	.60– .99
Ever diagnosed with hepatitis C	321	.80	.57– 1.00
Ever diagnosed with HIV	324	.92	.77– 1.00
Ever had sex partner with a sexually transmitted disease	331	.67	.61– .74
Ever had sex partner with genital warts	332	.71	.63– .78
Ever had sex partner with an abnormal Pap smear	330	.71	.65– .77
Circumcision	330	.93	.88– .99
Sexual behavior – lifetime			
Ever had vaginal sex	331	.98	.93– 1.00
Ever had anal sex	327	.95	.92– .98
Ever had oral sex	329	.76	.59– .93
Age at first sexual intercourse	311	.91	.89– .93
Lifetime number of female sexual partners	289	.89	.86– .91
Use of a condom at first sex with ‘steady’ partner	188	.76	.67– .85
Ever paid a woman for sex	311	.96	.92– 1.00
Ever had sex with a man	317	.94	.90– .99

Table II. Kappa and intraclass correlation coefficients by questionnaire item

Variable	*N*[a]	κ[b] or ICC[c]	95% CI[d]
Lifetime number of male anal sex partners	49	1.00	-
Ever paid a man for sex	63	.78	.49– 1.00
Sexual behavior – past three months			
Frequency of condom use for vaginal sex[e]	238	.83	.78– .89
Frequency of intercourse with women	219	.85	.80– .88
Frequency of condom use for anal sex[e]	157	.78	.68– .88

[a] *N* excludes refusals and missing observations.

[b] κ: kappa.

[c] ICC: intraclass correlation coefficient.

[d] CI: Confidence interval. For ICC interval estimation, ICCs were z transformed and then converted back to the original scale

[e] Weighted κ after Cicchetti and Allison (Cicchetti & Allison, 1971).

Table III. Factors predicting unreliable reporting between run-in and baseline visits for self-reported lifetime number of female sexual partners: bivariate analyses

Variable[a]	*N*[b]	OR[c]	95% CI[d]
Age	286	1.13	1.07– 1.20
Race			
White	199	*reference*	
Black	10	4.34	1.03–18.23
Other	39	1.49	0.52–4.28
Ethnicity			
Non–Hispanic	230	*reference*	
Hispanic	55	1.23	0.47– 3.20
Marital status			
Single, never married	174	*reference*	
Married	45	1.44	0.49–4.23
Cohabitating	29	1.33	0.36–4.94
Divorced/Widowed	36	2.30	0.82–6.46
Education, years			
Less than 12	13	2.19	0.55–8.69
12–15	149	*reference*	
16 or more	126	0.43	0.17– 1.06
Gross income/month			

Table III. Factors predicting unreliable reporting between run-in and baseline visits for self-reported lifetime number of female sexual partners: bivariate analyses

Variable[a]	*N*[b]	OR[c]	95% CI[d]
Less than $1500	105	*reference*	
$1500–$3999	110	1.07	0.42–2.74
$4000 or more	31	1.14	0.29–4.51
Country of birth			
US	269	*reference*	
Other	19	0.50	0.06–3.88
Years since first sexual intercourse	285	1.12	1.07– 1.18
Lifetime number of female sexual partners	289	1.03	1.02– 1.05
Length of test-retest interval, days			
9-14	109	*reference*	
15-30	150	0.76	0.34– 1.69
31 or more	30	0.26	0.03–2.03

[a] At baseline.

[b] Numbers do not add to 334 due to refusals and missing observations.

[c] OR: odds ratio.

[d] CI: confidence interval.

Table IV. Factors predicting unreliable reporting between run-in and baseline visits for self-reported lifetime number of female sexual partners: multivariate analyses

Variable[a]	Adjusted OR[b]	95% CI[c]
Age	1.12	1.06–1.20
Education, years		
Less than 12	0.90	0.18–4.57
12–15	*reference*	
16 or more	0.33	0.13–0.88
Lifetime number of female sexual partners	1.02	1.01– 1.04

[a] At baseline.

[b] Odds ratios adjusted for other variables in the model.

[c] CI: confidence interval.

APPENDIX B – ANAL HPV PREVALENCE STUDY

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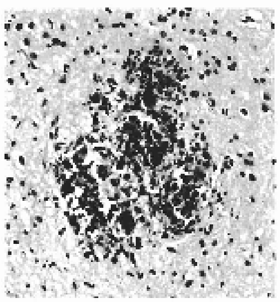

On the cover: Immunohistochemical detection of macrophages, using HAM56 [illegible], in a brain section from a simian immunodeficiency virus (SIV)–infected macaque with SIV encephalitis, demonstrating a glial nodule with macrophages, including multinucleated giant cells. (See [illegible] et al., on pp. 1695–1700.)

EDITORIAL COMMENTARY

MAJOR ARTICLES AND BRIEF REPORTS

VIRUSES

HIV/AIDS

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MAJOR ARTICLE

Prevalence of and Risk Factors for Anal Human Papillomavirus Infection in Heterosexual Men

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In US men, the incidence of anal cancer, the primary cause of which is human papillomavirus (HPV) infection, has increased almost 3-fold in 3 decades; however, little is known about the epidemiology of anal HPV infection, especially in heterosexual men. In 2 US cities, behavioral data and anal biological specimens were collected from 253 men who acknowledged having engaged in sexual intercourse with a woman during the preceding year. On the basis of DNA analysis, overall prevalence of anal HPV infection was found to be 24.8% in 222 men who acknowledged having had no prior sexual intercourse with men. Of the men with anal HPV infection, 33.3% had an oncogenic HPV type. Risk factors independently associated with anal HPV were lifetime number of female sex partners and frequency of sex with females during the preceding month. These results suggest that anal HPV infection may be common in heterosexual men.

Between 1973 and 2004, the incidence of anal cancer in US men increased from 0.5 to 1.3 per 100,000 [1]. Although human papillomavirus (HPV) is known to be the primary cause of anal cancer [2, 3], the prevalence of and the risk factors for HPV infection in heterosexual men, particularly at anal sites, have received little attention.

Two studies have reported 8% and 1.2% prevalences of anal HPV infection in asymptomatic men who did not acknowledge sex with other men [4, 5]; however, the prevalence of anal HPV can be >50% in other male populations, including heterosexual men with HIV infection [6, 7] and men who have sex with men [8]. When the penis and/or scrotum are the focus of HPV DNA testing in heterosexual men, prevalence estimates range widely, from 9% to 70%, depending on the testing method, study population, and anogenital locations of sampling [4, 5, 9–12].

Although no studies thus far have assessed factors associated with anal HPV infection in healthy heterosexual men, 2 studies of heterosexual men with anal warts and of heterosexual men with HIV infection found no risk factors associated with anal HPV infection [6, 13].

Investigations of the risk factors for genital HPV infection in men may also be important for understanding the risk factors for anal HPV infection. Such investigations have reported inconsistent results for genital HPV risk factors but include younger age, nonwhite race, Hispanic ethnicity, younger age at first sexual activity, lack of a steady sex partner, single marital status, increased frequency of sex, higher lifetime number of female sex partners and/or higher number of recent female sex partners, lack of circumcision, lack of condom use, smoking, and presence of genital warts [10, 12, 14–19]. The purpose of the present study was to assess the prevalence of and risk factors for anal HPV infection in asymptomatic men from 2 US cities who acknowledge having sex only with women.

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SUBJECTS, MATERIALS, AND METHODS

Study design and questionnaire. Study design and participant recruitment have been reported elsewhere [20, 21]. In brief, using a cross-sectional study design, we recruited men in Tucson, Arizona, and Tampa, Florida, who acknowledged having had sexual intercourse with a woman within the preceding year. Participants were 18–40 years old; had no current diagnosis of sexually transmitted disease (STD), no pain during urination, and no penile discharge; and acknowledged no history of genital warts, anal cancer, or penile cancer. Recruitment was promoted via flyers posted on college and university campuses, newspaper advertisements, radio, direct mail, and face-to-face enrollment at an STD clinic. All participants consented to the study protocol, which was approved by the human subjects–protection committees of the University of Arizona, University of South Florida, Centers for Disease Control and Prevention, and US Department of Defense.

Participants completed a self-administered 51-item written questionnaire that included questions regarding demographic characteristics, alcohol and tobacco consumption, and sexual behavior. Approximately halfway through recruitment, 11 questions dealing with same-sex sexual behavior were added to the questionnaire.

Collection of biological samples. Using a different saline-wetted Dacron swab for each anatomical site, clinicians sampled the following 6 anogenital sites from each of the men: urethra, coronal sulcus/glans penis, penile shaft (including prepuce if present), scrotum, perianal region, and lower anal canal between the anal verge and the dentate line. In addition, participants self-collected a semen sample for analysis. The urethral and semen sampling were discontinued in the third year of the study because the proportions of HPV-positive samples from these sites were much lower than those for other sites. For the 253 men who completed the expanded survey instrument, 2 clinicians completed all sampling of the men. Each clinician was trained in sampling techniques, which included instruction on how to avoid contamination of the sampling sites. The clinicians also drew blood and examined the anal region and genitals for lesions, abrasions, discharges, or other abnormalities. Lesions and warts were sampled via a wet Dacron swab, and their locations were recorded.

To preserve DNA for analyses of HPV, the clinician placed each wet Dacron swab into its own vial, along with Digene Specimen Transport Medium, and then immediately refrigerated the samples at 4°C. Samples were then transferred to a freezer at −70°C and were stored there until HPV testing was conducted.

HPV testing. All samples were analyzed for HPV DNA and β-globin, as described elsewhere [20, 21]. In brief, to identify HPV DNA, laboratory staff used the polymerase chain reaction (PCR) consensus primer system (PGMY 09/11) to amplify a fragment of the HPV L1 gene. HPV genotyping was then conducted on all samples, by use of DNA probes labeled with biotin, to detect 37 HPV types: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–56, 58, 59, 61, 62, 64, 66–73, 81–84, IS39, and CP6108. A sample was considered to be positive if either the PCR or genotyping tests detected HPV DNA. Oncogenic HPV types were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 [22]. For any of the 37 types, a sample that was found to be positive by PCR but was not found to be positive by genotyping was labeled as having "unclassified" HPV. Accuracy and possible contamination were assessed by use of nontemplate negative control samples and CaSki DNA positive control samples. β-globin positivity by genotyping was 95.5% and 90.5% at the anal canal and perianal region, respectively.

Statistical analyses. Of the total study population of 463 men, 253 participants completed the expanded questionnaire. Of these 253 men, 29 men (11.6%) acknowledged having had anal and/or oral sex with another man, and another 2 men (0.8%) either refused to answer questions about sex with men or left the questions blank. The remaining 222 men, who denied having ever had anal and/or oral sex with men, were included in the study. Tests of proportion were used to assess sociodemographic differences between the study population and the men excluded from the study.

We combined test results from the anal canal and perianal region and then created a binary-outcome variable that indicated either the presence or absence of anal HPV DNA, regardless of the presence of genital, urethral, and seminal HPV infection. The case group consisted of men with anal HPV infection (at the anal canal and/or perianal region); the comparison group consisted of men who did not have anal HPV infection but may have had such infection at a genital site or in semen. Therefore, the comparison group consisted of both men with semen or a genital site positive for HPV and men with semen or a genital site negative for HPV.

A high proportion (7.7%) of men in the study had "unclassified" infection at anal sites. To lessen the potential for misclassification, the analysis of factors associated with anal HPV infection was restricted to men with HPV infection detected by genotyping, thus reducing the study population from 222 to 198 men.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by univariate and multivariate logistic regression. Variables having statistically significant univariate associations with anal HPV infection ($P < .05$) and variables with $P < .20$ by a likelihood-ratio test were initially included in the model. Independent risk factors for anal HPV infection were identified by a backwards-elimination logistic regression with robust variances. Variables with $P > .10$ by a Wald test were individually removed until a final set of risk factors remained. Variables that previously had been rejected by the Wald test were again assessed both for significance (considered to be $P < .10$) in the final

Table 1. Characteristics of men included in the study, compared with men excluded from the study.

Characteristic	Included men (n = 222)	Excluded men (n = 241)
Age		
18–29 years	159 (71.6)	162 (67.2)
30–40 years	63 (28.4)	79 (32.8)
Race/ethnicity		
Non-Hispanic white	133 (59.9)	172 (71.4)
Hispanic	40 (18.0)	39 (16.2)
African American	22 (9.9)	7 (2.9)
Other/unknown	27 (12.2)	23 (9.5)
Marital status[a]		
Single/divorced/separated	179 (80.2)	184 (76.4)
Married/cohabitating	33 (14.9)	55 (22.8)
Age at sexual debut[a]		
<18 years	139 (63.0)	148 (64.1)
⩾18 years	81 (37.0)	83 (35.9)
Lifetime female sex partners[a]		
1–5 partners	77 (36.0)	81 (35.5)
6–10 partners	49 (22.9)	43 (18.9)
11–20 partners	42 (19.6)	63 (27.6)
⩾21 partners	46 (21.5)	41 (18.0)
Female sex partners during preceding 3 months[a]		
0–1 partners	139 (68.0)	169 (73.9)
⩾2 partners	65 (32.0)	60 (26.2)
Ever had diagnosed STD[a]		
No	167 (77.7)	187 (79.6)
Yes	48 (22.3)	48 (20.4)
Warts (reported by clinician) at any site		
Absent	213 (96.0)	232 (96.3)
Present	9 (4.1)	9 (3.7)
HIV infection[a]		
No	217 (98.6)	234 (99.2)
Yes	0 (0.0)	1 (0.4)
Don't know	3 (1.4)	1 (0.4)
Circumcision (reported by clinician)		
No	45 (20.3)	29 (12.0)
Yes	177 (79.7)	212 (88.0)
Condom use for vaginal sex during preceding 3 months[a]		
Less than half the time	102 (52.6)	119 (55.6)
At least half the time	92 (47.4)	95 (44.4)
Smoking status[a]		
Never	140 (63.9)	123 (52.3)
Former	42 (19.2)	45 (19.2)
Current	37 (16.9)	67 (28.5)
Cigarettes smoked currently[a]		
0–9 per day	205 (93.6)	199 (84.3)
⩾10 or more per day	14 (6.4)	37 (15.7)
Alcohol consumption[a]		
0–30 drinks per month	130 (60.8)	143 (62.5)
31–60 drinks per month	32 (15.0)	34 (14.9)
⩾61 drinks per month	52 (24.3)	52 (22.7)
City of residence		
Tucson	129 (58.1)	230 (95.4)
Tampa	93 (41.9)	11 (4.6)

NOTE. Data are no. (%) of subjects. STD, sexually transmitted disease.

[a] Because some observations were missing, category entries do not sum to 100%.

Table 2. Prevalence of human papillomavirus in 222 men who reported having had only heterosexual behavior.

HPV	Either or both anal sites	Anal canal	Perianal	Glans, shaft, or scrotum	Any site[a]
Any[b]	55 (24.8)	36 (16.6)	45 (21.3)	140 (63.1)	158 (71.2)
Any oncogenic[c]	13 (5.9)	12 (5.4)	9 (4.1)	70 (31.5)	80 (36.0)
Any nononcogenic[d]	29 (13.1)	20 (9.0)	24 (10.8)	93 (41.9)	104 (46.9)
Types 6 and 11	2 (0.9)	2 (0.9)	1 (0.5)	10 (4.5)	12 (5.4)
Types 16 and 18	5 (2.3)	5 (2.3)	2 (0.9)	29 (13.1)	33 (14.9)
Types 6, 11, 16, and 18	7 (3.2)	7 (3.2)	3 (1.4)	35 (15.8)	42 (18.9)
Unclassified	17 (7.7)	7 (3.2)	15 (6.8)	32 (14.4)	46 (20.7)
Oncogenic types[e]					
16	2 (0.9)	2 (0.9)	1 (0.5)	27 (12.2)	28 (12.6)
18	3 (1.4)	3 (1.4)	1 (0.5)	3 (1.4)	6 (2.7)
52	3 (1.4)	2 (0.9)	1 (0.5)	9 (4.1)	12 (5.4)
Nononcogenic types[f]					
6	2 (0.9)	2 (0.9)	1 (0.5)	10 (4.5)	12 (5.4)
11	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
69	10 (4.5)	5 (2.3)	9 (4.1)	13 (5.9)	18 (8.1)
84	3 (1.4)	3 (1.4)	1 (0.5)	25 (11.3)	27 (12.2)
CP6108	5 (2.3)	5 (2.3)	5 (2.3)	25 (11.3)	27 (12.2)

NOTE. Data are no. (%) of subjects.

[a] Includes coronal sulcus/glans, shaft, scrotum, anal canal, perianal region, urethra, and semen.
[b] Includes oncogenic, nononcogenic, and unclassified HPV.
[c] Presence of at least 1 of the 13 oncogenic types, regardless of the presence of any other HPV type.
[d] Presence of at least 1 nononcogenic type, regardless of the presence of any other HPV type.
[e] Types 31, 45, 51, 59, and 66 are not shown; each of them was detected at either one or both of the anal sites, but the prevalence was <1%. Types 33, 35, 39, 56 and 58 were not detected.
[f] Types 42, 53, 55, 61, 62, 67, 73, and 81 are not shown; each of them was detected at either one or both of the anal sites, but the prevalence was <1%. Types 11, 26, 40, 54, 64, 69–72, 82, 83, and IS39 were not detected.

model and for their potential role as confounders. Confirmed confounders were then included in the final model.

Multivariate analyses were adjusted by time of laboratory analysis because a trend of increasing prevalence was observed during the first half of the laboratory-analysis period. This trend was attributed to improvements in laboratory methods. Data were analyzed by use of Intercooled Stata (version 9.2) for Windows and SAS (version 9.1; SAS Institute, Inc.) programs.

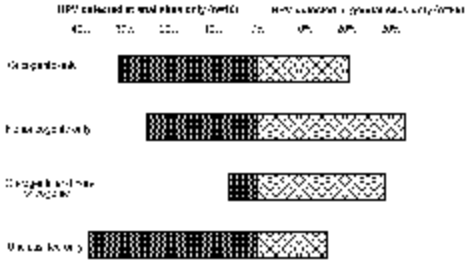

Figure 1. Distribution of human papillomavirus (HPV) in HPV-positive heterosexual men: anal sites (including perianal area and anal canal) vs. genital sites (including glans/coronal sulcus, penile shaft, and scrotum).

RESULTS

Prevalence. In table 1, sociodemographic data on the 222 men included in the study are compared with those on the 241 men who were part of the parent study but who were excluded from the study. Men were excluded if they acknowledged having had sex with men or had not been asked or had refused to answer questions about it. There were 7 factors in which the men included in the study were statistically different from the men excluded from it: city of residence, race/ethnicity, marital status, lifetime number of female sex partners, circumcision status, smoking status, and level of smoking.

Of the men included in the study, 71.6% were 18–29 years of age, 59.9% were non-Hispanic white and 18.0% were Hispanic, and most men were single, divorced, or separated (80.0%). None of the men in this group acknowledged having HIV infection. Although 9 men had visible warts or lesions at genital sites, none of the men had visible warts or lesions at anal sites. Participants reported having had sexual intercourse with a median of 1 woman during the preceding 3 months and a lifetime median of 9 women.

Table 2 presents HPV-type distribution, by anatomical site, in the 222 men included in the study. In these men, the prevalence of HPV infection at the anal canal and the perianal region was

Table 3. Factors associated with anal human papillomavirus (HPV) infection in 198 heterosexual men: univariate analyses.

	Any anal HPV genotype	
Factor	Subjects, no. (%)	OR (95% CI)
Age		
19–29 years	39 (27.9)	2.41 (1.05–5.55)
30–40 years	9 (13.9)	Reference
Race/ethnicity		
Non-Hispanic white	24 (20.7)	Reference
Hispanic	13 (33.3)	1.92 (0.86–4.28)
African American	4 (21.1)	1.02 (0.31–3.36)
Other/unknown	6 (25.0)	1.29 (0.46–3.57)
Marital status		
Single/divorced/separated	42 (26.1)	1.62 (0.59–4.54)
Married/cohabitating	5 (17.9)	Reference
Lifetime female sex partners		
1–5 partners	10 (15.9)	Reference
6–10 partners	11 (25.6)	1.92 (0.70–4.77)
11–20 partners	13 (33.3)	2.65 (1.03–6.94)
≥21 partners	11 (23.9)	1.67 (0.64–4.34)
Female sex partners during preceding 3 months		
0–1 partners	28 (23.0)	Reference
≥2 partners	14 (23.3)	1.02 (0.49–2.12)
Frequency of sex with females during preceding month		
0–1 times	5 (12.2)	Reference
2–4 times	12 (30.8)	3.20 (1.01–10.17)
5–10 times	7 (18.9)	1.68 (0.49–5.84)
≥11 times	9 (20.6)	1.96 (0.55–6.27)
Age at sexual debut		
<18 years	34 (26.2)	1.74 (0.82–3.71)
≥18 years	11 (16.9)	Reference
History of anal sex with women		
No	21 (22.6)	Reference
Yes	26 (25.0)	1.14 (0.59–2.20)
Ever had diagnosed STD		
No	35 (24.1)	Reference
Yes	11 (23.9)	0.99 (0.45–2.15)
Ever had sex with partner with diagnosed STD		
No	15 (22.4)	Reference
Yes	11 (19.0)	0.81 (0.34–1.94)
Don't know	21 (28.8)	1.40 (0.65–3.01)
Last partner was new sex partner		
No	34 (21.7)	Reference
Yes	11 (32.4)	1.73 (0.77–3.90)
Last sex was with steady partner		
No	6 (35.3)	Reference
Yes	27 (22.5)	0.53 (0.19–1.57)
Genital warts (reported by clinician)		
No	43 (22.9)	Reference
Yes	4 (44.4)	2.72 (0.70–10.56)
Genital HPV (by genotyping)		
No	12 (15.9)	Reference
Yes	35 (28.7)	2.15 (1.03–4.46)
Circumcision (reported by clinician)		
No	12 (31.6)	Reference
Yes	35 (21.9)	0.47 (0.19–1.14)

(continued)

Table 3. *(Continued)*

Factor	Any anal HPV genotype	
	Subjects, no. (%)	OR (95% CI)
Smoking status		
Never	28 (22.4)	Reference
Former	9 (25.7)	1.20 (0.50–2.85)
Current	10 (27.8)	1.33 (0.57–3.09)
Cigarettes smoked currently		
0–9 per day	41 (22.5)	Reference
≥10 per day	6 (42.9)	2.58 (0.95–7.96)
Alcohol consumption		
0–30 drinks per month	21 (19.6)	Reference
31–60 drinks per month	9 (30.0)	1.88 (0.75–4.68)
≥61 drinks per month	15 (31.3)	1.99 (0.92–4.31)
City of residence		
Tucson	24 (20.7)	Reference
Tampa	23 (29.1)	1.49 (0.77–2.89)

NOTE. The no. of men considered in the analysis was 198, because 24 men who were positive only for unclassified HPV were excluded. The case subjects ($n = 47$) include only men with oncogenic and/or nononcogenic anal HPV infection; the comparison group ($n = 151$) includes men who did not have anal HPV infection but who may have had oncogenic and/or nononcogenic HPV infection either at a genital site or in semen. CI, confidence interval; OR, odds ratio; STD, sexually transmitted disease.

16.6% ($n = 36$) and 21.3% ($n = 45$), respectively, whereas the overall prevalence of anal HPV was 24.8% ($n = 55$). Of the 55 men with anal HPV infection, 16 (29.1%) had it only at an anal site, and the remaining 39 (70.9%) had it both at an anal site and either at another anatomical site or in semen (data not shown). The prevalence of any oncogenic HPV type at an anal site was 5.9% ($n = 13$), and the prevalence of any nononcogenic type was 13.1% ($n = 29$). With regard to the anal canal specifically, 12 (33.3%) of the 36 men with HPV infection had an oncogenic HPV type; with regard to the perianal site, 9 (20.0%) of 45 men with HPV infection had an oncogenic HPV type. The most commonly detected HPV types at anal sites were types 68 and CP6108. In contrast to the prevalence of HPV infection at only an anal site, the prevalence of HPV infection at any of the 7 sites sampled was 71.2%, and the prevalence of oncogenic types was 36.0%. Of the 55 men with anal HPV infection, 65.5% ($n = 36$) had a single HPV type, whereas 34.5% ($n = 19$) had multiple HPV types, at one or both anal sites (data not shown).

Figure 1 presents the distribution of oncogenic, nononcogenic, or unclassified HPV infection in men with HPV DNA detected only at anal sites ($n = 16$) and in men with HPV DNA detected only at genital sites ($n = 95$). Of the 16 men with HPV DNA detected only at anal sites, 5 (31.3%) had only oncogenic types, whereas 6 (37.5%) had only unclassified HPV; of the 95 men with HPV only at genital sites, 20 (21.1%) had only oncogenic types, whereas 15 (15.8%) only had unclassified HPV.

A total of 25 men had an HPV genotype detected at both anal and external genital sites. These men afforded 61 opportunities to document concordance of identical HPV types at both anal and genital sites; a match of HPV types occurred only 21 times, for a 34.4% concordance between HPV types at anal and those at genital sites. Type 68 was the HPV type most commonly found at both anal and genital sites, with 6 men having it at both sites, and 1 man had 5 HPV types detected at both anal and genital sites.

Risk Factors. In univariate analyses (table 3), factors associated with anal HPV infection were younger age (OR, 2.41 [95% CI, 1.05–5.55] for men 18–29 years of age [compared with men 30–40 years of age]), a higher lifetime number of female sex partners (OR, 2.65 [95% CI, 1.03–6.84] for men with 11–20 sex partners [compared with men with 1–5 sex partners]), the frequency of sex with females during the preceding month (OR, 3.20 [95% CI, 1.01–10.17] for sex with females 2–4 times [compared with sex with females 0–1 times]), and the presence of genital HPV infection as confirmed by genotyping (OR, 2.15 [95% CI, 1.03–4.46] [compared with the absence of genital HPV infection]).

In multivariate analyses (table 4), the lifetime number of female sex partners (OR, 3.66 [95% CI, 1.06–12.62] for 11–20 female sex partners [compared with 1–5 female sex partners) and the frequency of sex with females during the preceding month (OR, 3.89 [95% CI, 1.03–14.63] for 2–4 times per month [compared with 0–1 times per month]) were independently associated with anal HPV infection. Circumcision had a marginally statistically significant and inverse association with anal HPV infection (OR, 0.34 [95% CI, 0.11–1.01]).

DISCUSSION

We believe that the present study is the largest to examine prevalence of anal HPV infection in men who do not acknowledge

Table 4. Factors associated with anal human papillomavirus (HPV) infection in 198 heterosexual men: multivariate analyses.

	Any anal HPV genotype
Factor	OR (95% CI)
Lifetime female sex partners	
1–5	Reference
6–10	1.29 (0.32– 5.30)
11–20	3.66 (1.06–12.62)
21+	2.29 (0.67–7.90)
Frequency of sex with females in last month	
0–1 times	Reference
2–4	3.89 (1.03–14.63)
5–10	1.56 (0.39–6.51)
11 or more	1.14 (0.26–5.09)
Circumcision, clinician-reported	
No	Reference
Yes	0.34 (0.11–1.01)

NOTE. The no. of men considered in the analysis was 198, because 24 men who were positive only for unclassified HPV were excluded. The case subjects ($n = 47$) include only men with oncogenic and/or nononcogenic anal HPV infection; the comparison group ($n = 151$) includes men who did not have anal HPV infection but who may have had oncogenic and/or nononcogenic HPV infection either at a genital site or in semen. The odds ratios are adjusted for alcohol consumption, date of laboratory analysis, and the remaining variables in the model. CI, confidence interval; OR, odds ratio.

oral or anal sex with other men and is the first to investigate factors associated with anal HPV infection in asymptomatic heterosexual men. The prevalence of anal HPV infection in the present study was 24.8%, which suggests that HPV may be a common anal infection in sexually active heterosexual men who have no visible anal warts or lesions. This finding parallels research indicating that anal HPV infection is also common among sexually active women [23]. Of the men with anal HPV infection, 33.3% had an oncogenic HPV type.

The prevalence of anal HPV reported in the present study may be higher than that in 2 previous studies [4, 5] because of (1) differences in sampling technique, (2) genotyping of samples regardless of PCR-based HPV results, and (3) genotyping of 37 HPV types detectable in the assay [21]. Van Doornum et al. tested 85 men from a sexually transmitted disease clinic who acknowledged sex only with women and found that 1.2% of them were positive for anal HPV infection [5]. Those investigators detected DNA by using a 4-primer PCR system that detected 5 HPV types. Nicolau et al., using hybrid capture technology that detected 18 HPV types, reported an 8% prevalence of anal-canal HPV infection in 50 Brazilian men who were heterosexual partners of women with confirmed HPV infection [4].

Given the composition of the samples in these 2 previously published studies, the present study's use of a general community sample may not help to explain the higher prevalence that it found. Also, although the prevalence of anal HPV infection can be >50% in some male populations, including heterosexual men with HIV infection [6, 7] and men who have sex with men [8], none of the men in the present study acknowledged either having HIV infection or having ever had sex with other men. It is possible that we may have misclassified some of the men's sexual behavior. Same-sex sexual behavior remains a highly socially stigmatized behavior, and some men avoid acknowledging it [24]. If we incorrectly classified bisexual men as men who only have sex with women, then the prevalence of anal HPV infection in heterosexual men may be lower. However, in the men who completed the expanded questionnaire and acknowledged ever having had oral or anal sex with another man ($n = 29$), the prevalence of anal HPV infection was comparable to that in men who did not acknowledge ever having had sex with another man (20.7% vs. 24.8%; $P = .63$). In fact, there were no statistically significant differences between these 2 groups, with the exception that men who acknowledged ever having had sex with another man were more likely to be smokers ($P = .005$). However, a limitation of the present study is that its sample size was insufficient to allow adequate evaluation of the differences between men who acknowledged ever having had sex with another man and those who did not. Future studies are necessary to fill this information gap.

The most common HPV types detected at anal sites in the 222 men included in the study were types 68 (4.5%) and CP6108 (2.3%). Neither of these types is known to have oncogenic potential [22].

The estimate of the prevalence of HPV infection includes 37 types of HPV in addition to unclassified HPV types. Compared with men with only genital HPV infection, men with only anal HPV infection had a higher proportion of unclassified HPV types (37.5% vs. 15.8%; $P = .04$). These results may be due to either different mechanisms being responsible for virus transmission or a different rate of transmission to different anatomical regions. Also, Hernandez et al. reported a higher proportion of unclassified HPV types in women with only anal HPV infection, compared with women with concurrent anal and cervical infection [23].

It is unlikely that these results are due to study-related contamination caused by inadvertent transfer of HPV DNA either from genital to anal sites or from the perianal region to the anal canal, because rigorous sampling methods were used by the study's clinicians. However, the unclassified HPV types observed in the present study may include types not thought to be sexually transmitted or may be false-positive results of PCR testing. For this reason, when we analyzed risk factors associated with anal HPV infection, we excluded men with only unclassified HPV types, thereby reducing, from 55 to 47, the number of men with anal HPV infection who were analyzed.

The risk factors that the present study found to be associated with anal HPV infection are similar to those which previous studies have found to be associated with genital HPV infection [10, 12, 16, 19, 21]. In the present study, the lifetime number of female sex partners and the frequency of sex during the preceding month were independently associated with anal HPV infection, whereas lack of circumcision was marginally associated with it. The result regarding the frequency of sex during the preceding month is noteworthy because it was limited to men who acknowledged a sex frequency of 2–4 times per month. Conversely, men who acknowledged the higher frequencies of sex—that is, 5 or more episodes—during the preceding month were not at increased risk for anal HPV infection. This finding may be spurious. Another explanation is that heterosexual men who have the most-frequent sex are more likely to be in a monogamous relationship and therefore are less likely to have exposure to HPV infection.

Finally, the data of the present study suggest the possibility that the prevalence of anal HPV infection is lower in heterosexual men in their 30s than in younger heterosexual men. Conversely, in their study of men who have sex with men, Chin-Hong et al. reported a stable age-specific prevalence of anal HPV infection [8]. If such a trend of decreasing age-specific prevalence in heterosexual men is confirmed by future studies, it could be considered to be due to a number of reasons, including a lack of persistence of anal HPV infection in older heterosexual men or a difference between the sexual behavior of younger heterosexual men and that of older heterosexual men.

There may be other, unmeasured factors that are associated with anal HPV infection, because none of the factors identified in the present study's univariate or multivariate analyses explain how HPV was transmitted to the anal region. Our questionnaire gathered data about penetrative sexual practices—specifically, vaginal, anal, and oral intercourse—implicated in HPV transmission between men and women; however, none of these behaviors seems able to transmit HPV to the anal region of a man who acknowledges having had sex only with women. Our questionnaire did not ask about other sexual behaviors, such as self-initiated or partner-initiated anal massage or anodigital insertion. It is noteworthy that one study has reported an association between nonpenetrative sex (finger-vulvar, penile-vulvar, and oral-penile) and genital HPV infection in female virgins [25]. In addition to sexual behaviors involving the perianal region or anal canal, nonsexual behaviors may also help explain the prevalence of anal HPV infection in heterosexual men. Three studies hint at nonsexual HPV transmission via hand carriage [26, 27] and objects [28].

If HPV DNA can be transmitted by fingers or objects, then self-transference from the penis or scrotum to the perianal region or anal canal may occur as a result of sexual or nonsexual behaviors. This explanation requires that male genital infection be included in the causal pathway between the risk factors that we measured and anal HPV infection. Accordingly, it is possible that the present study identified risk factors associated with genital, in addition to anal, HPV infection. Indeed, in univariate analysis, the presence of genital HPV DNA and the presence of anal HPV DNA were associated in these men; however, type-specific concordance between genital and anal HPV infection was limited.

Additional limitations to the present study include its sample size. It did not have sufficient power to detect risk factors for HPV infection at specific anatomical sites, such as the perianal region or the anal canal. Another limitation is that it is possible that detection of HPV DNA on the skin surface might occur in the absence of viral infection of the basal layer of the epithelium.

The subsample of men included in the study differed from the men excluded, with regard to the following 7 factors: city of residence, race/ethnicity, marital status, lifetime number of female sex partners, circumcision, smoking status, and level of smoking. Because recruitment occurred in Tampa and Tucson, variation in geography and/or recruitment practices may explain some differences in these variables [29, 30]. However, the prevalence (22.8%) of anal HPV infection in the excluded men was comparable to that in the included men, a finding that makes it less likely that exclusionary characteristics affected the results.

To our knowledge, the present study is an important first examination of prevalence anal HPV infection in a community sample of healthy heterosexual men. We do not believe that its data should be used, at this time, the basis for a change in clinical practice; however, further research that characterizes anal HPV infection in other populations of men who acknowledge sex only with women is necessary. We believe that the present study is also the first examination to assess risk factors for anal HPV infection in healthy heterosexual men. However, a clear understanding of the full complement of risk factors for anal HPV infection in heterosexual men will require more study. Future studies should collect sexual- and nonsexual-exposure information that may clarify routes of transmission to the perianal region and anal canal. Finally, it is important to assess factors associated with persistent oncogenic anal infection in prospective cohort studies of both younger and older men.

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APPENDIX C – HIM RELIABILITY STUDY

Running head: Test-retest reliability of a sexual behavior interview for men in three countries

The test-retest reliability of a sexual behavior interview for men residing in Brazil, Mexico, and the United States: The HIM study

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Abstract

The collection of sexual behavior data is central to the development of prevention strategies for sexually transmitted diseases. To create efficiencies in prevention programs, it may be helpful to gather sexual behavior data from cross-national populations; however, the reliability and validity of cross-national sexual behavior surveys using computer-assisted self-interview (CASI) methods is unknown. We completed a test-retest reliability study with 1069 men in Brazil, Mexico, and the United States who had completed the same 88-item sexual behavior CASI approximately three weeks apart. Refusal rates, kappa coefficients, and intraclass correlation coefficients (ICC) were calculated for the full sample, by country, by age, and by lifetime number of female sexual partners. The rate of refused questions in each country was, in general, very low with the lowest rate in Mexico and the highest in Brazil. κ reliability coefficients for each study site and the combined sample were substantial ($\kappa = 0.61 – 0.80$) or almost perfect ($\kappa \geq 0.81$) for all questions. Likewise, ICC scores for the Mexico site, the US site, and the combined sample were $\geq .61$ for all questions. Three questions asking for the number of sexual partners had lower reliability in Brazil: the lifetime number of male anal sex partners (ICC = 0.50), the number of different female sexual partners in the past three months (ICC = 0.58), and the number of sexual partners in the past three months other than a 'steady' sexual partner (ICC = 0.10); however, the Brazil ICC for each of these questions increased to ≥ 0.79 when a small number (≤ 2) of outlying observations were removed. With few exceptions, we found high test-retest reliability with a sexual behavior CASI used in three culturally and linguistically distinct countries.

As part of prevention efforts to fight HIV, the Global Programme on AIDS of the United Nations (UNAIDS) recognizes the importance of sexual behavior data collection from diverse communities at risk for HIV (1). Likewise, understanding the natural history of human papillomavirus (HPV) infection and related disease in men requires the collection of sexual behavior data from men; however, assessing these behaviors with one common instrument across multiple countries may pose a threat to data quality (2) because the reliability and validity of sexual behavior data collected across cultures are impacted not only by diverse population characteristics, but also by the survey method and the demands it places on the participant (3, 4, 5).

While validating human behavioral surveys, including sexual behavior surveys, is difficult, test-retest studies can be used to assess their reliability. These studies assess the consistency of participant responses over two time periods (6). High consistency does not ensure validity of data but low consistency can highlight potentially invalid data (4). In other words, reliability is necessary for validity, but not sufficient (7).

CASI methods, including its audio version, audio-CASI, have been found to elicit higher quality data for sensitive sexual behaviors than either face-to-face interviews or paper and pencil self-administered questionnaires (8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20). CASI may also allow for more efficient cross-national collection of sexual behavior data since the method has been found cost-effective when used with larger sample sizes or when used for repeated studies (21); however, a number of studies have found that CASI methods may yield lower quality data in some situations, including those more likely to occur in cross-national studies (11, 22, 23, 24, 25, 26, 27, 28, 29).

For example, computer-assisted methods may elicit fewer sensitive sexual and drug use behaviors depending upon a participant's age, race, ethnicity, language ability, or familiarity with computers (11, 28, 29). Also, while CASI and audio-CASI generally produce lower rates of item non-response (23, 24), they may generate higher item refusal rates than other survey methods in some settings like sexually transmitted disease (STD) clinics (10).

To our knowledge, no cross-national test-retest reliability studies have been completed with CASI. Three studies have assessed the test-retest reliability of a sexual behavior audio-CASI with adults (24, 30, 31) but none of the studies assessed the reliability of the survey method in the context of cross-national populations. In addition, two of these three studies report composite reliability coefficients instead of question-specific coefficients (30, 31); however, composite coefficients obscure measurement error associated with data collected for specific sexual behaviors (6) and also reduce the ability to change or delete specific items that demonstrate less than adequate reliability.

The HPV in Men (HIM) Study is a cross-national epidemiological study that collects sexual behavior data from men in three countries: Brazil, Mexico, and the US. The objective of the current study was to assess test-retest reliability and item-refusal rates for a non-audio computer-assisted self-interview used in the HIM Study. The interview collected sexual health history and sexual behavior information from men recruited from three distinct target populations in three countries.

MATERIALS AND METHODS

Study Population

Men were recruited in Mexico (Cuernavaca), Brazil (São Paulo), and the US (Tampa) beginning in March, 2005 for a cohort study of the natural history of anogenital human papillomavirus. Men were enrolled if they were between the ages of 18 and 70 years; resided in the targeted recruitment areas; had no prior anal cancer, penile cancer or genital warts; no current STD diagnosis including HIV; no history of imprisonment, homelessness, or drug treatment in the prior six months; and were willing to comply with visits every six months for four years. Details of the study design and population have been previously described (32, 33).

Men were recruited in a different manner at each study site. In Mexico, men were recruited through the largest health plan in Morelos state in Mexico. In Brazil, men were recruited from the largest clinic in São Paulo that tests for HIV and STDs. In the US, men were recruited from a large university campus and the general community. Participants received a nominal monetary incentive to join the study. All enrolled participants consented to the HIM Study protocol which was approved by human subjects protection committees of the University of South Florida, National Institute of Public Health of Mexico, and the Ludwig Institute for Cancer Research, Brazil.

The first 1069 men to complete their run-in and baseline visits using the CASI were the participants in the current test-retest reliability study. They had a mean age of 31.5 years (SD = 10.5); however, age varied by study site with the median age of participants in Brazil and Mexico (33 years for both countries) higher than participants recruited in

the US (23 years). As expected, the racial and ethnic characteristics of the sample also varied by study site. Overall, approximately one-half of the sample reported a non-white race (50.8%) while 41.4% reported a Hispanic ethnicity. Also noteworthy is that Brazil participants reported a higher median number of female sexual partners during the lifetime (10 partners) than the participants in Mexico (5 partners) or the US (6 partners). Other population characteristics are provided in Table 1.

Procedure

Men expressing interest in participating in the study received an appointment to come to the clinic for a first visit. At this run-in visit, men who consented to the research protocol experienced all of its aspects to help them determine if they wanted to remain in the longitudinal study which would require their participation for an additional four years. Specifically, after receiving instruction, participants completed a computer-assisted self-interview and then were sampled at anogenital sites for HPV. The CASI was written in the primary language of the region and elicited information about participant demographics, substance use, sexual health history, and sexual behaviors implicated in the transmission of HPV. Men were then scheduled for a follow-up visit which was completed approximately three weeks later (median = 21 days) at which time they again completed the CASI. There was a lack of congruity in the median time between test-retest interviews across study sites with a median interval of 21, 25, and 16 days for Brazil, Mexico, and the US, respectively. A Kruskal-Wallis test confirmed a statistically significant difference in test-retest interval by site ($X^2 = 315.5$, $df = 2$, $p < .0001$). Men

did not receive their first HPV test results until six months later at the subsequent clinical visit.

Interview measures

The interview contained 88 items with eight demographic questions, eight alcohol use questions, nine tobacco use questions, 18 sexual health history questions, and 45 sexual behavior questions. The majority of the questions had previously been administered in a paper and pencil format with US men and generally were found to have excellent reliability (34).

Participants' sexual health was assessed with questions about their history of STD infections, the existence of a current sexual partner, and circumcision status. Participants were also asked about the sexual health history of their partners. The sexual behavior items assessed incidence and frequency of penetrative sexual behaviors (vaginal, anal, and oral sex) with women and men; age at first intercourse; number of female and male partners; frequency of condom use for vaginal and anal sex; incidence and frequency of sex with 'steady' and casual partners; time since last vaginal sex and anal sex; and history of paying for sex. Participants were asked to recall the frequency of sexual intercourse and number of partners for varying periods of time including the last month, the last three months, and lifetime. The sexual behavior items include questions that parallel the core indicators recommended by UNAIDS for monitoring a population's risk profile for HIV (35).

Data analysis

A subset of items from the interview was selected for assessment of reliability with preference given to items where reliability coefficients would not be biased by the test-retest interval. For example, while the interview required recall of behaviors over several time periods, items with only a one-month recall period were not assessed because the time interval between test and retest (M = 21 days) would lead the participant to recall sexual behavior for largely different time periods. A total of 38 variables were assessed including 25 categorical, four ordinal, and nine discrete variables. Variables assessed included 14 sexual health history variables and 24 sexual behavior variables. Refusal rates for each interview item were calculated. A refusal was defined as the choice of the refusal option on any particular item.

For each interview item, reliability coefficients were calculated for each of the three study sites and for the combined sample. Combined sample coefficients were calculated by averaging study site coefficients after weighting by the inverse of the variance. Reliability coefficients were also calculated for each item by age (< 30 years vs ≥ 30 years) and by lifetime number of female sexual partners (≤ the median of seven partners vs > seven).

For categorical variables, κ was calculated. Unlike percent agreement, κ identifies the level of agreement after correcting for chance agreement (36). Benchmarks for interpreting κ values followed Landis and Koch (37): poor, $\kappa < 0.00$; slight, $\kappa = 0.00 – 0.20$; fair, $\kappa = 0.21 – 0.40$; moderate, $\kappa = 0.41 – 0.60$; substantial, $\kappa = 0.61 – 0.80$; and, almost perfect, $\kappa \geq 0.81$. Because the κ statistic can be unstable in situations where there

are sparse data (38), κ was not computed for variables where the number of cases or non-cases was less than five (4).

For ordinal variables a weighted κ statistic was calculated (39) in order to distinguish between levels of disagreement. For instance, in responding to a question about the frequency of condom use with five possible responses, if a subject chooses the adjacent categories of "more than half the time" and "half the time" on run-in and baseline, respectively, simple κ will identify zero agreement between the two responses; however, weighted κ will give credit for the partial agreement.

Discrete variables were assessed using the ICC (40). All ICCs created using non-normal variables were transformed using Fisher's z transformation before calculating confidence intervals (41). Confidence intervals were then transformed back to the original scale. ICCs approaching 1.0 indicate high test-retest reliability.

Outliers in the bivariate distributions of each discrete variable were assessed using scatter plots. During exploratory analysis, extreme outliers were identified in two variables: number of different female sexual partners in the past three months, a value of 11,111,109,632 on both run-in and baseline; and age at first sexual intercourse with women, a value of 1993 on run-in. Each was removed before ICCs were calculated for these variables. A small number of other extreme values, while improbable, were retained and assessed for their influence on ICCs

RESULTS

With exceptions for skip patterns, participants at each study site answered virtually all of the 38 questions under study. For example, 19 variables, including all sexual health history variables, had study site-specific and combined sample refusal rates of under 1% (data not shown). For the combined sample, refusal rates for sexual behavior questions (e.g., vaginal sex, oral sex, and age at first sexual intercourse) were generally 5.0% or lower except for lifetime number of female sexual partners (6.0% on test and retest, respectively) and frequency of condom use for paid vaginal or anal intercourse (11.8% on both run-in and baseline) (Table 2).

When refusal rates were averaged by study site, Mexico participants were the least likely to refuse to answer questions (1.0% on both run-in and baseline) and Brazil participants were the most likely to refuse to answer (2.4% and 2.5% on run-in and baseline, respectively) (data not shown). For example, on the baseline questionnaire, 12.6% of Brazilian men refused to report their lifetime number of female sexual partners compared with 1.9% of Mexican men, and 4.0% of US men. Brazilian participants had higher refusal rates than either Mexican or US participants for 14 of the 19 sexual behavior variables in Table 2.

κ and weighted κ reliability coefficients for each study site and the combined sample were almost perfect ($\kappa \geq 0.81$) or substantial ($\kappa = 0.61 - 0.80$) for all questions (Table 3). The categorical questions with lower, but still substantial, κ coefficients, asked men if they had ever been diagnosed with HIV and if they had ever paid a man for sex ($\kappa = 0.68$ for both questions in the combined sample). Stable κ and weighted κ statistics for two

variables (ever diagnosed with syphilis and the frequency of condom use for paid vaginal or anal sex) could not be calculated for any of the three study sites because there were too few cases or non-cases.

Combined sample, Mexico, and US ICC scores for all discrete variables were ≥ 0.86 except for the Mexico ICC for number of sex partners other than the 'steady' partner (ICC = 0.61). ICC scores in Brazil dropped for three items asking men to report their number of sexual partners; specifically, the items asked for the lifetime number of male anal sex partners (ICC = 0.50), the number of different female sexual partners in the past three months (ICC = 0.58), and the number of sexual partners in the past three months other than a 'steady' sexual partner (ICC = 0.10). Scatter plots identified a small number of extreme outliers in the bivariate distributions of all three variables. For lifetime number of male anal sex partners, one outlier was identified in the Brazil scatter plot. When this participant was removed from the data set, the ICC for Brazil increased from 0.50 (n = 94) to 0.99 (n = 93). For the variable number of different female sexual partners in the past three months, one outlier was identified that, when removed, resulted in the Brazil ICC increasing from 0.58 to 0.92. For the variable number of sexual partners in the past three months other than a 'steady' partner, one outlier was identified in the Mexico scatter plot while two outliers were identified in the Brazil scatter plot. When the one outlying participant in the Mexico sample was removed, the Mexico ICC increased from 0.61 to 0.84. When the two outlying participants in the Brazil sample were removed, the Brazil ICC increased from 0.10 to 0.79.

When κ and weighted κ coefficients were calculated by age (< 30 years vs ≥ 30 years), all categorical and ordinal items had substantial or almost perfect reliability regardless of age (Table 4). All discrete variables had ICC scores ≥ 0.85 with the exception of the same three discrete variables discussed above: the lifetime number of male anal sex partners (ICC = 0.50 for an age ≥ 30 years), the number of different female sexual partners in the past three months (ICC = 0.60 for an age ≥ 30 years), and the number of sexual partners in the past three months other than a 'steady' sexual partner (ICC = 0.12 for an age ≥ 30 years). In these three variables, the lower reliability was traced to the same outliers identified above who were all participants aged 32 and 44 years.

Reliability coefficients were also calculated by lifetime number of female sexual partners (Table 4). Men who had both above and below the median number of seven partners had substantial or almost perfect reliability coefficients for all categorical and ordinal variables except two: ever had vaginal, anal or oral sex (κ = 0.39 for > seven partners); and ever paid a man for sex (κ = 0.54 for ≤ seven partners). Two discrete variables also showed lower reliability: lifetime number of male anal sex partners (ICC = 0.50 for ≤ seven partners) and number of sex partners other than a 'steady' sexual partner (ICC = 0.29 for > seven partners). Removal of a small number of outliers again increased the ICC of these two discrete variables to ≥ 0.85.

DISCUSSION

In this test-retest reliability study, 1069 men in Brazil, Mexico and the US were asked the same sexual health history and sexual behavior questions at run-in and baseline study visits using CASI. For each study site and the three study sites combined, reliability coefficients for all categorical and ordinal questions were substantial (0.61 – 0.80) or almost perfect (≥ 0.81). However, while the combined sample ICC scores of all discrete variables were ≥ 0.85, the study site-specific reliability of three discrete variables were of concern: the lifetime number of male anal sex partners (ICC = 0.50 for Brazil), the number of different female partners in the past three months (ICC = 0.58 for Brazil), and the number of sex partners in the past three months other than a 'steady' partner (ICC = 0.10 for Brazil and 0.61 for Mexico).

The poorer reliability in these variables is due to the presence of outliers identified in scatter plots. For lifetime number of male anal sex partners and number of different female sexual partners in the past three months, an extreme outlier in each variable was identified in the Brazil sample. When these observations were removed, the Brazilian ICC of each of these variables increased to ≥ 0.92. For the third discrete variable, number of sex partners in the past three months other than a 'steady' partner, three outliers were identified: two in Brazil and one in Mexico. When these observations were removed, the ICC increased from 0.10 to 0.79 for Brazil and from 0.61 to 0.84 for Mexico.

The influence of the four participants responsible for these outliers (three in Brazil and one in Mexico) was also apparent when reliability coefficients were stratified for men < 30 years old and those ≥ 30 years old. These outlying participants were all older

than age 30 years. Therefore, while reliability coefficients for all questions completed by the younger men were ≥ 0.71, older men's reliability suffered for the same three discrete variables discussed above: lifetime number of male anal sex partners (ICC = 0.50), the number of different female partners in the past three months (ICC = 0.60), and the number of sex partners in the past three months other than a 'steady' partner (ICC = 0.12). When the four outlying participants were once again removed, the ICC of the three variables increased to ≥ 0.89.

When stratified by the median lifetime number of female sexual partners, these outliers also distorted the reliability coefficients for two discrete variables: lifetime number of male anal sex partners (ICC = 0.50 for men with ≤ 7 female sexual partners) and number of sex partners in the past three months other than a 'steady' partner (ICC = 0.29 for men with > 7 female sexual partners). After removal of the same Brazilian outlier identified above in the variable for lifetime number of male anal sex partners, the ICC score increased from 0.50 to 0.99. After removing the same three outliers identified above (two Brazilian and one Mexican) for number of sex partners in the past three months other than a 'steady' partner, the ICC increased from 0.29 to 0.85.

During subsequent calculation of reliability coefficients stratified by the median lifetime number of female sexual partners, lower reliability was also identified in two categorical variables: ever had vaginal, anal, or oral sex (κ = 0.39 for men with > seven partners) and ever paid a man for sex (κ = 0.54 for men with ≤ seven partners). For the first variable, ever had vaginal, anal, or oral sex, seven of 441 men with greater than the median number of sexual partners reported at run-in that they had *never* had anal,

vaginal, or oral sex. In addition to inviting concern about validity, this small number of cases may have contributed to instability in the κ coefficient. Likewise, for the second variable, only six men at baseline with fewer than seven partners acknowledged ever paying a man for sex, possibly lending instability to the κ coefficient. During the design of this study, we were aware that a small number of cases could create instability in the κ coefficient; therefore, we decided to not report coefficients where the number of cases or non-cases was less than five. Future investigations may wish to consider increasing this minimum requirement for number of cases or non-cases.

The existence of outliers and variable levels with sparse data in this study could have occurred for a variety of reasons. First, a conspicuous difference in answers on test and retest for number of sex partners may have occurred because the true number of partners was different at test and retest (6). It was also possible that sparse data for reporting certain sex behaviors was a result of cultural stigmatization attached to these behaviors (3), for example, paying a man for sex. Or, the sparse data may simply reflect a lack of behavioral heterogeneity in the population.

Lower reliability scores for Brazil on some questions may have occurred if this cross-national instrument was less culturally competent for Brazil vs Mexico or the US. Indeed, the questionnaire from which the current study's CASI was created was developed in the Southwest US near the Mexican border. It is possible that the genesis of the questionnaire in this region lent itself to an instrument that was somewhat more culturally competent with US and Mexican participants and less so with Brazilian participants. Lower reliability in Brazil could also have been the result of different levels of exposure to

computer technology. Not only was there a higher median age in Brazil, but also a higher percentage of Brazil participants were over the age of 45 years compared with Mexico and the US (14.8%, 6.1%, and 7.7% respectively). It is possible these older men in Brazil had less exposure to computers which may have led to less comfort with the technology and therefore may have promoted increased reporting errors (11, 22, 27).

Reliability may also have been affected by the number of days between test and retest. The US study site had the lowest median interval (16 days) while the Mexican men had the highest median interval (25 days); however, this potential cause for different reliability by site seems unlikely because reliability coefficients for the Mexican men were, in general, comparable to the US men. Also, reliability coefficients for discrete variables showed no declining pattern as the number of days between test and retest increased (data not shown). A large test-retest interval also does not seem responsible for the extremely discrepant outliers discussed above since each of these four participants had test-retest intervals of ≤ 22 days.

However, even with the above potential threats to reliability noted, it is important to remember that, absent the small number of extreme outliers and presence of sparse data in two questions, virtually all coefficients indicate the HIM Study instrument reported these men's sexual behavior in a highly reliable manner. This result with a CASI instrument may be due, in part, to the fact that in all countries, participants were primarily educated men living in an urban setting. In collecting data on abortions from Mexican women, Lara, et al. found audio-CASI more appropriate for urban and educated participants than for rural residents in Mexico (22). Our findings are also in accord with

two studies of audio-CASI in Brazil. Simões and colleagues compared audio-CASI with a face-to-face interview and found that audio-CASI was not only acceptable to men recruited at a health clinic, but that it also elicited more reports of sensitive sexual behaviors (18, 42).

To our knowledge, no studies have reported test-retest reliability for a sexual behavior survey delivered with CASI; however, three reliability studies with adults have reported results for audio-CASI (24, 30, 31). For a variety of reasons, these studies are difficult to compare with the current study. First, the published studies use a different survey method. Also, the shorter test-retest interval for two of the published studies (three days or less) (24, 30) invites concern about participants recalling answers from the initial interview; however such explanations have been disputed as a significant source of bias (43). In addition, unlike the three audio-CASI studies, the current study recruited men from a variety of community settings in three countries. Finally, it is difficult to compare two of these studies' composite measures of reliability (30, 31) with the item-specific coefficients of the current study.

We are aware of one other cross-national test-retest reliability study of sexual behavior measures. Schlect, et al. assessed the reliability of data collected in face-to-face interviews and by self-administered questionnaires using a pooled dataset from six studies (44). That study found women in diverse cultures could report age at first sexual intercourse with high reliability (ICC = 0.68 – 0.97); however, reliability suffered substantially, and differed considerably by study site, when the women reported their lifetime number of sexual partners (ICC = 0.08 – 0.94). In contrast, the current study

found almost perfect reliability for this question across all three study sites. These heterogeneous results may be due to important methodological differences between the two studies. Schlect, et al. assessed the reliability of separate and distinct studies that not only had different survey methods and study protocols, but also different and lengthy test-retest intervals (six weeks to five years). The current study then may be more suited for a comparison of cross-national reliability since each study site used identical protocols with relatively similar test-retest intervals. Of course, differences in the reliability findings of the two studies may also be due to the different survey methods being assessed (CASI vs. face-to-face interview or self-administered questionnaire).

Refusal rates were generally low which has been found previously with surveys of human sexuality (23, 45). All sexual health history questions had refusal rates less than 1% while overall refusal rates for some sexual behavior items were higher. Lifetime number of female sexual partners was refused by 4.0% of US respondents on test and retest. This rate is comparable to the 6.1% refusal rate reported in the US for the General Social Survey of the National Opinion Research Center for the number of sexual partners in the last 12 months (46). In contrast, the Brazilian men's rate of refusal for this question was 11.7% and 12.6% on run-in and baseline, respectively. The difference between US and Brazilian men may be due to the targeted recruitment for Brazilian men in a clinic setting vs US men at a university. Higher refusal rates from participants using audio-CASI in an STD clinic compared with a face-to-face interview have been reported previously (10). Also, a 2006 Brazilian study noted higher refusal rates for audio-CASI in a health facility in Rio de Janeiro. The authors speculated that study participants had an

expectation of more personal service in a health facility and therefore were more likely to refuse questions posed by a computer (42).

Higher refusal rates (11.8% on both run-in and baseline) also occurred for a question asking about the frequency of condom use for paid vaginal or anal sex; however, these proportions may be misleading since only 17 participants in the study answered this question (primarily because of skip patterns). Also noteworthy is that items requiring the participant to provide a numeral, as opposed to a nominal answer, were approximately twice as likely to be refused in Brazil and Mexico compared to the US where numerical items and nominal items were refused at about the same rate (data not shown).

This study has limitations. Reliability cannot be used as a surrogate measure for validity since item reliability is not sufficient for validity. Also, due to the targeted recruitment in each country, the results should not be generalized to the rest of the population in each country.

Comparisons of sexual behavior by country may be helpful for programs that attempt to deliver large scale prevention programs for STDs; however, if sexual behavior measures are to be used cross-nationally, then the measures should produce reliable data for each locale (2). With few exceptions, we found very high reliability using the same computer-assisted self-interview instrument in three culturally and linguistically different countries. While not guaranteeing validity, these results indicate that, for the current instrument, data collection with CASI from men in diverse settings may result in reliable sexual behavior data for most questions.

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Table 1. Characteristics of study participants at baseline

Variable	Brazil (n=338)		Mexico (*n*=327)		United States (*n*=404)		Combined sample (*n*=1069)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Age, years								
18-19	11	(3.3)	14	(4.3)	93	(23.0)	118	(11.0)
20-24	51	(15.1)	48	(14.7)	153	(37.9)	252	(23.6)
25-29	63	(18.6)	70	(21.4)	41	(10.2)	174	(16.3)
30-34	71	(21.0)	65	(19.9)	30	(7.4)	166	(15.5)
35-39	44	(13.0)	56	(17.1)	34	(8.4)	134	(12.5)
40-44	50	(14.8)	60	(18.4)	26	(6.4)	136	(12.7)
45-70	48	(14.2)	14	(4.3)	27	(6.7)	89	(8.3)
Refuse†	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Median	33		33		23		30	
Race								
White	207	(61.2)	15	(4.6)	296	(73.3)	518	(48.5)
Black	101	(29.9)	0	(0.0)	53	(13.1)	154	(14.4)
Asian/Pacific Islander	3	(0.9)	0	(0.0)	22	(5.5)	25	(2.3)
American Indian	20	(5.9)	0	(0.0)	0	(0.0)	20	(1.9)
Mixed/other	0	(0.0)	311	(95.1)	33	(8.2)	344	(32.2)
Refuse	7	(2.1)	1	(0.3)	0	(0.0)	8	(0.8)

Table 1. Characteristics of study participants at baseline

Variable	Brazil (n=338)		Mexico (*n*=327)		United States (*n*=404)		Combined sample (*n*=1069)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Ethnicity								
Hispanic	63	(18.6)	327	(100.0)	52	(12.9)	442	(41.4)
Non-Hispanic	265	(78.4)	0	(0.0)	351	(86.9)	616	(57.6)
Refuse	10	(3.0)	0	(0.0)	1	(0.3)	11	(1.0)
Marital status								
Single, never married	148	(43.8)	87	(26.6)	294	(72.8)	529	(49.5)
Married	99	(29.3)	186	(56.9)	58	(14.4)	343	(32.1)
Cohabitating	59	(17.5)	36	(11.0)	19	(4.7)	114	(10.7)
Divorced/widowed	31	(9.2)	18	(5.5)	31	(7.7)	80	(7.5)
Refuse	1	(0.3)	0	(0.0)	2	(0.5)	3	(0.3)
Education, years‡								
Less than 12	82	(24.9)	112	(34.3)	3	(0.7)	197	(18.6)
12	14	(4.2)	77	(23.6)	57	(14.1)	148	(14.0)
13-16	194	(58.8)	123	(37.6)	306	(75.7)	623	(58.7)
17 or more	40	(12.1)	14	(4.3)	36	(8.9)	90	(8.5)
Refuse	0	(0.0)	1	(0.3)	2	(0.5)	3	(0.3)
Age at first sexual intercourse‡								

Table 1. Characteristics of study participants at baseline

Variable	Brazil (n=338)		Mexico (*n*=327)		United States (*n*=404)		Combined sample (*n*=1069)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
< 15	93	(30.7)	32	(10.6)	54	(14.1)	179	(18.1)
15-17	137	(45.2)	129	(42.9)	189	(49.4)	455	(46.1)
18-19	42	(13.9)	71	(23.6)	92	(24.0)	205	(20.8)
20-42	24	(7.9)	68	(22.6)	38	(9.9)	130	(13.2)
Refuse	7	(2.3)	1	(0.3)	10	(2.6)	18	(1.8)
Median	16		17		17		17	
Lifetime no. of female sexual partners‡								
0	23	(7.1)	23	(7.1)	19	(4.8)	65	(6.2)
1	23	(7.1)	22	(6.8)	45	(11.3)	90	(8.6)
2-9	92	(28.3)	191	(59.1)	174	(43.8)	457	(43.7)
10-19	50	(15.4)	41	(12.7)	58	(14.6)	149	(14.3)
20-49	72	(22.2)	35	(10.8)	58	(14.6)	165	(15.8)
50-1,000	24	(7.4)	5	(1.6)	27	(6.8)	56	(5.4)
Refuse	41	(12.6)	6	(1.9)	16	(4.0)	63	(6.0)
Median	10		5		6		6	
Ever had sex with a man‡								

Table 1. Characteristics of study participants at baseline

Variable	Brazil (n=338)		Mexico (*n*=327)		United States (*n*=404)		Combined sample (*n*=1069)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Yes	110	(34.5)	39	(12.8)	42	(10.7)	191	(18.8)
No	204	(63.8)	266	(87.2)	348	(89.0)	818	(80.5)
Refuse	6	(1.9)	0	(0.0)	1	(0.3)	7	(0.7)

† Refuse is defined as participants who chose the refuse option for a specific question.

‡ Numbers do not add to 1069 due to missing observations.

Table 2. Number of participants who refused to answer each sexual behavior interview item (%)†

Interview item	Brazil				Mexico				United States				Combined sample			
	run-in		baseline		run-in		baseline		run-in		baseline		run-in		baseline	
Sexual behavior, lifetime																
Ever had vaginal, anal, or oral sex	7	(2.1)	7	(2.1)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	8	(0.8)	8	(0.8)
Ever had oral sex	7	(2.2)	7	(2.2)	3	(0.1)	1	(0.3)	1	(0.3)	1	(0.3)	11	(1.1)	9	(0.9)
Ever had sex with a man	5	(1.6)	6	(1.9)	2	(0.7)	0	(0.0)	1	(0.3)	1	(0.3)	8	(0.8)	7	(0.7)
Ever had oral sex with a man	7	(5.6)	4	(3.2)	1	(2.1)	1	(2.1)	1	(2.1)	1	(2.1)	9	(4.1)	6	(2.7)
Ever had anal sex with a man	5	(4.0)	4	(3.2)	1	(2.1)	2	(4.2)	1	(2.1)	0	(0.0)	7	(3.2)	6	(2.7)
Ever paid a woman for sex	1	(3.3)	1	(3.3)	0	(0.0)	0	(0.0)	2	(7.7)	2	(7.7)	3	(3.6)	3	(3.6)
Ever paid a man for sex	2	(1.6)	2	(1.6)	1	(2.1)	1	(2.1)	1	(2.1)	0	(0.0)	4	(1.8)	3	(1.4)
Age at first sexual intercourse with women	4	(1.2)	7	(2.1)	3	(0.9)	1	(0.3)	12	(3.0)	10	(2.5)	19	(1.8)	18	(1.7)
Lifetime no. of female sexual partners	38	(11.2)	41	(12.6)	9	(2.8)	6	(1.9)	16	(4.0)	16	(4.0)	63	(6.0)	63	(6.0)
Lifetime no. of male anal sex partners	6	(1.8)	10	(3.0)	0	(0.0)	0	(0.0)	1	(0.3)	3	(0.7)	7	(0.7)	13	(1.2)
Sexual behavior, past three months																
Freq. of sexual intercourse with women	33	(9.8)	32	(9.5)	9	(2.8)	9	(2.8)	12	(3.0)	11	(2.7)	54	(5.1)	52	(4.9)
No. of different female sexual partners	17	(5.0)	17	(5.0)	5	(1.5)	7	(2.1)	2	(0.5)	2	(0.5)	24	(2.3)	26	(2.4)

Table 2. Number of participants who refused to answer each sexual behavior interview item (%)†

Interview item	Brazil				Mexico				United States				Combined sample			
	run-in		baseline		run-in		baseline		run-in		baseline		run-in		baseline	
No. of new female sexual partners	29	(8.6)	31	(9.2)	12	(3.7)	11	(3.4)	5	(1.2)	8	(2.0)	46	(4.3)	50	(4.7)
No. of sex partners other than ‘steady’ partner	6	(1.8)	7	(2.1)	0	(0.0)	1	(0.3)	2	(0.5)	3	(0.7)	8	(0.8)	11	(1.0)
Sex with someone other than ‘steady’ partner	3	(1.2)	3	(1.1)	1	(0.4)	1	(0.4)	0	(0.0)	1	(0.4)	4	(0.5)	5	(0.6)
Freq. of condom use for vaginal sex	6	(2.0)	5	(1.6)	3	(1.0)	3	(1.0)	3	(0.8)	2	(0.5)	12	(1.2)	10	(1.0)
Freq. of condom use for anal sex	8	(3.3)	6	(2.5)	6	(3.2)	6	(3.2)	3	(1.6)	4	(2.1)	17	(2.8)	16	(2.6)
Freq. of condom use with other partners	6	(4.9)	6	(5.0)	2	(2.3)	3	(3.5)	1	(1.2)	1	(1.2)	9	(3.1)	10	(3.4)
Freq. of condom use for paid anal/vaginal sex	1	(14.3)	1	(14.3)	0	(0.0)	0	(0.0)	1	(20.0)	1	(20.0)	2	(11.8)	2	(11.8)

† Nineteen variables are omitted from the table because each study site refusal rate was less than 1%.

Table 3. Kappa and intraclass correlation coefficients for 36 interview items by study site

Interview item	Brazil			Mexico			United States			Combined sample|		
	No.†	κ* or ICC*	95% CI*§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§
Sexual health history												
Ever diagnosed with an STD*	336	0.84	0.81, 0.87	327	0.80	0.76, 0.84	404	0.89	0.87, 0.91	1067	0.85	0.83, 0.87
Ever diagnosed with Chlamydia	338	0.74	0.69, 0.78	327	0.79	0.75, 0.83		‡		1069	0.77‖	0.74, 0.79
Ever diagnosed with genital warts	337	0.74	0.69, 0.78		‡		404	0.81	0.77, 0.84	1068	0.76‖	0.73, 0.78
Ever diagnosed with herpes	337	0.81	0.77, 0.84		‡		403	0.90	0.88, 0.92	1067	0.81‖	0.79, 0.83
Ever diagnosed with gonorrhea	338	0.89	0.87, 0.91	327	0.87	0.84, 0.89	404	0.97	0.96, 0.98	1069	0.92	0.91, 0.93
Ever diagnosed with hepatitis B	337	0.79	0.75, 0.83		‡			‡		1068	0.76‖	0.73, 0.78
Ever diagnosed with hepatitis C	337	0.71	0.65, 0.76	327	0.85	0.82, 0.88	404	0.85	0.82, 0.88	1068	0.80	0.78, 0.82
Ever diagnosed with HIV*	337	0.68	0.62, 0.73		‡			‡		1068	0.68‖	0.65, 0.71
Ever diagnosed with NGU*	337	0.84	0.81, 0.87		‡			‡		1067	0.81‖	0.77, 0.81
Ever had sex partner with an STD	338	0.73	0.68, 0.78	327	0.78	0.73, 0.82	404	0.80	0.76, 0.83	1069	0.77	0.74, 0.79
Ever had sex partner with genital warts	337	0.78	0.73, 0.82	327	0.78	0.73, 0.82	404	0.76	0.72, 0.80	1068	0.77	0.74, 0.79
Ever had sex partner with abnormal Pap	336	0.82	0.78 0.85	327	0.75	0.70, 0.79	404	0.79	0.75, 0.82	10670.79		0.77, 0.81

Table 3. Kappa and intraclass correlation coefficients for 36 interview items by study site

Interview item	Brazil			Mexico			United States			Combined sample|		
	No.†	κ* or ICC*	95% CI*§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§
Circumcision	336	0.94	0.93, 0.95	327	0.91	0.89, 0.93	404	0.98	0.98, 0.98	1067	0.96	0.96, 0.96
Sexual behavior, lifetime												
Ever had vaginal, anal, or oral sex	327	0.74	0.69, 0.79	326	0.80	0.76, 0.84	404	0.80	0.76, 0.83	1057	0.78	0.76, 0.80
Ever had oral sex	309	0.92	0.90, 0.94	302	0.88	0.85, 0.90	390	0.78	0.74, 0.82	1001	0.88	0.87, 0.89
Ever had vaginal sex	315	0.96	0.95, 0.97		‡		390	0.91	0.89, 0.93	1010	0.93‖	0.92, 0.94
Ever had sex with a man	311	0.93	0.91, 0.94	303	0.90	0.88, 0.92	389	0.96	0.95, 0.97	1003	0.94	0.93, 0.95
Ever had oral sex with a man	119	0.90	0.86, 0.93	47	0.87	0.78, 0.93		‡		213	0.88‖	0.85, 0.91
Ever had anal sex with a man	121	0.94	0.92, 0.96	46	0.90	0.83, 0.94	47	0.94	0.89, 0.97	214	0.93	0.91, 0.95
Condom use at first sex with 'steady'	258	0.85	0.81, 0.88	281	0.84	0.80, 0.87	283	0.86	0.83, 0.89	822	0.85	0.83, 0.87
Ever exchanged sex for money/drugs	315	0.90	0.88, 0.92	305	0.85	0.82, 0.88	390	0.78	0.74, 0.82	1010	0.86	0.84, 0.88
Ever paid a woman for sex	29	0.93	0.85, 0.97		‡		24	1.00	–	80	0.97‖	0.95, 0.98
Ever paid a man for sex	124	0.63	0.51, 0.73		‡			‡		218	0.68‖	0.60, 0.75
Age at first SI* with women††	296	0.93	0.91, 0.94	298	0.88	0.85, 0.90	371	0.96	0.95, 0.97	965	0.95	0.94, 0.96

Table 3. Kappa and intraclass correlation coefficients for 36 interview items by study site

	Brazil			Mexico			United States			Combined sample|		
Interview item	No.†	κ* or ICC*	95% CI*§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§
Lifetime no. of FSPs*	258	0.93	0.91, 0.94	292	0.97	0.96, 0.98	366	0.95	0.94, 0.96	916	0.96	0.95, 0.96
Lifetime no. of male anal sex partners	94	0.50	0.33, 0.64	32	0.98	0.96, 0.99	35	0.99	0.98, 0.99	161	0.99	0.99, 0.99
Sexual behavior, past three months												
Frequency of SI with women	264	0.85	0.81, 0.88	289	0.89	0.86, 0.91	369	0.87	0.84, 0.89	922	0.87	0.85, 0.88
No. of different FSPs**	281	0.58	0.50, 0.65	292	0.88	0.85, 0.90	380	0.95	0.94, 0.96	953	0.94	0.93, 0.95
No. of new FSPs	266	0.99	0.99, 0.99	285	0.86	0.83, 0.89	375	0.89	0.87, 0.91	926	0.99	0.99, 0.99
No. of sex partners other than ‘steady’	114	0.10	0.00, 0.28	86	0.61	0.46, 0.73	81	0.96	0.94, 0.97	281	0.95	0.94, 0.96
No. of different male anal sex partners	103	0.97	0.96, 0.98	31	1.00	–	36	0.91	0.83, 0.95	139	0.97‡‡	0.97, 0.99
No. of new male anal sex partners	102	0.98	0.97, 0.99	29	0.92	0.84, 0.96	37	0.97	0.94, 0.98	168	0.98	0.97, 0.99
Sex with someone other than ‘steady’	257	0.93	0.91, 0.94	282	0.83	0.79, 0.86	283	0.96	0.95, 0.97	822	0.93	0.92, 0.94
Condom use for vaginal sex§§	296	0.84	0.80, 0.87	297	0.90	0.88, 0.92	381	0.89	0.87, 0.91	974	0.88	0.87, 0.89
Condom use for anal sex§§	236	0.87	0.84, 0.90	178	0.83	0.78, 0.87	182	0.79	0.73, 0.84	596	0.84	0.81, 0.86
Condom use with other partners§§	115	0.88	0.83, 0.92	84	0.95	0.92, 0.97	83	0.90	0.85, 0.93	282	0.93	0.91, 0.94

Table 3. Kappa and intraclass correlation coefficients for 36 interview items by study site

	Brazil			Mexico			United States			Combined sample|		
Interview item	No.†	κ* or ICC*	95% CI*§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§

\| Unless otherwise noted, the total coefficient is derived by averaging the three study site coefficients after weighting by the inverse of the variance of each site as described by Fleiss, 1981.

* κ, kappa; ICC, intraclass correlation coefficient; CI, confidence interval; STD, sexually transmitted disease; HIV, human immunodeficiency virus; NGU, non-gonococcal urethritis; SI, sexual intercourse; FSP, female sexual partners.

† Number of participants excludes refusals and missing observations.

§ κ and ICC coefficients were z transformed for confidence interval estimation as described by Rosner, 2000.

‡ κ was unstable due to a low number of cases or non-cases; likewise, a stable κ could not be calculated for any study site for 'ever diagnosed with syphilis' and 'condom use for paid anal/vaginal sex.'

|| Due to instability in κ for at least one study site in this item, the total κ is derived from the combined total n of the three samples.

†† One outlier (an age of "1993" on run-in) was removed before calculating ICC statistics.

** One outlier (a value of 11,111,109,632 for number of different female sexual partners in past 3 months on both run-in and baseline) was removed before calculating ICC statistics.

Table 3. Kappa and intraclass correlation coefficients for 36 interview items by study site

	Brazil			Mexico			United States			Combined sample‖		
Interview item	No.†	κ* or ICC*	95% CI*§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§	No.	κ or ICC	95% CI§

‡‡ Due to ICC of 1.0 for Mexico, the country was excluded from the calculation for total ICC.

§§ Weighted κ after Cicchetti and Allison (39).

Table 4. Kappa and intraclass correlation coefficients for interview items by age and lifetime number of female sexual partners

	Age < 30		Age ≥ 30		FSPs* ≤ 7		FSPs > 7	
Interview item	κ* or ICC*	95% CI*§	κ or ICC	95% CI§	κ or ICC	95% CI§	κ or ICC	95% CI§
Sexual health history								
Ever diagnosed with an STD*	0.82	0.79, 0.85	0.86	0.84, 0.88	0.81	0.78, 0.84	0.85	0.82, 0.87
Ever diagnosed with Chlamydia	0.72	0.68, 0.76	0.80	0.77, 0.83	0.77	0.73, 0.80	0.80	0.76, 0.83
Ever diagnosed with genital warts	0.81	0.78, 0.84	0.73	0.69, 0.77	0.70	0.66, 0.74	0.79	0.75, 0.82
Ever diagnosed with herpes	‡		0.86	0.84, 0.88	0.77	0.73, 0.80	0.80	0.76, 0.83
Ever diagnosed with gonorrhea	0.89	0.87, 0.91	0.91	0.89, 0.92	0.89	0.87, 0.91	0.91	0.89, 0.92
Ever diagnosed with hepatitis B	‡		0.76	0.72, 0.79	0.69	0.64, 0.73	0.78	0.74, 0.81
Ever diagnosed with hepatitis C	0.79	0.76, 0.82	0.78	0.74, 0.81	0.72	0.68, 0.76	0.85	0.82, 0.87
Ever diagnosed with HIV*	‡		0.72	0.68, 0.76	0.61	0.56, 0.66	0.76	0.72, 0.80
Ever diagnosed with NGU*	‡		0.77	0.73, 0.80	0.79	0.76, 0.82	‡	
Ever had sex partner with an STD	0.73	0.68, 0.78	0.74	0.70, 0.78	0.76	0.72, 0.79	0.77	0.73, 0.81
Ever had sex partner with genital warts	0.82	0.79, 0.85	0.74	0.70, 0.78	0.81	0.78, 0.84	0.73	0.68, 0.77
Ever had sex partner with abnormal Pap	0.78	0.74 0.81	0.79	0.76, 0.82	0.77	0.73, 0.80	0.81	0.78, 0.84

Table 4. Kappa and intraclass correlation coefficients for interview items by age and lifetime number of female sexual partners

	Age < 30		Age ≥ 30		FSPs* ≤ 7		FSPs > 7	
Interview item	κ* or ICC*	95% CI*§	κ or ICC	95% CI§	κ or ICC	95% CI§	κ or ICC	95% CI§
Circumcision	0.96	0.95, 0.97	0.96	0.95, 0.97	0.95	0.94, 0.96	0.97	0.96, 0.98
Sexual behavior, lifetime								
Ever had vaginal, anal, or oral sex	0.81	0.78, 0.84	0.73	0.69, 0.77	0.81	0.78, 0.84	0.39	0.31, 0.47
Ever had oral sex	0.89	0.87, 0.91	0.82	0.79, 0.85	0.88	0.86, 0.90	0.76	0.72, 0.80
Ever had vaginal sex	0.95	0.94, 0.96	0.91	0.89, 0.92	0.93	0.92, 0.94	‡	
Ever had sex with a man	0.94	0.93, 0.95	0.93	0.92, 0.94	0.97	0.96, 0.97	0.88	0.86, 0.90
Ever had oral sex with a man	0.92	0.90, 0.93	0.87	0.84, 0.89	0.82	0.75, 0.87	0.92	0.88, 0.95
Ever had anal sex with a man	0.89	0.83, 0.93	0.96	0.94, 0.97	1.00	–	0.82	0.75, 0.87
Condom use at first sex with ‘steady’	0.87	0.84, 0.89	0.83	0.80, 0.86	0.89	0.87, 0.91	0.82	0.78, 0.85
Ever exchanged sex for money/drugs	0.86	0.84, 0.88	0.84	0.81, 0.86	0.81	0.78, 0.84	0.85	0.82, 0.87
Ever paid a woman for sex	1.0	–	0.93	0.88, 0.96	1.00	–	1.00	–
Ever paid a man for sex	0.71	0.58, 0.80	0.67	0.56, 0.75	0.54	0.39, 0.66	0.75	0.65, 0.83
Age at first SI* with women†	0.91	0.89, 0.92	0.94	0.93, 0.95	0.94	0.93, 0.95	0.92	0.90, 0.93

Table 4. Kappa and intraclass correlation coefficients for interview items by age and lifetime number of female sexual partners

	Age < 30		Age ≥ 30		FSPs* ≤ 7		FSPs > 7	
Interview item	κ* or ICC*	95% CI*§	κ or ICC	95% CI§	κ or ICC	95% CI§	κ or ICC	95% CI§
Lifetime no. of FSPs*	0.99	0.99, 0.99	0.93	0.92, 0.94	0.88	0.86, 0.90	0.93	0.92, 0.94
Lifetime no. of male anal sex partners	0.89	0.82, 0.93	0.50	0.34, 0.63	0.50	0.33, 0.64	0.62	0.45, 0.75
Sexual behavior, past three months								
Freq. of SI with women	0.85	0.82, 0.87	0.89	0.87, 0.91	0.88	0.86, 0.90	0.83	0.80, 0.86
No. of different FSPs**	0.91	0.89, 0.92	0.60	0.54, 0.65	0.88	0.86, 0.90	0.93	0.92, 0.94
No. of new FSPs	0.90	0.88, 0.92	0.99	0.99, 0.99	0.87	0.85, 0.89	0.88	0.86, 0.90
No. of sex partners other than ‘steady’	0.74	0.65, 0.81	0.12	0.00, 0.28	0.86	0.80, 0.90	0.29	0.15, 0.42
No. of different male anal sex partners	0.99	0.98, 0.99	0.94	0.91, 0.96	0.96	0.94, 0.97	1.00	–
No. of new male anal sex partners	1.00	–	0.99	0.94, 0.97	0.97	0.96, 0.98	1.00	–
Sex with someone other than ‘steady’	0.93	0.92, 0.94	0.89	0.87, 0.91	0.88	0.86, 0.90	0.92	0.90, 0.93
Condom use for vaginal sex§§	0.87	0.85, 0.89	0.88	0.86, 0.90	0.82	0.79, 0.85	0.90	0.88, 0.92
Condom use for anal sex§§	0.81	0.76, 0.85	0.88	0.85, 0.90	0.78	0.73, 0.82	0.85	0.82, 0.88
Condom use with other partners§§	0.89	0.85, 0.92	0.93	0.90, 0.95	0.88	0.82, 0.92	0.90	0.87, 0.93

Table 4. Kappa and intraclass correlation coefficients for interview items by age and lifetime number of female sexual partners

	Age < 30		Age ≥ 30		FSPs* ≤ 7		FSPs > 7	
	κ* or		κ or		κ or		κ or	
Interview item	ICC*	95% CI*§	ICC	95% CI§	ICC	95% CI§	ICC	95% CI§

* FSP, female sexual partners; κ, kappa; ICC, intraclass correlation coefficient; CI, confidence interval; STD, sexually transmitted disease; HIV, human immunodeficiency virus; NGU, non-gonococcal urethritis; SI, sexual intercourse.

§ κ and ICC coefficients were z transformed for confidence interval estimation as described by Rosner, 2000.

‡ Unstable κ due to a low number of cases or non-cases; likewise, a stable κ could not be calculated for any category for 'ever diagnosed with syphilis' and 'frequency of condom use for paid anal/vaginal sex.'

† One outlier (an age of "1993" on run-in) was removed before calculating ICC statistics.

** One outlier (a value of 11,111,109,632 for number of different female sexual partners in past 3 months on both run-in and baseline) was removed before calculating ICC statistics.

§§ Weighted κ after Cicchetti and Allison (39).

APPENDIX D – ADCRC QUESTIONNAIRE
[Run-in and Baseline for ADCRC]

HEALTH QUESTIONNAIRE
University of Arizona, Tucson AZ
(Version 1, 7-03)

The University of Arizona is conducting a research study in order to learn more about Human Papillomavirus (HPV) in men. HPV is a virus that is passed on when people have sex. It is very common in men and women. With your assistance, the information gained from this study will be used to better serve you and the community.

We appreciate your willingness to participate in this project.

All of the information you provide for us is strictly confidential, and your name will not be associated with this questionnaire and will never be used in reports.

Please read each question and fill in the answer that best fits your situation. Remember, you have the option of refusing to answer any question that you do not wish to answer.

If you have any questions feel free to ask the project interviewer.

INSTRUCTIONS

- **Please do not fold, cut, stable, punch or separate pages.**
- **Use a No. 2 pencil only (DO NOT USE PEN).**
- **Make no stray marks.**
- **Fill the ovals completely.**
- **Erase all changes cleanly.**

1. Date: __ __/__ __/__ __ __ __
   mo/day/year

2. Which one or more of the following would you say is your race? (Mark all that apply)
   ___ White
   ___ Black or African American
   ___ Asian
   ___ Native Hawaiian or Other Pacific Islander
   ___ American Indian, Alaska Native
   ___ Other - Specify_____
   ___ Don't know/Not sure
   ___ Refuse

   If more than one response to Question 2, continue.
   Otherwise, go to Question 4.

3. Which one of these groups would you say best represents your race? (Mark only one)
   ___ White
   ___ Black or African American
   ___ Asian
   ___ Native Hawaiian or Other Pacific Islander
   ___ American Indian, Alaska Native
   ___ Other - Specify_____
   ___ Don't know/Not sure
   ___ Refuse

4. Do you consider yourself Mexican/Spanish/Hispanic/Latino?
   ___Yes
   ___No
   ___Refuse

5. In which country were you born?
   ___ US
   ___ Mexico
   ___ Other – Specify_____
   ___Refuse

6. If not born in the U.S., how many years have you lived in the U.S.?

   __ __ Years

___ Less than 1 year
___Refuse

7. In which country have you lived most of your life?
___ US
___ Mexico
___ Other – Specify_____
___Refuse

8. Date of Birth: __ __/__ __/__ __ __ __
mo/ day/year

9. What is your current marital status?
____ Single, never married
____ Married
____ Cohabiting, Living together
____ Divorced/Separated
____ Widowed
____ Refuse

10. How many years of school did you complete?

___0	___10
___1	___11
___2	___12 (Completed High School)
___3	___13
___4	___14
___5	___15
___6	___16
___7	___17+
___8	___Refuse
___9	

11. What is your total household income per <u>month</u> before taxes?

____ Less than $500	____ $3000 - $3999
____ $500 - $999	____ $4000 - $4999
____ $1000 - $1499	____ Over $5000
____ $1500 - $1999	____ Don't know
____ $2000 - $2999	____ Refuse

12. How many family members are supported by your total household income? (Include yourself, all other adults and children that depend on this income.)
__ __# Family members
____Refuse

13. What is your occupation?

_____
____Refuse

If you are not in the military, please skip to question 17.
The following 3 questions are for military personnel only.

14. What is your work status?
_____Active duty
_____Reserve
_____Retired
_____Refuse

15. Have you been deployed to another base or overseas during the last year?
___Yes ___ No (Skip to question 17)____Refuse

16. If yes, what region(s) of the world? (Mark all that apply)
___ Asia
___ Africa
___ South Pacific
___ Europe
___ Middle East
___ Other - Specify _____
___ Refuse

17. A drink of alcohol is 1 can or bottle of beer, 1 glass of wine, 1 can or bottle of wine cooler, 1 cocktail, or 1 shot of liquor. During the past 1 month, how many days per week or per month did you have at least one drink of alcoholic beverage? (Mark only one)
__ Days per week
__ __ Days in past month
____ No drinks in past month (Skip to question 19)
____ Refuse (Skip to question 19)

18. On the days when you drank, about how much did you drink on average? (Mark all that apply)
__ __Bottles of beer
__ __Glasses of wine
__ __Bottles of wine cooler
__ __Number of cocktails
__ __Shots of liquor
__ __Other types of alcohol
_____ Refuse

19. Have you ever used any form of tobacco (cigarettes, pipes, cigars, chew, snuff)?
____Yes ____No (Skip to question 26)____Refuse

20. During your entire life, have you smoked at least 100 cigarettes, which is about 5 packs of cigarettes?
____Yes ____No (Skip to question 25)____Refuse

21. How old were you when started smoking cigarettes?
__ __Years old
____Refuse

22. Do you smoke cigarettes now?

____Yes ____No ____Refuse

23. About how many years have you smoked cigarettes?
__ __Years
____Refuse

24. How many cigarettes on average do/did you smoke per day?
__ __Cigarettes per day
____Refuse

25. Do you currently use chewing tobacco or snuff?
___Every day
___Some days
___Not at all
___Refuse

26. During the past month, approximately how many hours were you exposed to other people's cigarette smoke in an enclosed location (i.e. home, vehicle, work, bar, restaurant)? (Mark only one)

__ __Hours per day
__ __Hours per week
__ __Hours per month
____Refuse

The next questions we are going to ask you are sensitive. It is useful to have this information because HPV infection may differ depending on your sexual history.

27. Have you ever been diagnosed with a sexually transmitted disease or infection by a doctor or health care provider?
____Yes ____No ____Don't know ____Refuse

28. Have you ever had a sex partner who has had a sexually transmitted disease or infection?
____ Yes ____ No ____ Don't know ____Refuse

29. Have you ever had a sex partner who has had genital warts?
____ Yes ____ No ____ Don't know ____Refuse

30. Have you ever had a sex partner who has had an abnormal Pap smear?
____ Yes ____ No ____ Don't know ____Refuse

31. Has a doctor or health care provider ever diagnosed you with any of the following?

Genital warts	___Yes	___No	___ Don't know	____Refuse
Genital herpes	___Yes	___No	___ Don't know	____Refuse
Chlamydia	___Yes	___No	___ Don't know	____Refuse
Gonorrhea	___Yes	___No	___ Don't know	____Refuse
Syphilis	___Yes	___No	___ Don't know	____Refuse
NGU (Non-gonococcal urethritis)	___Yes	___No	___ Don't know	____Refuse
Hepatitis B	___Yes	___No	___ Don't know	____Refuse
Hepatitis C	___Yes	___No	___ Don't know	____Refuse
HIV	___Yes	___No	___ Don't know	____Refuse

32. Have you been circumcised?
___Yes ___No ____Refuse

We are going to ask you questions about sexual relations. For the questions on sexual intercourse, we define sexual intercourse as your penis in someone else's vagina or anus.

33. Have you ever performed:
Vaginal sex (your penis in partner's vagina) ___Yes ___No ____Refuse
Anal sex (your penis in partner's anus) ___Yes ___No ____Refuse
Oral sex (your penis in partner's mouth) ___Yes ___No ____Refuse

If you answered No to all of the above, you have completed the questionnaire. Thank you for your time.

34. How old were you when you first had sexual intercourse?
__ __Years old
___ Never (Thank you for your time, you have completed the questionnaire.)
___Refuse

35. In your life, what is the number of women with whom you have had sexual intercourse?
__ __ # Women
___ Have not had sexual intercourse with a woman (Skip to question 43)
___ Refuse

36. <u>In the past 3 months</u>, how many different women have you had sexual intercourse with?
__ __# Women
____ No sexual intercourse in the past 3 months (Skip to question 41)
___ Refuse

37. <u>In the past 3 months</u>, how many women have you had sexual intercourse with <u>for the first time</u>?
__ __ # Women
___ Refuse

38. In the past 3 months, when you had vaginal sex, how often did you use condoms?
___ Always
___ More than half the time
___ Half the time
___ Less than half the time
___ Never
___Refuse

39. In the past 3 months, how many times did you have sexual intercourse with a woman?
__ __# Times
___Refuse

40. In the past 1 month, how many times did you have sexual intercourse with a woman?
__ __# Times
___No sexual intercourse in the past 1 month
___Refuse

41. How long has it been since you had vaginal sex? (Mark only one)
__ __ Hours
__ __ Days
__ __ Weeks
__ __ Months
__ __ Years
___ Never
___Refuse

42. Did you use a condom the last time you had vaginal sex?
___ Yes
___ No
___ Don't remember
___ Never had vaginal sex
___ Refuse

43. How long has it been since you had anal sex? (Mark only one)
__ __ Hours
__ __ Days
__ __ Weeks
__ __ Months
__ __ Years
___ Never
___ Refuse

44. Did you use a condom the last time you had anal sex?
___ Yes
___ No
___ Don't remember
___ Never had anal sex

___ Refuse

45. In the past 3 months, when you had anal sex, how often did you use condoms?
___ Always
___ More than half the time
___ Half the time
___ Less than half the time
___ Never
___Refuse

46. When you had sex the last time, was the partner a new partner (a partner you had sex with for the first time)?
___ Yes ___ No___ Refuse

For the next few questions, we are going to ask you about your steady partner(s), or partner(s) you see regularly.

47. Do you have a steady sex partner?
___ Yes ___ No (Skip to the introduction to question 55) ___ Refuse

48. The last time you had sex, was the partner a steady partner?
___ Yes ___ No___ Refuse

49. How long have you been having sexual intercourse with your steady partner? (Mark only one)
__ __ Days
__ __ Weeks
__ __ Months
__ __ Years
___ Refuse

50. In the past 3 months, when you had sexual intercourse with your steady partner, how often did you use condoms?
___ Always
___ More than half the time
___ Half the time
___ Less than half the time
___ Never
___ Have not had sex with steady partner in past 3 months
___ Refuse

51. The first time you had sex with your steady partner, did one of you use a condom?
___ Yes ___ No___ Don't remember ___ Refuse

52. In the past 3 months did you have sex with someone other than your steady partner?
___ Yes ___ No (Skip to the introduction to question 55) ___ Refuse

53. How many people other than your steady partner have you had sex with in the past 3 months?
__ __ # Person(s) ___ Refuse

54. In the past 3 months, when you had sexual intercourse with your other partner(s), how often did you use condoms?
___ Always
___ More than half the time
___ Half the time
___ Less than half the time
___ Never
___ Refuse

The next questions we are going to ask are sensitive, and have to do with some private sex practices. Your answers are private and used only for research purposes.

55. Have you ever paid a woman to have sex (vaginal or anal or oral) with you?
___ Yes
___ No (Skip to the introduction to question 61)
___ Refuse

56. In the past 3 months, have you paid a woman to have sex with you?
___Yes
___No (Skip to the introduction to question 61)
___ Refuse

57. If yes, how many times?
__ __ # Times
___ Refuse

58. In the past 3 months, when you paid for sex, was it in: (Mark all that apply)
___ In the U.S.
___ Outside the U.S.
___ Refuse

59. In the past 3 months, what kind of sex did you pay for? (Mark all that apply.)
___ Vaginal sex (your penis in partner's vagina)
___ Oral sex (your penis in partner's mouth or partner's vagina in your mouth)
___ Anal sex, insertive (your penis in partner's anus)
___Other
___ Refuse

60. In the past 3 months, when you paid for vaginal or anal sex, how often did you use condoms?
___ Always

___ More than half the time
___ Half the time
___ Less than half the time
___ Never
___ Have not paid for vaginal or anal sex in the past 3 months
___ Refuse

We are now going to ask you additional sensitive questions. It is useful to have this information because HPV infection may differ depending on the type of sex. Your questions are strictly confidential and used only for research purposes.

61. Have you ever had sex with a man (your penis in partner's anus or mouth, or partner's penis in your anus or mouth)?
___Yes
___ No (Thank you for your time, you have completed the questionnaire)
___ Refuse

62. The last time you had vaginal or anal sex, was your partner a woman or a man?
___ Woman
___ Man
___ Refuse

63. In your life, what is the number of men with whom you have had anal sex (your penis in partner's anus or partner's penis in your anus)?
__ __ # Men
___ Refuse

64. <u>In the past 3 months</u>, how many different men have you had anal sex with?
__ __ Men
___ Refuse

65. <u>In the past 3 months</u>, how many different men have you had anal sex with for the first time?
__ __ Men
___ Refuse

66. Have you ever paid a man to have sex (anal or oral) with you?
___ Yes ___No ___ Refuse

67. <u>In the past 3 months</u> have you paid a man to have sex with you?
___ Yes
___ No (Thank you for your time, you have completed the questionnaire.)
___ Refuse

68. <u>If yes</u>, how many times?
__ __ # Times
___ Refuse

69. In the past 3 months, when you paid for sex with a man, was it: (Mark all that apply)
___ In the U.S.
___ Outside the U.S.
___ Refuse

70. In the past 3 months, what kind of sex (with a man) did you pay for? (Mark all that apply)
___ Oral sex (your penis in partner's mouth)
___ Anal sex, insertive (your penis in partner's anus)
___ Other
___ Refuse

71. In the past 3 months, when you paid for anal or oral sex with a man, how often did you use condoms?
___ Always
___ More than half the time
___ Half the time
___ Less than half the time
___ Never
___ Refuse

YOUR CONTRIBUTION IS VERY IMPORTANT TO OUR STUDY. YOU ARE HELPING US TO PLAN FOR BETTER HEALTH CARE IN THE COMMUNITY. THANK YOU VERY MUCH FOR YOUR COOPERATION.

APPENDIX E – HIM INTERVIEW
[Run-in and Baseline for HIM Study]

HIM Interview
RISK FACTOR QUESTIONNAIRE

VISIT 1 – The HIM Study

Moffitt Cancer Center is conducting a research study in order to learn more about Human Papillomavirus (HPV) in men. HPV is a virus that is passed on when people have sex. It is very common in men and women. With your assistance, the information gained from this study will be used to better serve you and the community.

We appreciate your willingness to participate in this project.

All of the information you provide for us is strictly confidential, and your name will not be associated with this questionnaire and will never be used in reports.

Please read each question and provide the answer that best fits your situation. Remember, you have the option of refusing to answer any question that you do not wish to answer.

If you have any questions feel free to ask the project interviewer.

1. Do you consider yourself Spanish/Hispanic/Latino?
   _____ Yes
   _____ No
   _____ Refuse

2. Which one of the following would you say best represents your race?
   _____ White
   _____ Black or African American
   _____ Asian
   _____ Native Hawaiian or Other Pacific Islander
   _____ American Indian, Alaska Native
   _____ Other
   _____ Refuse

3. In which country were you born?
   _____ U.S.
   _____ Mexico
   _____ Brazil
   _____ Other
   _____ Refuse

4. How many years have you lived in the U.S.?
   _____ Years
   _____ Refuse

5. In which country have you lived most of your life?
   _____ U.S.
   _____ Mexico
   _____ Brazil
   _____ Other
   _____ Refuse

6. Date of birth
   Month: _____ Day: _____ Year: _____

7. What is your current marital status?
   _____ Single, never married
   _____ Married
   _____ Cohabiting, Living together
   _____ Divorced/Separated
   _____ Widowed
   _____ Refuse

8. How many years of school did you complete?
   _____ Did not complete 6th grade
   _____ 6th-8th grade

_____ 9th-11th grade
_____ Completed high school/GED
_____ Vocational school
_____ Some college
_____ Graduated college
_____ Postgraduate or professional school
_____ Refuse

9. Have you had at least one drink of any alcoholic beverage in the past month?
_____ Yes
_____ No (Skip to question 12.)
_____ Refuse

10. A drink of alcohol is 1 can or bottle of beer, 1 glass of wine, 1 can or bottle of wine cooler, 1 cocktail, or 1 shot of liquor. During the past 1 month, how many days did you have at least one drink of any alcoholic beverage?
_____ Days
_____ Refuse

11. On the days when you drank, about how much did you drink on average? (Choose all that apply)
_____ Bottles of beer
_____ Glasses of wine
_____ Bottles of wine cooler
_____ Number of cocktails
_____ Shots of liquor
_____ Other types of alcohol
_____ Refuse

12. Have you ever used any form of tobacco (cigarettes, pipes, cigars, chew, snuff)?
_____ Yes
_____ No (Skip to question 20.)
_____ Refuse

13. During your entire life, have you smoked at least 100 cigarettes, which is about 5 packs of cigarettes?
_____ Yes
_____ No (Skip to question 19.)
_____ Refuse

14. How old were you when you started smoking cigarettes?
_____ Years
_____ Refuse

15. About how many years have you smoked cigarettes?
_____ Years
_____ Refuse

16. How many cigarettes on average do/did you smoke per day?
    _____ Cigarettes
    _____ Refuse

17. Do you smoke cigarettes now?
    _____ Yes
    _____ No
    _____ Refuse

18. During the past 12 months have you stopped smoking for 1 day or longer because you were trying to quit?
    _____ Yes
    _____ No
    _____ Don't' know
    _____ Refuse

19. Do you currently use chewing tobacco or snuff?
    _____ Every Day
    _____ Some Days
    _____ Not at all
    _____ Refuse

20. During the past month, approximately how many hours were you exposed to other people's cigarette smoke in an enclosed location (i.e., home, vehicle, work, bar, restaurant)? If never, enter a 0 and select "Hours per day".
    _____ Hours _____ Per Day
    _____ Per Week
    _____ Per Month
    _____ Refuse

The next questions we are going to ask you are sensitive. It is useful to have this information because HPV infection may differ depending on your sexual history.

21. Have you ever been diagnosed with a sexually transmitted disease or infection by a doctor or health care provider?
    _____ Yes
    _____ No
    _____ Don't know
    _____ Refuse

22. Has a doctor or health care provider ever diagnosed you with any of the following?

	Yes	No	Don't know
Genital warts	_____	_____	_____
Genital herpes	_____	_____	_____
Chlamydia	_____	_____	_____

Gonorrhea	_____	_____	_____
Syphilis	_____	_____	_____
NGU (non-gonococcal urethritis)	_____	_____	_____
Hepatitis B	_____	_____	_____
Hepatitis C	_____	_____	_____
HIV	_____	_____	_____

23. Have you ever had a sex partner who has had a sexually transmitted disease?
    _____ Yes
    _____ No
    _____ Don't know
    _____ Refuse

24. Have you ever had a sex partner who has had genital warts?
    _____ Yes
    _____ No
    _____ Don't know
    _____ Refuse

25. Have you ever had a sex partner who has had an abnormal Pap smear?
    _____ Yes
    _____ No
    _____ Don't know
    _____ Refuse

26. Have you ever had a female sex partner who has received an HPV vaccine?
    _____ Yes
    _____ No (skip to question 29)
    _____ Don't know (skip to question 29)
    _____ Refuse (skip to question 29)

27. How many of your female partners have had an HPV vaccine?
    _____ partner(s)
    _____ Refuse

28. Has your current partner had an HPV vaccine?
    _____ Yes
    _____ No
    _____ Don't know
    _____ Refuse

29. Have you been circumcised?
    _____ Yes
    _____ No
    _____ Don't know
    _____ Refuse

We are going to ask you questions about sexual relations. For the questions on sexual intercourse, we define sexual intercourse as your penis in someone else's vagina or anus.

30. Have you ever performed vaginal, anal, or oral sex (your penis in partner's vagina, anus, or mouth or your partner's penis in your anus or mouth)?
_____ Yes
_____ No (Skip to Medical History Questionnaire)
_____ Refuse

31. Have you ever performed oral sex (your penis in partner's mouth or your partner's penis in your mouth)?
_____ Yes
_____ No
_____ Refuse

32. Have you ever performed vaginal sex (your penis in partner's vagina)?
_____ Yes
_____ No (Skip to question 42)
_____ Refuse

33. How old were you when you first had sexual intercourse with a woman?
_____ Years
_____ Refuse

34. In your life, what is the number of women with whom you have had sexual intercourse?
_____ Women
_____ Refuse

35. In the past 3 months, how many different women have you had sexual intercourse with?
_____ Women
_____ Refuse

36. In the past 3 months, how many women have you had sexual intercourse with for the first time?
_____ Women
_____ Refuse

37. In the past 3 months, when you had vaginal sex, how often did you use condoms?
_____ Always
_____ More than half the time
_____ Half the time
_____ Less than half the time
_____ Never
_____ No vaginal sex in past 3 months
_____ Refuse

38. In the past 3 months, how many times did you have sexual intercourse with a woman?
_____ Times
_____ Refuse

39. In the past 1 month, how many times did you have sexual intercourse with a woman?
_____ Times
_____ Refuse

40. How long has it been since you had vaginal sex?
_____ Hours
_____ Days
_____ Weeks
_____ Months
_____ Years
_____ Refuse

41. Did you use a condom the last time you had vaginal sex?
_____ Yes
_____ No
_____ Don't remember
_____ Never used a condom with vaginal sex
_____ Refuse

42. Have you ever performed insertive anal sex (your penis in partner's anus)?
_____ Yes
_____ No
_____ Refuse

43. Have you ever performed receptive anal sex (your partner's penis in your anus)?
_____ Yes
_____ Never had anal sex (Skip to question 47)
_____ No
_____ Refuse

44. How long has it been since you had anal sex?
_____ Hours
_____ Days
_____ Weeks
_____ Months
_____ Years
_____ Refuse

45. Did you use a condom the last time you had anal sex?
_____ Yes
_____ No
_____ Don't remember
_____ Never used a condom with anal sex (Skip to question 47)

_____ Refuse

46. In the past 3 months, when you had anal sex, how often did you use condoms?
_____ Always
_____ More than half the time
_____ Half the time
_____ Less than half the time
_____ Never
_____ Did not have anal sex in the past 3 months
_____ Refuse

47. The last time you had sex, did you have sex with a new partner?
_____ Yes
_____ No
_____ Refuse

For the next few questions, we are going to ask you about your steady partner you see regularly.

48. Do you have a steady sex partner?
_____ Yes
_____ No (Skip to introduction to question 56)
_____ Refuse

49. The last time you had sex, was the partner a steady partner?
_____ Yes
_____ No
_____ Refuse

50. How long have you been having sexual intercourse with your steady partner?
_____ Days
_____ Weeks
_____ Months
_____ Years
_____ Refuse

51. In the past 3 months, when you had sexual intercourse with your steady partner, how often did you use condoms?
_____ Always
_____ More than half the time
_____ Half the time
_____ Less than half the time
_____ Never
_____ Have not had sex with steady partner in past 3 months
_____ Refuse

52. The first time you had sex with your steady partner, did one of you use a condom?
_____ Yes
_____ No
_____ Don't remember
_____ Refuse

53. In the past 3 months, did you have sex with someone other than your steady partner?
_____ Yes
_____ No (Skip to introduction to question 56)
_____ Refuse

54. How many people other than your steady partner have you had sex with in the past 3 months?
_____ People
_____ Refuse

55. In the past 3 months, when you had sexual intercourse with your other partner(s), how often did you use condoms?
_____ Always
_____ More than half the time
_____ Half the time
_____ Less than half the time
_____ Never
_____ Refuse

The next questions we are going to ask are sensitive, and have to do with some private sex practices. Your answers are private and used only for research purposes.

56. Have you ever exchanged sex for money or drugs?
_____ Yes
_____ No (Skip to introduction to question 63)
_____ Refuse

57. Have you ever paid a woman to have sex (vaginal or anal or oral) with you?
_____ Yes
_____ No (Skip to introduction to question 63)
_____ Refuse

58. In the past 3 months, have you paid a woman to have sex with you?
_____ Yes
_____ No (Skip to introduction to question 63)
_____ Refuse

59. In the past 3 months, how many times have you paid a woman to have sex with you?
_____ Times

_____ Refuse

60. In the past 3 months, when you paid for sex, was it: (Choose all that apply)
_____ In the U.S.
_____ Outside the U.S.
_____ Refuse

61. In the past 3 months, what kind of sex did you pay for? (Choose all that apply)
_____ Vaginal sex (your penis in partner's vagina)
_____ Oral sex (your penis in partner's mouth or partner's vagina in your mouth)
_____ Anal sex, insertive (your penis in partner's anus)
_____ Other
_____ Refuse

62. In the past 3 months, when you paid for vaginal or anal sex, how often did you use condoms?
_____ Always
_____ More than half the time
_____ Half the time
_____ Less than half the time
_____ Never
_____ Have not paid for vaginal or anal sex in the past 3 months
_____ Refuse

We are now going to ask you additional sensitive questions. It is useful to have this information because HPV infection may differ depending on the type of sex. Your answers are strictly confidential and used only for research purposes.

63. Have you ever had sex with a man (your penis in partner's anus or mouth, or your partner's penis in your anus or mouth)?
_____ Yes
_____ No (Skip to Medical History Questionnaire)
_____ Refuse

64. Have you performed oral sex with a man (your penis in partner's mouth or your partner's penis in your mouth)?
_____ Yes
_____ No
_____ Refuse

65. Have you ever performed anal sex with a man (your penis in partner's anus or your partner's penis in your anus)?
_____ Yes
_____ No (Skip to question 70)
_____ Refuse (Skip to question 70)

66. In your life, what is the number of men with whom you have had anal sex (your penis in partner's anus or partner's penis in your anus)?
_____ Men
_____ Refuse

67. In the past 3 months, how many different men have you had anal sex with?
____ Men
____ Refuse

68. In the past 3 months, how many different men have you had anal sex with for the first time?
_____ Men
_____ Refuse

69. The last time you had vaginal or anal sex, was your partner a woman or a man?
_____ Woman
_____ Man
_____ Refuse

70. Have you ever paid a man to have sex (anal or oral) with you?
_____ Yes
_____ No (Skip to Medical History Questionnaire.)
_____ Refuse

71. In the past 3 months, have you paid a man to have sex with you?
_____ Yes
_____ No (Skip to Medical History Questionnaire)
_____ Refuse (Skip to Medical History Questionnaire)

72. In the past 3 months, how many times have you paid a man to have sex with you?
_____ Times
_____ Refuse

73. In the past 3 months, when you paid for sex with a man, was it: (Choose all that apply)
_____ In the U.S.
_____ Outside the U.S.
_____ Refuse

74. In the past 3 months, what kind of sex (with a man) did you pay for? (Choose all that apply)
_____ Oral sex (your penis in partner's mouth)
_____ Anal sex, insertive (your penis in partner's anus)
_____ Other
_____ Refuse

75. In the past 3 months, when you paid for anal or oral sex with a man, how often did you use condoms?
_____ Always

_____ More than half the time
_____ Half the time
_____ Less than half the time
_____ Never
_____ Refuse

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