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Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review

Elizabeth A. Stier, MD¹, Meagan C. Sebring, BBA, BA², Audrey E. Mendez, PhD, MS², Fatimata S. Ba, MPH², Debra D. Trimble, PhD, RN², and Elizabeth Y. Chiao, MD, MPH^{2,3}

¹Department of Obstetrics and Gynecology, Boston Medical Center, Boston, MA

²Department of Medicine, Baylor College of Medicine, Houston, TX

³Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey VA Medical Center, Houston, TX

Abstract

Objective—The aim of this study was to systematically review the findings of publications addressing the epidemiology of anal HPV infection, anal intraepithelial neoplasia and anal cancer in women.

Data Sources—We conducted a systematic review among publications published from January 1, 1997 to September 30, 2013 in order to limit to publications from the combined antiretroviral therapy (cART) era. Three searches were performed of the National Library of Medicine PubMed database using the following search terms: “women and anal HPV”, “women anal intraepithelial neoplasia”, and “women and anal cancer.”

Study Eligibility Criteria—Publications were included in the review if they addressed any of the following outcomes: (1) prevalence, incidence, or clearance of anal HPV infection, (2) prevalence of anal cytological or histological neoplastic abnormalities, or (3) incidence or risk of anal cancer. Thirty-seven publications addressing anal HPV infection and anal cytology remained after applying selection criteria, and 23 anal cancer publications met the selection criteria.

Results—Among HIV-positive women, prevalence of HR-HPV in the anus was 16-85%. Among HIV-negative women, prevalence of anal HR-HPV infection ranged from 4 - 86%. The prevalence of anal HR- HPV in HIV-negative women with HPV-related pathology of the vulva, vagina and cervix compared with women with no known HPV-related pathology, varied from 23-86%, and 5-22%, respectively. Histologic anal HSIL (AIN 2+) was found in 3-26% of the women living with HIV, 0-9% among women with lower genital tract pathology, and 0-3% for women who are HIV-negative without known lower genital tract pathology. The incidence of anal cancer among HIV-infected women ranged from 3.9-30 per 100,000. Among women with a history of cervical

Corresponding author: Elizabeth Chiao, M.D., M.P.H., Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd (152), Houston, TX 77030, echiao@bcm.edu, Phone: 713-440-4485, Fax: 713-748-7359.

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cancer or CIN 3, the IR of anal cancer ranged from 0.8-63.8/100,000 person-years, and in the general population, the IRs ranged from 0.55-2.4/100,000 person-years.

Conclusions—This review provides evidence that anal HPV infection and dysplasia are common in women, especially in those who are HIV-positive or have a history of HPV-related lower genital tract pathology. The incidence of anal cancer continues to grow in all women, especially those living with HIV, despite the widespread use of cART.

Keywords

Anal Cancer; anal intraepithelial neoplasia; epidemiology; HPV; systematic review

Introduction

Squamous cell cancer of the anus (SCCA) incidence has been increasing over the past several decades, among women and men. Historically women have had a higher incidence of anal cancer than men, and recent publications have shown that the incidence rate for cancers of the anus, anal canal and anorectum in all ages and races of women has more than doubled, with an increase from 0.946 per 100,000 in 1975 to 1.827 per 100,000 in 2008.¹ It is estimated that 3,000 cases of anal cancer related to HPV occur in women in the United States each year.

Recently, many epidemiologic studies have highlighted the increase in anal cancer of certain sub-populations of men; specifically, men who have sex with men and HIV-positive individuals have a significantly higher incidence of cancer compared to the general population.² There have been fewer publications addressing the changing epidemiology of anal cancer among women, and these publications have demonstrated that the risk of anal cancer has significantly increased among HIV-positive women,³ with the incidence of anal cancer in HIV-positive women increasing from 0 between 1980 and 1989 to approximately 11 per 100,000 in the years between 1996 and 2004.⁴ Thus, SCCA, is a growing problem for women in the United States, especially those who are HIV-positive.

SCCA shares biologic similarities with cervical cancer, including detectable precancerous lesions and high-risk (HR) human papilloma virus (HPV) infection. HPV has been detected in 99% of cervical cancers and 80 to 90% of anal cancers, with HR HPV types 16 or 18 detected in about 70% of cervical and 80% of anal cancers.⁵ Thus, anal HPV infection, in conjunction with other yet to be determined factors, leads to the development of high-grade squamous anal intraepithelial lesion (AIN 2+), a likely precursor to anal cancer.^{6,7}

As programmatic screening for cervical cancer with cytology has been associated with markedly decreased incidence and mortality of cervical cancer, anal cytology (from a Dacron swab inserted into the anal canal) has been evaluated as a screening method for anal neoplasia. Individuals with abnormal anal screening cytology are referred for a colposcopic evaluation of the anus called high resolution anoscopy (HRA) where the anal canal is examined with a colposcope after the application of 5% acetic acid and/or lugol solution and lesions are biopsied for histologic diagnosis. A growing body of literature has utilized screening of the anal canal using HRA and anal detection of HPV. However, the majority of

literature evaluating the epidemiology of anal HPV infection, anal neoplasia and anal cancer has focused on HIV-positive men who have sex with men.

Objective

The aim of this paper is to systematically review and to summarize the findings of publications addressing the epidemiology of anal HPV infection, anal neoplasia and anal cancer in women.

Methods

We performed a systematic review for publications of anal HPV infection, anal histological and cytological abnormalities in women, and anal cancer in women published from January 1997 to September 30, 2013. Because the publications evaluating HPV-related disease were so heterogeneous (different methodologies for HPV testing, different types of publications, different types of cohorts), and because we wanted to include as many publications as possible to get a full perspective of the research that has been done to date, we conducted a systematic review rather than a meta-analysis. We confined the search to publications published after January 1, 1997 in order to limit the publications to the combined antiretroviral therapy (cART) era.

Information Sources and Search Strategy

We performed three searches of the National Library of Medicine PubMed database using the following search terms: “women” and “anal HPV”, “women” and “anal intraepithelial neoplasia”, and “women” and “anal cancer”. The searches were limited to humans, published in English language with full text available during the time period specified. The searches produced a total of 798 manuscripts. After duplicate papers, review papers, and other non-relevant papers were removed, a total of 535 papers remained for screening. We also enriched the search by examining germane journals and reviewed reference lists from retrieved publications to identify additional manuscripts not captured by the searches. Seven additional manuscripts were identified as meeting inclusion criteria through this method.

Study Selection Criteria

All potentially relevant publications were then evaluated by 4 individuals and were included in this review if they addressed any of the following outcomes: (1) prevalence, incidence, or clearance of anal HPV infection, (2) prevalence of anal cytological or histological neoplastic abnormalities, or (3) incidence or risk of anal cancer. Publications were excluded if they were case reports, did not include original data, did not include women, or did not stratify data by gender, or did not report results related to the aforementioned outcomes. Initial search terms yielded 244 publications for anal HPV infection and cytological and histological pathology; 37 publications addressing anal HPV infection and anal cytology remained after applying selection criteria, with 23 publications that presented findings on both outcomes. Two-hundred and ninety-one publications were identified for the anal cancer search terms, of which 23 met selection criteria (figure 1).

Data Extraction

For all publications, we recorded the following variables: study location, years of study, methodology, number of participants, and a description of the study population including HIV-status. We grouped together publications from the same cohort or population in our tables when appropriate and included the most recent and complete prevalence data presented. The final column in each table allowed us to present the unique findings from each publication. For publications evaluating HIV-positive women, we recorded the effect of HIV viral load on HPV detection, cytologic or histologic outcomes based on whichever the primary outcome reported was reported in the paper. For the anal HPV publications, we recorded the method of HPV testing, incidence/prevalence findings, and concurrent cervical HPV testing findings, if available. Methods of HPV testing included PCR, and hybrid capture2 (HC2). The publications varied by overall HPV types detected (high risk or oncogenic HPV genotypes only or high risk combined with low risk) as well as which specific HPV genotypes were included. Of note, there is lack of standardization of HPV testing in the anus (as in the cervix). HPV testing by PCR allows for the identification of specific high and low risk HPV genotypes, but HC2 testing does not allow for HPV genotyping, only aggregate data for high risk genotypes or low risk genotypes are available through HC2 tests. In addition, PCR has been shown to have a higher sensitivity for detecting low-level HPV infection compared to HC2.^{8,9}

For the anal cytology publications we recorded prevalence of abnormal anal cytology findings, criteria for undergoing high-resolution anoscopy (HRA), number of individuals who received HRA and prevalence of abnormal histologic findings. Several publications evaluated both anal HPV prevalence and prevalence of abnormal anal cytology. For those publications that presented both outcomes, we divided the outcomes and presented the HPV findings with all the other HPV publications, and the cytology findings with the other cytology publications. For the anal cancer publications, we recorded the anal cancer incidence described in each publication and included the standardized incidence ratio if available and other factors associated with increased incidence of anal cancer identified by the publication.

Results

Study Characteristics—A total of 60 publications were included in the review. Many of the publications were conducted in women with specific risk factors for anal cancer. Of the anal HPV prevalence publications, 10 publications specified that the population included only HIV-positive women. Among the publications that did not specify HIV infection, 6 publications were conducted in women with a history of abnormal cervical cytology or IN1+ of the lower genital tract, 1 publication was conducted among women with non-HIV related immune suppression and 9 publications were conducted in the general female population. Among the publications evaluating anal cytological findings, 14 publications evaluated study cohorts of HIV-positive women, twelve publications evaluated study cohorts of women with abnormal cervical cytology or intraepithelial neoplasia (IN) 1+ of the lower genital tract; and seven publications assessed anal cytology among the general population. Among the anal cancer publications there were 7 publications among HIV-positive women,

7 publications evaluated women with a history of HPV-related disease of the vulva or cervix, and 9 publications included women from the general population.

Synthesis of Results

Anal HPV infection in HIV-positive women—There were ten publications, utilizing 7 different study cohorts that specifically evaluated the prevalence and/or incidence of anal HPV infection in HIV-positive women (Table 1). With the exception of two papers,^{8,10} all publications reported data on HR-HPV. The prevalence of anal HR HPV was calculated from baseline, point prevalence or cross-sectional data from the seven study cohorts.^{8,11-16} Two publications calculated incidence of new anal HPV infections from cohort studies.^{15,17} Six of the seven study cohorts were from the United States.^{8,11-15} Most publications used polymer chain reaction (PCR) to test for HPV although the publications differed in HPV types detected (see table 1 footnotes). Three publications utilizing PCR combined LR and HR HPV for their prevalence data.^{8,10,17} One publication used both PCR and hybrid capture 2 test (HC2),⁸ and one cohort used HC2 only.^{11,15} Prevalence of HPV in the anus (16-85%) was higher than that of the cervix (17-70%) in the majority of publications. Concordant HPV genotypes between the anus and cervix were found in 9-16% of HIV-positive women (compared with only 2% having concordant HPV genotypes in the HIV- matched cohorts).

The most common prevalent HPV types identified in the anus were 16, 53, 45, 52, 18 and 35 (compared with the concurrent cervical HPV types 16, 52, 53, 58, and 31). Baranoski et al.,¹⁵ reported the incidence of new anal HR-HPV infections was 74/1,000 person years for HIV-positive women over an average follow-up time of 704 days. Risk factors for prevalent anal HPV included cervical HPV,⁸ CD4 < 200,⁸ smoking,¹⁴ and perianal warts.^{10,17} CD4 500¹⁴ was shown to be significantly protective for anal HPV infection. Of note, reported history of anal intercourse was not associated with anal HPV.^{8,14} Only one publication, Palefsky et al.,⁸ evaluated the effect of most current HIV viral load on the detection of both high risk and low risk HPV types by both HC and PCR, and did not find any differences in detection of HPV using either method between individuals with high HIV viral load compared to low HIV viral load.

Anal HPV infection in predominantly HIV negative female cohorts—Eighteen publications (representing 13 different study cohorts) reported data on anal HPV prevalence, incidence, or clearance in women not known to be HIV positive (Table 2). The 13 study cohorts varied widely by age, recruitment criteria, population pool and other inclusion criteria. Six of the cohorts were recruited from women attending colposcopy clinics;¹⁸⁻²³ however, the inclusion criteria among these cohorts varied from an abnormal referral cervical cytology, to histologic CIN3+.

The majority of publications were cross-sectional. Study cohort size ranged from 40 to 2,107 participants. Eleven of the publications were done in the United States,^{8,10,13,17,21,24-29} four in Europe,^{18,19,22,30} and three in Central/South America.^{20,23,31} The vast majority of publications used PCR to test for HPV. Eight publications utilized PCR combined LR and HR HPV for their prevalence data.^{8,10,17-20,24,31} Two publications used PCR and either HC2 or flow cytometry,^{8,22} and one publication used only HC2.²³ Ten publications reported

prevalence of anal HR-HPV infection in their study cohorts ranging from 4 - 36%.^{13,21-23,25-30} The prevalence of anal HR- HPV in women with HPV-related pathology of the vulva, vagina and cervix compared with women with no known HPV-related pathology, varied from 23 - 36%²¹⁻²³ compared with 4-22%^{13,23,25,27-30} respectively. Veo et al.,²³ reported the prevalence of HPV in the anal canal of the women with CIN III was greater than in the women without CIN III ($p=0.014$). Several publications found that detection of cervical HPV were associated with prevalent anal HPV infection.^{22-25,27,31} Other risk factors for anal HPV detection among HIV-negative women include: reported history of anal intercourse;³¹ number of lifetime partners;^{25,31} and history of perianal and/or vulvar condyloma.¹⁷ Hernandez (2013) et al.,²⁷ found that age < 30 increased the risk for anal HPV and Goodman et al.,²⁵ found that age > 45 *decreased* the likelihood of anal HPV.

The data regarding incidence and clearance of anal HR HPV infection were reported from the Reaching for Excellence in Adolescent Care and Health Project (REACH) and Hawaii Cohorts. The REACH cohort (mean age 17) reported an incident anal HR-HPV infection rate of 5.3/100 person-years,¹⁷ whereas the Hawaii cohort (mean age 39) reported an incident anal HR-HPV infection rate of 19.5/1000 person-months.²⁵ In this Hawaii cohort the mean duration of anal HR HPV infection was 5 months (compared to cervical HR HPV infections which lasted a mean of 8 months) and the clearance rate of anal HPV was 9.16/100 woman-months.²⁸ A longitudinal study of cervical and anal HPV infection (Hawaii cohort) found the risk of anal HPV infection after cervical infection with concordant genotype was 20.5 (95% CI, 16.3–25.7); compared with the risk of a cervical HPV infection after an anal HPV infection with a concordant genotype was 8.8 (95% CI, 6.4–12.2).²⁶

Results of anal cytology and histology in women—Tables 3 and 4 summarize publications that evaluated abnormal anal cytology and/or histology in women. Ten publications reported results for only women living with HIV,^{11,12,14,15,32-37} three publications reported comparative results for both HIV-positive and negative women.^{10,13,38}

Twelve publications evaluated study cohorts of women with abnormal cervical cytology or IN1+ of the lower genital tract. Five of these 12 publications included a small number of HIV+ women,^{20,21,40-42} one publication included a cohort of HIV-positive women with IN1-3 (compared with HIV-negative immune compromised and HIV-negative immune competent with IN1-3),³⁹ and two publications included a comparative cohort of women without a history of IN1-3.^{43,44} Two publications included only women from the general population.^{30,45} The prevalence of cytologic high-grade squamous intraepithelial lesions (HSIL) was 0 - 5% of women living with HIV,^{10-12,14,15,33-38} 0 - 29% among women with lower genital HPV disease,^{18,20,21,40,41,46} and 0 – 0.3% among women who were HIV-negative with unspecified or no known genital HPV.^{10,13,30,38,45} Among HIV-positive women, 5 publications evaluated the effect of HIV viral load on abnormal anal cytologic findings, and none of the publications found that HIV viral load was associated with detection of abnormal anal cytology.^{11,15,33,35,38}

Twenty publications reported histology results from high-resolution anoscopy (HRA) (Tables 3 and 4). HRA examination was done on all participants in seven publications.^{20,39-41,43,44,47} In the remaining ten reports, HRA was performed only on those

with abnormal anal cytology^{13,21,35-37,45} or as in the publications on those with abnormal anal cytology or anal HPV infection.^{11,15,22} Abramowitz et al.,³² reports on biopsies from simple anoscopy. Histologic anal HSIL (AIN 2+) was found in 3-26% of the women living with HIV,^{11-15,32-39} 0 – 9% among women with lower genital tract pathology,^{20-22,39-44,47} and 0-3% for women who are HIV-negative without known lower genital tract pathology.^{13,43-45} In a publication of women with intraepithelial neoplasia (IN) 1+ who were either HIV-positive, immunosuppressed and HIV-negative, or immunocompetent, the prevalence of AIN2/3 was 26%, 9%, and 4% respectively ($p<0.001$).³⁹ Among HIV-positive women, 4 publications the effect of HIV viral load on histologic diagnosis of Histologic anal HSIL (AIN 2+).^{13,17,32,36} Hou et al³⁶ found that poor HIV-control was associated with a higher percentage of histologic anal HSIL detection in a univariate analysis of 75 women. Mullins et al¹⁷ found that poor HIV-control was associated with a higher risk of anal condyloma (HR 1.55, 95% CI 1.12-2.17) in a multivariable analysis, but there was no effect of HIV viral load control on anal dysplasia risk in 278 HIV-infected adolescent women. The other two publications did not find an association between HIV virologic control and histologically defined anal dysplasia.

Anal cancer in women—Twenty-three publications describing the incidence rates (IR) or standardized incidence ratio (SIRs) of anal cancer involving women were included in this review (Table 5). Of these publications, 11 included women in the North America⁴⁸⁻⁵⁸ and the majority of the other publications were from Europe (United Kingdom and Scandinavia).⁵⁹⁻⁷¹ Seven publications identified women living with HIV.^{50-53,64-66} Four publications evaluated the IR or SIR in women with CIN3, cervical cancers or other HPV-related genital cancers,^{48,49,61,62} and three other publications evaluated the SIR of anal cancer in women with genital warts.^{59,60,63} Nine publications reported IRs and risk factors of anal cancer within the general population.^{54-58,68-71}

The incidence of anal cancer among HIV-positive women ranged from 3.9-30 per 100,000 among the 4 publications that reported incidence rates.^{52,53,64,66} The standardized incidence ratio (SIR) ranged from 3.2 to 41.2 compared to the general population.^{50,51,64,66} There was only one publication that compared HIV-positive and HIV-negative women and found that the SIR for HIV-positive women was 18.5 and the SIR for HIV-negative women studied was 0.⁵⁰ In addition, other publications demonstrated that the standardized incidence ratio was higher among subsets of HIV-positive women. For example, Piketty et al.,⁶⁶ and Silverberg et al.,⁵³ found that the SIR among women diagnosed more recently (2005-2008 for Piketty and 2004-2007 for Silverberg) were both higher than SIRs in earlier years. Other publications also found that the SIR and relative risk (RR) among younger women was higher than among older women.^{52,66} Of note, the lowest SIR (3.23) included only women through 1994, and therefore did not include women diagnosed during the era of combined antiretroviral therapy (cART) era.⁵¹

Among women with a history of cervical cancer or CIN 3, the IR of anal cancer ranged from 0.8-63.8/100,000 person years;^{48,49,61,62} however, it should be noted that the 63.8/100,000 IR reported by Chaturvedi et al.,⁴⁸ included rectal cancers as well as anal cancers. The SIRs ranged from 1.8,⁴⁸ (including women with rectal cancer) to 13.6⁴⁹. The SIRs for anal cancer in women with genital warts ranged from 7.8,⁵⁹ to 9.0.⁶³

In the general female population, the IRs ranged from 0.55/100,000 person-years to 2.4/100,000 person-years.^{54-58,68-71} Nelson et al.,⁵⁸ reported the highest incidence rate (2.4, CI 2.3-2.5) and included cases through 2009, which is the most up to date publication. Multiple publications from different countries found that the incidence of anal cancer has been increasing over the past several decades.^{56-58,69-71} In addition, several publications also reported that individuals with lower median household income had significantly higher rates of anal cancer.^{54,68}

Comment

Main Findings

Our systematic review of the literature revealed that anal HPV infection in women is prevalent in general, and comparable to rates of cervical HPV infection. In particular, HIV positive women and women with HPV-related pathology of the lower genital tract were found to have high rates of HR -HPV infection, high rates of high-grade anal intraepithelial lesions (AIN 2+) on biopsy, and elevated rates of anal cancer. Of note, few longitudinal publications evaluating anal HR HPV infection and AIN 2+ on women have been conducted, thus there are few publications describing the natural history of HR HPV infection in HIV-positive, or HIV negative women. In addition, for all populations, the retrospective publications evaluating anal cancer incidence in women demonstrate a significant increase in anal cancer incidence during the last several decades.

The prevalence of HR-HPV anal infection appears to be higher among women who are HIV-positive and women with HPV-related lower genital tract disease compared with that in the general population. Publications with both HIV-positive and negative cohorts found that HIV infection was associated with an increased prevalence of anal HPV,^{8,13} consistent with the findings of a meta-analysis on anal HPV infection in men who have sex with men (MSM), which reported a greater pooled prevalence of anal HR-HPV in HIV-positive men than in HIV-negative men ($p=0.010$).⁷²

Interestingly, all of the reporting simultaneously collected specimens for HPV from the cervix and the anus found comparable or higher detection rates of HR-HPV in the anus compared with the cervix. Most publications found that HPV infection of the cervix was a significant risk factor for anal HPV. In addition, there was significant concordance of HR-HPV genotypes between the cervix and anus. Reported history of prior anal intercourse was not a consistent risk factor for anal HPV. This data supports the likelihood that HPV has a field effect on the lower genital tract; that anal HPV is often found in women who have no history of anal receptive intercourse, and that anal HR HPV infection is as prevalent if not more prevalent than cervical HR HPV infection.

Comparison with Existing Literature

Although we were unable to conduct a meta-analysis with the publications identified for this review because of the heterogeneity in outcomes, and the small numbers of publications per outcome for women, the findings from our systematic review of women can be broadly compared to the meta-analysis and review by Machalek et al.,⁷² These authors conducted a meta-analysis reviewing publications evaluating the incidence and prevalence of HPV-16,

-18, anal squamous intraepithelial lesions (SILs) and anal cancer among men who have sex with men (MSM). Their review drew upon 31 publications evaluating HPV prevalence and 19 estimates of cytological abnormalities, and 11 publications evaluating the incidence of anal cancer. The authors were able to derive pooled prevalence and incidence estimates of both HPV-16 and -18 infection and high grade SIL (AIN 2+) lesions. In Machalek's review, the pooled incidence of high-risk HPV was 73.5 (95% CI 63.9-83.0) and 37.3 (27.4-47.0) for HIV-positive MSM and HIV-negative MSM respectively. These estimates are generally higher than the incidence and prevalence of high-risk HPV infection among both HIV-positive and negative women in the publications we reviewed.

The pooled prevalence of histological AIN2+ was found to be 29.1% (22.8-35.4) and 12.5% (9.8-15.4) among HIV-positive and HIV-negative MSMs respectively. The publications of anal HPV related disease in MSM included concurrent collection of anal HPV, anal cytology and high resolution anoscopy with directed biopsies at a single study visit. In comparison, in the majority of cohort studies conducted among women, the HRA was conducted based on abnormal anal cytology. Using this criteria, the prevalence of AIN 2+ among all female cohorts were lower than that of MSM. Finally, Machalek et al.,⁷² reported that the pooled incidence of anal cancer was 45.9 per 100,000 (31.2-60.3) in the cART era and 5.1 per 100,000 (0-11.5) among HIV-positive and HIV-negative men respectively, these are higher estimates than the majority of anal cancer publications reported in our review. Thus, although the publications in women were too heterogeneous to conduct a meta-analysis, the pooled estimates from the review by Machalek et al., for high-risk HPV, AIN 2+ and anal cancer in HIV-positive and negative MSM all appear higher than those found in the majority of publications among women reviewed in our current review.

Strengths and Limitations

Our systematic review of the literature regarding anal HPV infection, neoplasia, and cancer in women revealed significant heterogeneity in both study design and findings, and results should be considered accordingly. The study cohorts included differing combinations of HIV-positive women, HIV-negative and women with unknown HIV status. In addition, a number of cohorts included women with HPV-related disease of the lower genital tract; however, the inclusion criteria varied from anogenital condyloma, vulvar lesions, abnormal cervical cytology, and specifically CIN3+. Furthermore, several publications did not separate non-oncogenic from oncogenic HPV genotype expression such that the findings cannot be compared to those publications only investigating oncogenic HPV. There was significant variance in the methodology for HPV testing from HC2 to PCR. Since cervical HPV infection has itself been identified as a risk factor for anal HPV infection,²⁶ comparing publications that do not use a similar methodology to detect cervical HPV or HPV-related pathology will not represent the true relationship between HIV-status, cervical/vaginal/vulvar HPV-related disease and anal HPV infection. In addition, the publications of HIV-positive cohorts varied in their methods of accounting for immune reconstitution. Thus the findings vis a vis prevalence and risk factors of HPV anal infection detected in these publications varied dramatically.

Additional limitations should be considered. First, the heterogeneity of sampling methods utilized by the publications in this review may have over or under-estimated prevalence for each specific population, resulting in the large range of prevalences reported. Second, the majority of reported anal cytology results include publications that performed HRA only on those with abnormal cytology results, which may under-call the true rate of AIN2+. Third, some of the included publications reported composite anal cytological/histological diagnosis based on which was more advanced, which also only estimates true AIN2+ rates. Finally, our exclusion criteria were intentionally less rigorous in order to get a full perspective of the research that has been done to date, thus the data reported are extremely heterogeneous in regard not only to sampling method, but also study method and outcomes.

Conclusions and Implications

Despite the limitations of this review, the results of this review demonstrate the evolving importance of anal HPV-related pathology and cancer among women. To our knowledge, this is the first systematic review of anal HR-HPV infection, cytology, histology and anal cancer in women. Our findings show that anal HPV infection and dysplasia are common in women, especially in those who are living with HIV or have a history of HPV-related lower genital tract pathology. Furthermore, incidence of anal cancer continues to grow in all women and especially those living with HIV, despite the widespread use of cART. The lack of longitudinal data highlights the absence of conclusive knowledge in the prevention, detection, and management of anal HPV infection, dysplasia, and cancer in women. Further publications are needed to elucidate the natural history of anal HPV infection and HPV-related disorders of the anus in women in order to accurately and efficiently address this growing problem.

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Figure 1. Systematic Review Process for searching Published Literature with Defined Search Terms from January 1, 1997 through September 30, 2013

Table 1

HR-HPV anal infection in HIV-positive women

Study	Location	Years of study	Study design	No. of subjects	Population (age) *	Methodology for HPV testing	Anal HR-HPV Prevalence n (%)	Cervical HR-HPV Prevalence n (%)	<ul style="list-style-type: none"> HPV concordance between the anus and cervix Principal HPV types Notable findings
Durante ¹²	US	1995-1998	Baseline data from cohort study	86	HIV+ with negative anal cytology (M=38)	PCR ¹	38 (44)	27 (31)	<ul style="list-style-type: none"> 11 (13%) had concordance of at least 1 HPV genotype in both the anus and cervix
Goncalves ¹⁶	Brazil	1996-1997	Cross-sectional	102	HIV+	PCR ²	44 (43)	51 (37)	<ul style="list-style-type: none"> 70% had overall HR HPV concordance in the anus and cervix HPV genotype and No. of women with concordance in both the anus and cervix: HPV53 (13), HPV18 (12), and HPV16 (9)
Hessol 2009 ¹³ Hessol 2013 ²⁹	US	2001-2003	Point prevalence data within a cohort study	470	HIV+/WHIS	PCR ³	188 (40)	81 (17)	<ul style="list-style-type: none"> 42% had overall HPV (HR or LR) concordance in the anus and cervix HIV+ women, compared with the HIV- women, were significantly more likely to have overall HPV concordance in the cervix and anus: <ul style="list-style-type: none"> -Oncogenic HPV: aOR 4.6, 95% CI (1.4-15.5) -Non-oncogenic HPV: aOR 16.9, 95% CI (2.3-125)
Kojic ¹⁴	US	2004-2006	Baseline data from cohort study	120	HIV+/SUN (Mdn=38)	PCR ⁴	102 (85)	84 (70)	<ul style="list-style-type: none"> 75 (63%) had overall HR HPV

Study	Location	Years of study	Study design	No. of subjects	Population (age) *	Methodology for HPV testing	Anal HR-HPV Prevalence n (%)	Cervical HR-HPV Prevalence n (%)	<ul style="list-style-type: none"> HPV concordance between the anus and cervix Principal HPV types Notable findings
Tandon ¹¹ Baranoski ¹⁵	US	2006-2010	Baseline prevalence and incidence data from cohort study	100	HIV+ (M=40)	HC2	16 (16) ⁵	24 (24)	<ul style="list-style-type: none"> concordance in the anus and cervix concordance in the anus and cervix Most common HR HPV types: <ul style="list-style-type: none"> -Anal HPV: 53 (28%), 16 (24%), 45 (23%), 52 (22%), and 18 and 35 (19% each) -Cervical HPV: 16 (19%), 58 (15%), 52 (12%), 53 (11%), and 31 (10%) Univariate risk factors for anal HPV infection: <ul style="list-style-type: none"> -CD4 500 c/uI: OR 0.24, 95% CI (0.06–0.81) -Tobacco use: OR 6.84, 95% CI (1.61–43.5) Incidence of new overall anal HR HPV infection: 74.1 per 1000 person-years
The following publications did not separate the findings based on LR vs. HR HPV									
	Location	Years of study	Study design	No. of subjects	Population (age) *	Methodology for HPV testing	Anal (HR + LR) HPV Prevalence n (%)	Cervical (HR + LR) HPV Prevalence n (%)	<ul style="list-style-type: none"> HPV concordance between the anus and cervix Principal HPV types Notable findings

Study	Location	Years of study	Study design	No. of subjects	Population (age) *	Methodology for HPV testing	Anal HR-HPV Prevalence n (%)	Cervical HR-HPV Prevalence n (%)	<ul style="list-style-type: none"> HPV concordance between the anus and cervix Principal HPV types Notable findings
Mullins¹⁷ Moscicki 2003¹⁰	US	1996-2001	Cohort study	183	HIV+ adolescent (REACH) (M=17)	PCR (HR + LR)	59 (32) ⁶		<ul style="list-style-type: none"> Incidence of new anal HR HPV infection was 12 per 100 person-years, 95% CI (8.4-16) Multivariate risk factors for HR anal HPV: <ul style="list-style-type: none"> -Smoking: HR 3.46, 95% CI (1.21-9.89) -Late CDC AIDS definition: HR 4.28, 95% CI (1.29-14.19)
Palefsky⁸	US	1995-1997	Point prevalence data within a cohort study	PCR: 223 HC2 242	HIV+/WHHS (M=40)	PCR (HR + LR) HC2 (HR + LR)	170 (76) ⁶ 182 (75) ⁶	106 (53)	<ul style="list-style-type: none"> 36 (16%) had concordant HPV genotypes in both the anus and cervix Most common concordant HPV types: HPV 16 (15%), 58, 53 Multivariate risk factors for anal HPV (by HC2) <ul style="list-style-type: none"> -CD4<200: aRR 1.4, 95% CI (1.1-1.5) -Age 45: aRR 0.80, 95% CI (0.50-0.99) -Cervical HPV: aRR 1.3, 95% CI (1.1-1.4)

* Mean or median age reported when available: M = mean, Mdn = median
 HPV = human papillomavirus, HR = high risk; LR = low risk; PCR = polymerase chain reaction, HC2 = hybrid capture 2

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WITS = Women's Interagency HIV Study
SUN = Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy
OR = Odds Ratio
REACH = Reaching for Excellence in Adolescent Care and Health
aRR = Adjusted Relative Risk
¹ HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73
² HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
³ HR types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59 and 66
⁴ HR types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39
⁵ HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
⁶ HPV prevalence only reported as combined LR + HR types

HR-HPV anal infection in predominantly HIV-negative female cohorts

Table 2

Study	Location	Years of Study	Study design	No. of subjects	Population (age)*	Methodology for HPV testing	Anal HR- HPV Prevalence ** n (%)**	Cervical HR- HPV Prevalence ** n (%)**	<div><div><div>• HPV concordance between the anus and cervix</div><div>• Principal HPV types</div><div>• Notable findings</div></div></div>
Park ^{4,21}	US	2006-2007	Cross- sectional	92	IN2+ lower genital tract (including Ca) (HIV + : N=1) (M=32)	PCR	33 (36) ¹		<div><div>•</div><div>Site of IN2+ cervical vaginal vulvar multifocal</div><div>% with anal HPV 52% 75% 33% 57% (cervix + vagina, vulva or both)</div></div>
									<div><div>•</div><div>No statistical differences among prevalence anal HPV</div></div>
									<div><div>•</div><div>HPV type-specific genotype concordance between cervix and anus -Total 24.6%, -Partial 49.0% -None 26.4%</div></div>
									<div><div>•</div><div>Most common HR HPV types: -Anal HPV: 18 -Cervical HPV: 16</div></div>
Valari ²²	Greece	2009-2011	Cross-sectional	235	IN1+ (including cervical Ca: N=20 and vulva Ca: N=1) (M=34)	PCR mRNA (flow)	72 (31) ² 19 (8) ³	91 (39) 60 (26)	<div><div>•</div><div>Only statistically significant risk factor for anal HPV is cervical HPV: OR 3.25, 95% CI (1.67–6.33)</div></div>
Veø ²³	Brazil		Cross-sectional	40	CIN3 (M=33)	HC2	9 (23) ⁴	39 (98)	<div><div>•</div><div>Women with CIN3, compared to the women in the gynecology clinic with no CIN3 were significantly more likely to have a higher prevalence of HPV in their anal canal (p=0.014)</div></div>
				40	Gynecology clinic (no CIN 3) (M=40)	HC2	2 (5) ⁴	3 (8)	
Goodman 2008 ²⁵ Shvetsov ²⁸	US	1998-2003	Cohort study	431	Subset of Hernandez (2005) (M=39)****	PCR	96 (22) ⁵	143 (33)	<div><div>•</div><div>Incident rate of anal HR HPV: 19.5 per 1,000 woman-months, 95% CI (16.0–23.6)</div><div>•</div><div>Clearance rate: 9.16 per 100 woman-months, 95% CI (6.94–11.87)</div><div>•</div><div>Median duration of HR HPV infection: -Anal HPV: 5 months -Cervical HPV: 8 months</div></div>

Study	Location	Years of Study	Study design	No. of subjects	Population (age) *	Methodology for HPV testing	Anal HR- HPV Prevalence n (%) **	Cervical HR- HPV Prevalence n (%) **	<div><div><div>• HPV concordance between the anus and cervix</div><div>• Principal HPV types</div><div>• Notable findings</div></div></div>
									<div><div><div>• Risk factors for incident anal HR HPV:</div><div>-Cervix HR HPV: OR 1.81, 95% CI (1.09–3.02)</div><div>-Lifetime sex partners > 6: OR 3.64, 95% CI (1.25–10.66)</div><div>-Age > 45 (protective): OR 0.43, 95% CI (0.23–0.81)</div></div></div>

Study	Location	Years of Study	Study design	No. of subjects	Population (age)*	Methodology for HPV testing	Anal HR- HPV Prevalence n (%)**	Cervical HR- HPV Prevalence n (%)**	<div><div><div>• HPV concordance between the anus and cervix</div><div>• Principal HPV types</div><div>• Notable findings</div></div><div><div>• HPV 16 was two times greater compared to the next most common genotype, HPV 31, [paired t-test, two-tailed], 95% CI (10.7-19.59)</div></div></div>								
Heracio ²⁰	Brazil	2008-2009	Cross-sectional	303	CIN1+ (including Cervical Ca: N=26) (HIV+ :N=8)	PCR (LR + HR)	255 (84) ** ¹⁰										
Castro ³¹	Costa Rica	2004-2005	Cross-sectional	2107	Women, community (22-29 years)	PCR HR+LR PCR HR only	666 (32) ** 464 (22) ¹¹	768 (36) ** n/a	<div><div>• Risk factors for anal HPV: -Cervical HPV: aOR 4.8, 95% CI (3.9–5.9) -H/o anal intercourse: aOR 2.8, 95% CI (1.7–4.5) -No. lifetime sex partners >=4: aOR 2.3, 95% CI (1.7–3.1)</div></div>								
Hernandez 2005 ²⁴	US	1998-2004	Baseline data from cohort study	1378	Women, community	PCR (LR + HR)	368 (27) ** ¹²	369 (27) **	<div><div>• There were significant age differences among women with anal HPV compared to women with cervical HPV (race-adjusted): - <30 Reference - 30-39: OR 0.4, 95% CI (0.3-0.6) - 40-49: OR 0.1, 95% CI (0.1-0.2) - 50: OR 0.1, 95% CI (0.04-0.2) • Risk of concurrent anal HPV infection given cervical HPV infection: OR 3.3, 95% CI (2.5-4.4), adjusted for age and race/ethnicity.</div></div>								
Mullins ¹⁷ Moscicki 2003 ¹⁰	US	1996-2001	Cohort study	82	HIV-adolescent (REACH) (M=17)	PCR (HR + LR)	11 (13) **		<div><div>• Incidence new anal HR HPV infections: 5.3 per 100 person-years, 95% CI (2.6-11)</div><div>• Risk factors for anal HPV <table><tr><td><u>Risk factors for anal HPV</u></td><td><u>OR (95% CI)</u></td></tr><tr><td>Perianal condyloma</td><td>9.9 (1.9–51.30)</td></tr><tr><td>Vulvar condyloma</td><td>3.9 (1.5–10.0)</td></tr><tr><td>Cervical HPV infection</td><td>2.2 (1.1–4.5)</td></tr></table></div></div>	<u>Risk factors for anal HPV</u>	<u>OR (95% CI)</u>	Perianal condyloma	9.9 (1.9–51.30)	Vulvar condyloma	3.9 (1.5–10.0)	Cervical HPV infection	2.2 (1.1–4.5)
<u>Risk factors for anal HPV</u>	<u>OR (95% CI)</u>																
Perianal condyloma	9.9 (1.9–51.30)																
Vulvar condyloma	3.9 (1.5–10.0)																
Cervical HPV infection	2.2 (1.1–4.5)																

Study	Location	Years of Study	Study design	No. of subjects	Population (age) *	Methodology for HPV testing	Anal HR- HPV Prevalence ** n (%)	Cervical HR- HPV Prevalence ** n (%)	• HPV concordance between the anus and cervix • Principal HPV types • Notable findings
									• HIV status was a significant risk factor ONLY when girls with condyloma were excluded: OR 2.3, 95% CI (1.1–4.9)
Palefsky ⁸	US	1995-1997	Point prevalence within a cohort study	PCR: 57 HC2: 67	HIV- Subset of WIHS (M=40)	PCR (HR + LR) HC2 (HR + LR)	24 (42) **/13 HC2: 20 (30)	12 (24)	

* Mean or median age reported when available; M = mean, Mdn = median

** Publications reporting only combined HR and LR HPV data (and not separating out the HR HPV): Castro, Crawford et al., D'Hauwers, Goodman et al. (2010), Heraclio et al., Hernandez et al., and Palefsky et al.

*** Note that these publications are a subset of the cohort from Hernandez (2005) with sufficient follow-up

¥ Cohort has no history of HPV-related pathologies

Seven anal specimens were unable to be evaluated for HPV.
HPV = human papillomavirus, HR = high risk; LR = low risk, PCR = polymerase chain reaction, HC2 = hybrid capture 2
WIHS = Women's Interagency HIV Study
REACH = Reaching for Excellence in Adolescent Care and Health
CIN = cervical intraepithelial neoplasia,
INI+ = intraepithelial neoplasia of the lower genital tract (cervical, vaginal or vulvar) grade 1 or higher

¹ HR types 16, 18, 26, 31, 33, 35,39, 45, 51–53, 56, 58, 59, 66, 68, 73, 82, and IS39

² HR types not stated

³ Flow cytometry for E6&7 mRNA of 14 high-risk HPV types (not stated)

⁴ HR types not stated

⁵ HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, and 82

⁶ HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68

⁷ HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; possible HR 26, 34, 53, 66, 70, 73, and 82

⁸ HR types 6 E6, 11 E6, 16 E7, 18 E7, 31 E6, 33 E6, 35 E6, 39 E7, 45 E7, 51 E6, 52 E7, 53 E6, 56 E7, 58 E6, 59 E7, 66 E6, 67 L1 and 68 E7

⁹ HR types 16, 31, 33, 53, 59, 45, 56, 18, 66; probable HR-HPV types 26, 35, 39, 51, 52, 58, 68, 69, 70, 73, 82, IS39; LR-HPV types 6, 11, 40, 42, 54, 61, 72, 81, CP6108; undetermined risk types 55, 62, 64, 67, 71, 83 and 84

¹⁰ HR types not stated

¹¹ HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68/73b

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*I*² HR types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, CP6108, and IS39

*I*³ HR types 6, 11, 16, 18, 26, 31, 32, 33, 35, 39, 40, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 66, 68, 69, 70, 73, AE2, Pap 155, Pap 291, 2, 13, 34, 42, 57, 62, 64, 67, 72, W13B

Table 3

Prevalence of abnormal anal cytology and histology in HIV -positive women

Study	Location	Years of study	Sample size	Population (Age)*	Subjects with abnormal anal cytology		Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA)		<div><div><div>• Prevalence AIN2+ for cohort (if available)</div><div>• Notable findings (Including statistically significant Independent risk factors for AIN2+)</div></div></div>																						
					All abnormal n (%)	HSIL or ASC-H n (%)		AIN1-3 n (%)	AIN2-3 n (%)																							
Abramowitz ³²	France	2003-2004	150	HIV+ ID clinic			All 150 women underwent anoscopy	10 (7) ^I		<div><div>• Findings based on directed biopsies with simple anoscopy (HRA not performed)</div></div>																						
Chaves ³³	Brazil	2006-2008	184	HIV+ STD clinic (M=36)	26 (14)	0				<div><div>• Abnormal anal cytology associated with CD4<200: RR 4.87, 95% CI (1.67– 14.17)</div><div>• Abnormal anal cytology not associated with anal intercourse: RR 1.15, 95% CI (0.54-2.43)</div></div>																						
Durante ¹²	US	1995-1998	100	HIV+ (M=35)	14	0				<div><div>• Incident abnormal pap test: 22 per 100 person-years, 95% CI (14–33). (There was only 1 incident HSIL anal cytology)</div></div>																						
Galsa ³⁴	US	2009-2012	556	HIV+ ID clinic (M=48)	233 (42%)	29 (5%)	Abnormal anal cytology (170)	115 (68)	45 (26)	<div><div>• 8% prevalence of AIN2+ in the total female cohort</div></div>																						
Gingelmaier ³⁵	Germany	2007-2008	104	HIV+ gynecology clinic (M=38)	13 (13)	2 (2)	Abnormal anal cytology (13)	6 (46)	4 (31)	<div><div>• 4% prevalence of AIN2+ in the total cohort</div></div>																						
Hessol 2009 ¹³	US	2001-2003	470	HIV+ (WIHS) (M=33)			Abnormal anal cytology (n/a)	68 (92) ²	37 (50) ²	<div><div>• 8% prevalence of AIN2+ in the total cohort</div><div>• (Note that AIN2+ is a composite of cytology/histology)</div><div><table><tr><td colspan="2">Risk factor for AIN2+</td><td>OR</td><td>(95% CI)</td></tr><tr><td rowspan="3">anal HPV</td><td>Oncogenic</td><td>7.4</td><td>(1.3-37)</td></tr><tr><td>Non-oncogenic</td><td>2.2</td><td>(0.42-11)</td></tr><tr><td>Both HPV types</td><td>10</td><td>(2-50)</td></tr><tr><td colspan="2">Cervix HPV oncogenic</td><td>1.8</td><td>(0.57-5.9)</td></tr><tr><td colspan="2">h/o anal intercourse</td><td>1.2</td><td>(0.64-2.4)</td></tr></table></div><div><div>• Only 50% of women with abnormal anal cytology underwent HRA</div></div></div>	Risk factor for AIN2+		OR	(95% CI)	anal HPV	Oncogenic	7.4	(1.3-37)	Non-oncogenic	2.2	(0.42-11)	Both HPV types	10	(2-50)	Cervix HPV oncogenic		1.8	(0.57-5.9)	h/o anal intercourse		1.2	(0.64-2.4)
Risk factor for AIN2+		OR	(95% CI)																													
anal HPV	Oncogenic	7.4	(1.3-37)																													
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Cervix HPV oncogenic		1.8	(0.57-5.9)																													
h/o anal intercourse		1.2	(0.64-2.4)																													
Holly ³⁸	US	1995-1997	235	HIV+ (WIHS)	61 (26)	2 (1)	Abnormal anal cytology (46)	33 (72)	14 (30)	<div><div>• 8% prevalence of AIN2+ in the total cohort</div><div><table><tr><td colspan="2">Risk factor for abnormal anal cytology</td><td>RR</td><td>(95% CI)</td></tr><tr><td colspan="2">HIV infection</td><td>3.2</td><td>(1.3 to 7.5)</td></tr><tr><td colspan="2">h/o anal intercourse</td><td>2</td><td>(1.3-3.1)</td></tr></table></div></div>	Risk factor for abnormal anal cytology		RR	(95% CI)	HIV infection		3.2	(1.3 to 7.5)	h/o anal intercourse		2	(1.3-3.1)										
Risk factor for abnormal anal cytology		RR	(95% CI)																													
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h/o anal intercourse		2	(1.3-3.1)																													

Study	Location	Years of study	Sample size	Population (Age) [*]	Subjects with abnormal anal cytology		Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA)		<ul style="list-style-type: none">• Prevalence AIN2+ for cohort (if available)• Notable findings (Including statistically significant Independent risk factors for AIN2+)
					All abnormal n (%)	HSIL or ASC-H n (%)		AIN1-3 n (%)	AIN2-3 n (%)	
										<div>CD4<200</div> <div>5.5</div> <div>(2.2 to 16)</div>
Hou ³⁶	US	2008-2010	715	HIV+ ³ (M=49)	75 (10)	4 (0.6)	Abnormal anal cytology (75)	54 (72)	29 (29)	<ul style="list-style-type: none">• 4% prevalence of AIN2+ in the total cohort• p=.03 <div>Risk factor for AIN2+No. with abnormal anal cytology% AIN2</div> <div>CD4<2501861%</div> <div>CD4>500205%</div>
Kojic ¹⁴	US	2004-2006	120	HIV+ (SUN) (M=38)	46 (38)	4 (3)				
Moscicki 2003 ¹⁰	US	1996-2001	162	HIV+ adolescents (REACH) (M=17)	34 (21)	4				
Tandon ¹¹	US	2006-2007	100	HIV+ ID clinic (M=40)	17 (17)	0	Abnormal anal cytology or HR-HPV infection (HC2) (14)	10 (10)	3 (3)	<ul style="list-style-type: none">• 3% prevalence of AIN2+ in the total cohort <div>Risk factor for AIN2+OR(95% CI)</div> <div>CD4<20014.62(2.48 – 86.11)</div> <div>Abnormal cervical cytology3.79(1.05 – 13.72)</div> <ul style="list-style-type: none">• 74% of women referred underwent HRA
Baranoski ¹⁵		2006-2010			33	0	Abnormal anal cytology or HR-HPV infection (HC2) (36)		12 (12)	<ul style="list-style-type: none">• 12% period prevalence (up to 3 visits over 4 years) of AIN2+ for the entire cohort• 33% period prevalence of abnormal anal cytology for the entire cohort• 77% of women referred underwent at least 1 HRA
Tatti ³⁹	Argentina	2005-2011	31	HIV+ IN1-3 (M=37)			All participants (31)	16 (52)	8 (26)	<ul style="list-style-type: none">• 26% prevalence of AIN2+ in the total cohort• HIV+ women had higher prevalence of AIN2+ compared with immune-competent and other immunosuppressed women (p<.001) (see Table 4)
Weis ³⁷	US	2006-2008	204	HIV+ ID clinic (M=40)	64 (31)	1 (0.5)	Abnormal anal cytology (51)	50 (98)	35 (69)	<ul style="list-style-type: none">• 18% prevalence of AIN2+ in the total cohort• Note that 60% of women AIN2+ did not report anal intercourse• 80% of women referred underwent HRA <div>h/o anal intercourseNO h/o anal intercourse</div>

Study	Location	Years of study	Sample size	Population (Age) *	Subjects with abnormal anal cytology		Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA)		• Prevalence AIN2+ for cohort (if available) • Notable findings (Including statistically significant Independent risk factors for AIN2+)
					All abnormal n (%)	HSIL or ASC-H n (%)		AIN1-3 n (%)	AIN2-3 n (%)	
										Abnormal anal cytology 39% AIN2+ 26%
										27% 13%
										p=.004 p=.03

* Mean Age reported when available; M = mean
HSIL = high-grade squamous intra-epithelial lesion
ASC-H = Atypical squamous cells, cannot rule out high grade
HRA = high resolution anoscopy
ID = infectious disease
CIN = cervical intraepithelial neoplasia
VaIN = vaginal intraepithelial neoplasia
VIN = vulvar intraepithelial neoplasia
PAIN = perianal intraepithelial neoplasia
AIN = anal intraepithelial neoplasia
INI+ = intraepithelial neoplasia of the lower genital tract (cervical, vaginal or vulvar), grade 1 or higher
WIHS = Women's Interagency HIV Study
SUN = Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy
REACH = Reaching for Excellence in Adolescent Care and Health
h/o = history of

¹ combined AIN1-3 as "dysplasia"

² numbers don't add because grade of the lesion was defined as the more advanced diagnosis on cytology or histology. If no histological data was available, grade based only on cytology.

³ no gross anal disease on physical exam

Table 4

Prevalence of abnormal anal cytology and histology in predominantly HIV- female cohorts

Study	Location	Years of study	Sample size	Population (age)*	Subjects with abnormal anal cytology		Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA)		<ul style="list-style-type: none">• Prevalence AIN2+ for cohort (if available)• Notable findings (including statistically significant independent risk factors for AIN2+)		
					Any n (%)	HSIL or ASC-H n (%)		AIN1-3 n (%)	AIN2-3 n (%)			
Calore ⁴⁶	Brazil	Not stated	49	CIN1+ by cytology (no gross anal lesions) (M=32)	29 (59)	14 (29)						
D'Hauwers ¹⁸	Belgium	2007-2008	93	H/o abnormal cervical cytology: N=58 Normal screening: N=35 (M=30)	10 (11)	0						
ElNaggar 2013 ⁴¹ ElNaggar 2012 ⁴²	US	2006-2010	324	INI+ (including cervical Ca: N=4) (HIV+: N=16) (other immunosuppression: N=12) (M=39)	18 (6)	1 (0.3)	All participants (324)	64 (20)	28 (9)	<ul style="list-style-type: none">• 9% prevalence of AIN2+, in the total cohort		
										Risk factor for AIN1-3	OR	(95% CI)
										Immunosuppression	5.75	(2.58–12.8)
										h/o VIN	3.81	(1.84–7.87)
										H/o anal sex	1.85	(1.06–3.23)
<ul style="list-style-type: none">• Probability of AIN1-3 among women who are not immunosuppressed, have no h/o VIN or h/o anal sex is 9%• Probability of AIN-3 among women who are immunosuppressed, have a h/o VIN and h/o anal sex is 72%• Performance of anal cytology to detect AIN1-3:												

Study	Location	Years of study	Sample size	Population (age) *	Subjects with abnormal anal cytology		Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA)		<ul style="list-style-type: none">Prevalence AIN2+ for cohort (if available)Notable findings (including statistically significant independent risk factors for AIN2+)
					Any n (%)	HSIL or ASC-H n (%)		AIN1-3 n (%)	AIN2-3 n (%)	
										<div>VIN1-39.4(2–44.6)</div> <div>VaIN1-37.8(1.6–36.7)</div> <div>CIN1-37.0(1.5–32.5)</div>
Koppe ⁴⁴	Brazil	2008-2010	106	No h/o IN1-3 (28%) < age 40			All participants (106)	17 (30)	5 (5)	<ul style="list-style-type: none">5% prevalence of AIN2+, in the total cohort
			74	HIV- (no IN1-3) (M=50)			All participants (74)	1 (1)	0	
Park ²¹	US	2006-2007	102	IN2+ lower genital tract (including Ca) (HIV+; N=1) (M=32)	9 (9)	2 (2)	Abnormal anal cytology (7)	7 (100)	0	
Santoso ⁴⁰	US	2006-2009	205	Women with genital intraepithelial neoplasia (HIV+ : N=10)	12 (6)	0	All participants (205)	25 (12)	17 (8)	<ul style="list-style-type: none">5% prevalence of AIN2+, in total cohort
Likes ⁴⁷	US	2006-2009	310	abnormal cervical cytology or vulvar lesion (M=40)			All participants (310)	61 (19)	26 (8)	<ul style="list-style-type: none">Rates of AIN2+ comparable in immune-compromised vs. immune-competent (9% vs. 8% respectively) (p = 0.4543)Rates of VIN2+ higher in immune-compromised vs. immune-competent (55% vs. 23% respectively) (p<.0001)
			33					3 (9)	3 (9)	
Tatti ³⁹	Argentina	2005-2011	404	Immune-competent IN1-3 (M=30)				104 (26)	16 (4)	<ul style="list-style-type: none">CIN2.3 increased the risk of AIN1-3 regardless of immune status: OR 1.91, 95% CI (1.1-3.6)
			46	Immune-compromised IN1-3 (HIV-)2 (M=40)				15 (33)	4 (9)	
Valari ²²	Greece	2009-2011	235	IN1+ (including Ca: N=21) (M=34)			Abnormal anal cytology or positive HPV DNA or mRNA (25)	8 (32)	0	<ul style="list-style-type: none">AIN2+ was not detected. Prevalence of AIN1/condyloma was 3% in the total cohort.Low rate³ of women referred underwent HRA

Study	Location	Years of study	Sample size	Population (age) *	Subjects with abnormal anal cytology		Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA)		<ul style="list-style-type: none">Prevalence AIN2+ for cohort (if available)Notable findings (including statistically significant independent risk factors for AIN2+)
					Any n (%)	HSIL or ASC-H n (%)		AIN1-3 n (%)	AIN2-3 n (%)	
Hessol 2009 ¹³	US	2001-2003	185	HIV- (WIHS) (M=29)			Abnormal anal cytology	7 (9)	2 (3)	<ul style="list-style-type: none">1% prevalence of AIN2+, in total populationSee Hessol Table 3
Holly ³⁸	US	1995-1997	61	HIV- (WIHS)	5 (8)	0				
Moscicki 2003 ¹⁰	US	1996-2001	67	HIV- adolescents (REACH) (M=17)	4 (6)					
Pierangeli ³⁰	Italy	2005-2011	109	HIV- proctology clinic ⁴ (M=42)	38 (35)	0				
Moscicki 1999 ⁴⁵	US	1994	410	HIV-family planning clinics (M=23)	16 (4)	0	Abno mal anal cytology ⁽⁹⁾	5 (56)	2 (22)	<ul style="list-style-type: none">0.5% prevalence of AIN2+, in total cohortMultivariate analysis – risk factors for abnormal anal cytology<ul style="list-style-type: none">Risk factorAdjusted OR(95% CI)Anal HR HPV12.28(3.91–43.53)h/o cervical SIL4.13(1.29–4.85)h/o anal intercourse6.90(1.71–47.15)

* Age or mean age reported when available; M = mean
HSIL = high-grade squamous intra-epithelial lesion
ASC-H = Atypical squamous cells, cannot rule out high grade
HRA = high resolution anoscopy
CIN = cervical intraepithelial neoplasia
VaIN = vaginal intraepithelial neoplasia
VIN = vulvar intraepithelial neoplasia
PAIN = perianal intraepithelial neoplasia
AIN = anal intraepithelial neoplasia
INI+ = intraepithelial neoplasia of the lower genital tract (cervical, vaginal or vulvar), grade 1 or higher
Ca = cancer
WIHS = Women's Interagency HIV Study
REACH = Reaching for Excellence in Adolescent Care and Health
h/o = history of

¹ Immune-compromised-- 16 were HIV-positive, 5 were transplant patients, 7 had lupus and 1 had diabetes, 1 had celiac Bruce disease and 1 had Crohn's disease.
² Immune compromised by other causes—HIV- but otherwise not specified.

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³ Study reports “high fallout rate”, but rate not specified-- (4/19 with + HPV , and unknown of abnormal cytology)

⁴ Women seen at a proctology clinic with no history of HPV-related pathologies

Table 5

Incidence of anal cancer in women

Study	Location	Years of study	Population	Study design	Total no. of patients in cohort	No (%) women in cohort	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	Standardized Incidence Ratio (SIR) for Anal Cancer and other Notable Findings
Blomberg⁵⁹ Friis⁶⁰ I	Denmark	1978 – 2008	Patients with genital warts [†]	Danish National Patient Register	49,088	32,933 (67)	Genital warts	Not Reported	<ul style="list-style-type: none">SIR 7.8, 95% CI (5.4–11.0)SIR 21.5, 95% CI (14.4–30.9) in men
Chaturvedi⁴⁸	Denmark, Finland, Norway, Sweden, US	Varies by registry ²	One-year survivors of cervical cancer [†]	13 population based cancer registries from 5 countries	104,760	104,760 (100)	Cervical cancer	63.8 (no CI reported)	<ul style="list-style-type: none">SIR 1.84, 95% CI (1.72–1.98)³
Edgren⁶¹	Sweden	1968–2004	Women aged 18–50 with history of CIN 3	Sweden National Registry	3,747,698	All Women	CIN 3	<ul style="list-style-type: none">6.0 (No CI reported) for patients with CIN0.96 (No CI reported) for patients w/o hx CIN	<ul style="list-style-type: none">Adjusted Anal IRR 4.68, 95% CI (3.87–5.62)Risk of anal cancer increases with time since first CIN3 diagnosis, with greatest risk for women with CIN3 diagnosed >10 yearsRisk of anal cancer increase with younger age at first CIN3 diagnosis
Evans⁶²	UK	1960–1999	<ul style="list-style-type: none">Women with history of CIN 3[†]Women with history of invasive cervical cancer[†]	Thames Cancer Registry	CIN 3: 59,519; Cervical cancer: 21,605	All Women	CIN 3 or cervical cancer	<ul style="list-style-type: none">4.8 (CIN3) No CI Reported12.4 (cervical cancer) No CI Reported	<ul style="list-style-type: none">SIR 5.9, 95% CI (3.7–8.8) for women diagnosed with CIN3SIR 6.3, 95% CI (3.7–10) for women diagnosed with cervical cancer
Nordenvall⁶³	Sweden	1965 – 1999	Hospitalized patients with condylomata acuminata [†]	Sweden inpatient register and nationwide registers	10,971	9,286 (85)	Genital warts	4.8 (No CI reported)	<ul style="list-style-type: none">SIR 9.0, 95% CI (3.6–18.6)
Saleem⁴⁹	US	1973 – 2007	Patients with either in situ or invasive cervical, vulvar, or vaginal neoplasm [†]	SEER	189,206	All Women	HPV-related gynecologic neoplasm	0.8 (No CI reported)	<ul style="list-style-type: none">Overall SIR 13.6, 95% CI (11.9–15.3)Anal cancer SIRs highest in African American women with invasive vulvar cancer: SIR 45.5, 95% CI (14.3–95.0)

Study	Location	Years of study	Population	Study design	Total no. of patients in cohort	No (%) women in cohort	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	Standardized Incidence Ratio (SIR) for Anal Cancer and other Notable Findings
									<ul style="list-style-type: none">Anal cancer SIRs lowest in women with invasive vaginal cancer: SIR 1.8, 95% CI (0.8-5.3)
Hessol ⁵⁰	US	1994-2001	HIV-positive women over the age of 18	Women's Interagency HIV study & SEER	1,559 HIV-positive women 391 HIV-negative	All Women	HIV	Not reported	<ul style="list-style-type: none">HIV-positive: SIR 18.5, 95% CI (0.5–68)HIV-negative: SIR 0, 95% CI (0–289)
Fordyce ⁵¹	US	1981 – 1994	Women with AIDS, ages 15-69	New York State Cancer Registry and New York City AIDS registry	15,146	All Women	HIV	Not reported	<ul style="list-style-type: none">Adjusted SIR 3.23,³ 95% CI (1.39-6.36)Unadjusted SIR 2.68,³ 95% CI (1.16-5.29)Relative risk increased from 2.35 (early pre-AIDs: 60 to 25 months before AIDS diagnosis) to 5.08 (post-AIDs: 4 to 60 months after AIDS diagnosis)
Franzetti ⁶⁴	Italy	1985-2011	HIV-positive patients [‡]	L Sacco Department of Clinical Science at the University of Milan	5,924	1,542 (26)	HIV	13.8 (no CI reported)	<ul style="list-style-type: none">SIR 41.2, 95% CI (4.6 - 148.8)Incidence of non-AIDs defining cancers during the HAART period was higher in both women and menOnly SIR for vulva was higher in the HAART era for women: SIR 69.2, 95% CI (22.3-61.4)
Frisch (INCI) ⁵²	US	1995 -1998	Patients with HIV/AIDs [‡]	AIDs-cancer registry match in 11 state and metropolitan locations ⁴	309,365	51,760 (40)	HIV	3.9 (No CI reported)	<ul style="list-style-type: none">RR of invasive anal cancer<ul style="list-style-type: none">– Overall (all age groups): RR 6.8, 95% CI (2.7–14)– Age at AIDs onset < 30 years: RR 134.3, 95% CI (16.3–484.8) was highestRR for anal cancer similar to those of cervical and vulvar/vaginal cancer

Study	Location	Years of study	Population	Study design	Total no. of patients in cohort	No (%) women in cohort	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	Standardized Incidence Ratio (SIR) for Anal Cancer and other Notable Findings
Lanoy ⁶⁵	France	2006	HIV -positive patients with incident cases of cancer [†]	ONCOVIT cohort and FHDH	53,853	Not Reported	HIV	Not Reported	<ul style="list-style-type: none">55 incident cases of anal cancer, 6 in women
Piketty ^{66,67, 5}	France	1992-2008	HIV positive patients	French Hospital Database on HIV	109,771	Not Reported	HIV	9.4 (No CI Reported)	<ul style="list-style-type: none">SIR 13.1, 95% CI (6.7 - 22.8)⁶In women the Incidence Rates have increased in recent years:<ul style="list-style-type: none">– 1992-96: 0– 1997-2000: IR 6.3, 95% CI (0-13.4)– 2001-2004: IR 12.9, 95% CI(4.0-22.0)– 2005-2008: IR 18.3, 95% CI(8.0-28.7)In women, SIRs significantly higher at younger than older ages<ul style="list-style-type: none">– 25–34 yo: IR 83, 95% CI (9-300)– 45–54 yo: IR 8, 95% CI (2-17)
Silverberg ⁵³	US, Canada	1996-2007	HIV-positive and negative women [†]	NA-ACCORD, SEER	8,842 HIV-positive women 11,653 HIV-negative women	20,495	HIV	30 (17-50)	<ul style="list-style-type: none">No cases were observed for HIV-negative womenIncidence rate was lowest in 1996-1999 (early cART)<ul style="list-style-type: none">– 1996–99: 0– 2000–03: IR 41.5, 95% CI (16.7, 77.4)– 2004–07: IR 24.7, 95% CI (9.1, 48.0)
Benard ⁵⁴	US	1998-2003	Incident cases of HPV-associated cancers, Women 20 years of age	CDC, NPCR, SEER, BRFSS data	138,043	95,961 (70)	General Population	2.14 (2.10, 2.19)	<ul style="list-style-type: none">Lower median household income associated with significantly higher rates of anal cancer (compared to areas with income >50,000)<ul style="list-style-type: none">– <\$35,000: IR 2.20, 95% CI (2.11, 2.29)

Study	Location	Years of study	Population	Study design	Total no. of patients in cohort	No (%) women in cohort	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	Standardized Incidence Ratio (SIR) for Anal Cancer and other Notable Findings
									– \$35,000 - \$49,999; IR 2.22, 95% CI (2.17–2.77)
Brewster ⁶⁸	UK	1975–2002	Incident cases of squamous cell carcinoma of the anus [‡]	Scottish Cancer Registry	Not Reported	Not Reported	General Population	0.55 ⁷	<ul style="list-style-type: none">Significantly higher rates of SCCA in women in economically deprived areas (p = 0.027)Increase in Incidence rates<ul style="list-style-type: none">1970s: IR 0.23 to 0.271998 – 2002; IR 0.55⁷
Fisher ⁵⁵	US	1985–1992	Incident cancers of the lower anogenital tract in women [‡]	Michigan Tumor Registry	Not Reported	Not Reported	General Population	0.7 (No CI Reported)	<ul style="list-style-type: none">Blacks at a similar risk as Whites for anal cancer
Frisch (Cancer) ⁵⁶	US	1973 – 1996	Incident cases of squamous cell carcinoma of cervix, vulva, vagina, anus, penis, and tonsils [‡]	SEER (Hawaii and 8 other locations) ⁸	Not Reported	Not Reported	General Population	<ul style="list-style-type: none">US whites: 0.9* (No CI reported)Hawaii whites: 1* (no CI reported)Hawaii APIs: 0.4* (No CI reported)	<ul style="list-style-type: none">SCCA SIR significantly increased over study period only in US whites<ul style="list-style-type: none">Estimated annual increase of invasive SCCA 1.5% (p < 0.05)Estimated annual increase of in situ SCCA 4.6% (p < 0.05)
Jin ⁶⁹	Australia	1982–2005	Incident cases of invasive anal cancer [‡]	Australian National Cancer Statistics Clearing House database	Not Reported	Not Reported	General Population	1.10 (1.02 – 1.18) ^{*9} Rate adjusted to the 2001 US standard population	<ul style="list-style-type: none">Incidence of SCCA in women increased by 1.88% per annum, 95% CI (1.18–2.58)annual rate of increase of SCCA was almost 2 times higher in men than in women5-year survival of invasive anal cancer increased over time, and women had better outcomes than men
Joseph ⁵⁷	US	1998–2003	Incident cases of all types of anal cancer	NPCR, SEER (83% of US population)	Not Reported	Not Reported	General Population	1.51 (1.48 – 1.54) [*] rate adjusted to the 2000	<ul style="list-style-type: none">Women had a higher rate of SCCA than men

Study	Location	Years of study	Population	Study design	Total no. of patients in cohort	No (%) women in cohort	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	Standardized Incidence Ratio (SIR) for Anal Cancer and other Notable Findings
								US standard population US standard population	<ul style="list-style-type: none">Black women had a significantly RR of SCCA than did white womenRate was significantly higher in the South (RR 1.24, 95% CI [1.66–1.77]) and the West (RR 1.14, 95 % CI [1.51–1.63]) compared with the NortheastInvasive SCCA rates increased significantly from 1992 through 2004, by 2.8%During same period, rate of in situ tumors increased by 4%
Nelson ^{58, 10}	US	1973–2009	Incident cases of anal adenocarcinoma (AAC) or anal squamous cell carcinoma (SCCA)	SEER database	Not Reported	Not Reported	General Population	2.4 (2.3 – 2.5) ^{*11} Rate adjusted to the 2000 US standard population	<ul style="list-style-type: none">Rates of Anal Adenocarcinoma remained stable, while rates of SCCA were significantly increased in the time period after 1997<ul style="list-style-type: none">– 1973–1996: SIR 1.4, 95% CI (1.4–1.5)– 1997–2009: SIR 2.4, 95% CI (2.3–2.5)
Nielsen ⁷⁰	Denmark	1978 – 2008	Incident cases of anal cancer	Danish Cancer Registry and Danish Registry of Pathology	5.5 million	Not reported	General Population	1.48 ^{*12} (No CI reported)	<ul style="list-style-type: none">66% of incident cases of anal cancers were in womenAverage annual percentage change over study period: 2.9%, 95% CI (2.2 – 3.6)Increase in age-adjusted anal cancer SIR was significantly greater in women under 60 years (APC<60 = 5.2%, 95% CI [4.0–6.3]) than in women over 60 (APC>60 = 1.7%, 95% CI [0.9–2.5])80.7% of cases of anal cancer in women were associated with HPV (compared to 67.9% in men)

Study	Location	Years of study	Population	Study design	Total no. of patients in cohort	No (%) women in cohort	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	Standardized Incidence Ratio (SIR) for Anal Cancer and other Notable Findings
Robinson ^{7,1}	UK	1960-2004	Incident cases of anal, vulvar, vaginal, cervical, and penile cancers [†]	Thames Cancer Registry	12 million	Not reported	General Population	1.18 ^{*/13} (No CI reported)	<ul style="list-style-type: none">2,676 cases of anal cancer in women, 1,988 cases of anal cancer in menIncrease in age-standardized period rates in women was greater than that in men<ul style="list-style-type: none">– In women: 0.45, 95% CI (0.36-0.54) in 1960–64 to 1.18, 95% CI (1.08–1.29) per 100,000 in 2000–2004 (three-fold increase)– In men: 0.79, 95% CI (0.64-0.93) in 1960-1964 to 1.06, 95% CI (0.95-1.17) per 100,000 in 2000 - 2004

* age standardized incidence rate

[†] No age range reported

SIR = standardized incidence ratio

¹ Data in the table is from ^{59,60} is a previous analysis of the same data

² Denmark 1943 – 1998, US SEER 1973 – 2001, Sweden 1958 – 2001, Norway 1953 – 1999, Finland 1953 – 2001

³ Cancers of rectum and anus combined

⁴ Atlanta, Connecticut, Florida, Illinois, Los Angeles, Massachusetts, New Jersey, New York City/State, San Diego, San Francisco, Seattle

⁵ Data in the table is from^{66,67} is a previous analysis of the same data

⁶ for time period 2005 – 2008

⁷ for time period 1998 – 2002

⁸ San Francisco-Oakland, Detroit, Atlanta, Seattle, Connecticut, Iowa, New Mexico, and Utah

⁹ for the time period 2000 – 2005

¹⁰ Data in the table is from⁵⁸, is a previous analysis of the same data

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for time period 1997 - 2009
for the time period 2003 - 2008
for time period 2000 - 2004