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Prevalence of cervical, oral, and anal human papillomavirus infection in women living with HIV in Denmark - The SHADE cohort study

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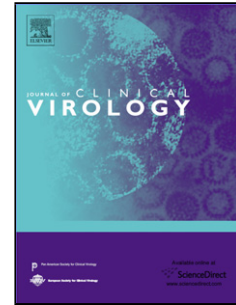
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**Prevalence of Cervical, Oral, and Anal Human Papillomavirus Infection in Women Living with HIV
in Denmark – the SHADE Cohort study**

Running title:

HPV at three anatomical sites in women living with HIV.

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Highlights

- Cervical and anal HPV infection is highly prevalent in women living with HIV
- Anal HPV infection is associated with cervical HPV infection
- Non-16/18 hrHPV genotypes were predominant at all anatomical sites
- Half of hrHPV infections could have been prevented by the 9-valent HPV vaccine

Description of paper:**Study on the Prevalence and Distribution of HPV at three Anatomical Sites in Women Living with HIV****Abstract****Background:**

Women living with HIV (WLWH) have elevated risk of human papillomavirus (HPV) related cancers.

Objectives:

To assess prevalence, distribution and concordance of cervical, oral, and anal HPV infection, and predictors of oral and anal HPV in WLWH in Denmark.

Study design:

WLWH followed in the **Study on HIV, cervical Abnormalities and infections in women in Denmark (SHADE)** were enrolled and examined for cervical, oral, and anal HPV infection. Logistic regression models were used to identify predictors of anal and oral HPV.

Results:

A total of 214 of 334 WLWH had sufficient DNA for analysis at all three anatomical sites and were included in analyses. Cervical, oral, and anal high-risk (hr) HPV prevalence were 28.0%, 3.7% and

39.3%. Most frequent i) cervical, ii) oral and iii) anal hrHPV genotypes were i) hrHPV58 (8.4%), 52 (5.1%), 16 (5.1%) and 51 (5.1%); ii) 52 (1.4%) and iii) 51 (9.3%), 58 (8.9%), 16 (7.0%) and 18 (7.0%). Among present cervical, oral, and anal hrHPV genotypes, 6.7%, 12.5% and 17.9% were targeted by the 2-or 4-valent HPV vaccines, whereas 50.0%, 50.0% and 42.9% of hrHPV genotypes were covered by the 9-valent HPV vaccine. Anal HPV infection was predicted by cervical HPV infection (adjusted OR 4.47 (95%CI 2.25-8.89)).

Conclusion:

Cervical and anal HPV infection were highly prevalent in WLWH. Non-16/18 hrHPV genotypes were predominant at all anatomical sites. Almost half of all hrHPV infections at the three anatomical sites could have been prevented by childhood/adolescent vaccination with the 9-valent HPV vaccine.

List of abbreviations used

AC	Anal cancer
AIN	Anal intraepithelial neoplasia
ART	Antiretroviral therapy
CC	Cervical cancer
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CRS	Civil Registration System
DF	Degrees of freedom
DHCS	Danish HIV Cohort Study
EACS	European AIDS Clinical Society

HR	High-risk
HPV	Human papillomavirus
MSM	Men who have sex with men
LR	Low-risk
OPC	Oropharyngeal cancer
OR	Odds ratio
PIN	Personal identification number
PLWH	People living with HIV
SHADE	<u>S</u> tudy on <u>H</u> IV, cervical <u>A</u> bnormalities and infections in women in <u>D</u> enmark
WLWH	Women living with HIV

Key words:

Women living with HIV; human papillomavirus; cervical cancer, anal cancer; oral cancer; genotype distribution; HPV vaccine, concordance, HPV prevalence.

Background

Five percent of the world's cancer burden is attributable to human papillomavirus (HPV) infection [1], and people living with HIV (PLWH) have elevated risk of HPV related cancers at different anatomical sites, compared to their HIV-negative peers [2-4]. Especially increased risk of HPV-related cervical cancer (CC) [2,5-9], oropharyngeal cancer (OPC) [5,10,11], and anal cancer (AC) [5,12] has been reported [2,5-9]. Whereas HPV is the causal agent of CC, the prevalence of HPV in OPCs is 25-46% [13,14] and 58-100% in ACs [15,16].

The exact mechanisms behind the interactions between HIV and HPV at a cellular level are not clearly understood; HIV may facilitate access and entry of HPV to basal epithelial cells by disrupting the epithelial tight junctions [17] and HIV-mediated immunodeficiency can increase HPV acquisition, reactivation and persistence. We previously reported that prevalent cervical high-risk (hr) HPV infection in WLWH participating in the Study on HIV, cervical Abnormalities and infections in women in Denmark (SHADE) was predicted by factors associated with immunosuppression; CD4 <350 cells/ μ L, prior AIDS and short duration of combined antiretroviral treatment (ART) [18].

HPV vaccine initiatives targeting PLWH require knowledge on concordant HPV genotype distribution at all anatomical sites to estimate multisite vaccine efficacy. While several studies on women living with HIV (WLWH) report cervical, oral, or anal HPV genotype distribution [19-25], only few, small studies have addressed concurrent cervical, oral, and anal HPV prevalence [26-28].

Objectives

The aim of the present study was to assess the prevalence, distribution and concordance of cervical, oral, and anal HPV in WLWH in Denmark. Furthermore, we aimed at identifying predictors of oral and anal HPV.

Study design:

Setting

Denmark has a population of 5.7 million [29] and an estimated HIV prevalence among adults of 0.1% [30]. Medical care, including ART, is tax-paid and provided free-of-charge to all PLWH [22].

Treatment of HIV is restricted to eight specialized medical centres. Six of these centres participated in the SHADE [22]. PLWH are visiting outpatient clinics at intended intervals of 3-6 months [31]. During the study period, HIV guidelines recommended cervical cytology twice the first year after HIV diagnosis and annually thereafter [32]. Cervical intraepithelial neoplasia (CIN) was treated according to guidelines of women from the general population. The Danish National Board of Health recommended that women from the general population aged 23–49 years received cervical cytological testing every three years and women aged 50–65 years every five years [33].

The SHADE cohort

The SHADE cohort is an ongoing, multicentre, prospective, observational cohort study of WLWH in Denmark attending regular outpatient care for HIV infection. Briefly, study participants were enrolled during outpatient visits from 1 February 2011–1 February 2012. Inclusion criteria were known HIV-1 infection and ≥ 18 years of age. Exclusion criteria were pregnancy, prior hysterectomy (due to CC or other reasons), and/or alcohol or drug abuse impeding adherence to protocol. Previous and current lesions related to HPV infection, such as condyloma acuminata, and prior treatment for this, were not an exclusion criterion. A full description of the cohort has previously been published [34].

Interview survey

Written informed consent was obtained at study entry and a standardized interview among others regarding smoking, age at sexual debut, lifetime sexual partners, and contraceptive use was

performed (Supplementary file 1). Double manual data entry of the questionnaires was performed using the EpiData Entry program [35].

Registries

Civil Registration System (CRS)

The CRS is a national registry of all Danish residents [36]. A unique personal identification number (PIN) is assigned to each individual. This PIN was used to link to the Danish HIV Cohort Study (DHCS).

Danish HIV Cohort Study (DHCS)

HIV demographics were retrieved from the DHCS, which is a prospective, observational, nationwide, multicentre, population-based cohort study of all PLWH seen at the Danish HIV clinics since 1 January 1995 [31].

Sample collection & HPV DNA testing

A trained doctor collected cervical, oral and anal HPV samples using flocked swabs (UTM-RT viral transport media Flocked Polyester Swabs, Copan Diagnostics, Inc., Murrieta, CA). Cervical samples were collected by inserting a cytobrush through a speculum and rotating it in the cervical canal. Oral samples were collected from the tonsils and posterior pharynx by means of firm strokes of a cytobrush on both sides. Finally, a cytobrush was inserted into the anal canal and rotated while applying gentle pressure to the walls of the canal to collect anal epithelial cells. Samples were stored at room temperature and transported to the Department of Pathology, Copenhagen University Hospital, Hvidovre. Samples were analysed for HPV using the CLART HPV2 assay

(Genomica, Madrid, Spain) detecting 35 HPV genotypes; 13 hrHPV (hrHPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and 22 non-oncogenic/low-risk (lr) HPV (lrHPV6, 11, 26, 40, 42, 43, 44, 53, 54, 61, 62, 66, 70, 71, 72, 73, 81, 82, 83, 84, 85, and 89) [37]. Samples returning invalid outcomes were retested. The second result was considered definitive [37].

Statistical analysis

Categorical variables were reported as counts and percentages and compared for prevalence and concordance using McNemars test and chi-square test or Fisher's exact test, respectively. Continuous variables were summarized as median and interquartile ranges (IQR) or mean and ranges and compared using the Wilcoxon rank sum test or Kendall's Tau-b test.

Univariate and multiple logistic regression analyses were used to identify predictors of overall oral and anal HPV/hrHPV presented as odds ratios (OR) and 95% confidence intervals (CI). Due to few patients being oral hrHPV positive only four predictor variables were predefined to assess predictors of oral HPV infection (Supplementary file 2). Nine candidate predictor variables were chosen *a priori* to study predictors of anal HPV based on knowledge on risk factors of cervical HPV [2,38-40] (Table 4). Since duration of ART, prior AIDS and CD4 count are dependent covariates, two models were computed for both of the above-mentioned analyses: First, a model where all variables except CD4 at inclusion were included and secondly, a model where duration of ART and prior AIDS were replaced by CD4. We only present the OR of the CD4 count from the second model [18]. The CD4 and HIV RNA values used in this study were the latest values measured before inclusion in the study. For variables with more than two outcome categories ($df > 1$), we controlled for repeated testing by estimating the combined p -value. Individuals with missing

explanatory values were excluded from the multiple regression analyses. The validity of the model was tested using the Hosmer and Lemeshow Goodness-of-Fit Test. SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for data analysis. HPV genotype distribution figures were performed in “R” 3.2.0 [41]. P-values <0.05 were considered statistically significant.

Results

Characteristics of the cohort

A total of 334 WLWH consented for study participation [22]. Of 326 cervical, 327 oral and 327 anal samples; 295 (90.5%), 273 (83.5%) and 270 (82.6%) yielded sufficient DNA for HPV assessment, leaving 214 (64.1%) participants with conclusive HPV test results from all three anatomical sites. Baseline characteristics of the 214 included WLWH are presented in Table 1. Median age at inclusion was 42.9 years (IQR 36.3-48.4) and median duration of HIV was 11.0 years (IQR 5.3-17.1). Overall, 95.3% of the patients were on ART and 80.6% of these had HIV-RNA<40 copies/mL (Table 1).

Cervical, oral and anal HPV prevalence

Overall cervical, oral, and anal HPV prevalence was 50.5%, 5.6% and 63.1% (cervical versus oral; $p<0.0001$, cervical versus anal; $p<0.0021$) (Table 2), hrHPV prevalence was 28.0%, 3.7% and 39.3% (cervical versus oral; $p<0.0001$; cervical versus anal; $p=0.0013$). Multiple cervical HPV infections were more frequent than oral (mean 1.1, range 0-9 vs. mean 0.1, range 0-6), but less frequent than anal co-infections (mean 1.5, range 0-14) (Table 2).

Cervical, oral, and anal concordance

We found no concordance between cervical and oral HPV findings, but anal HPV prevalence was positively correlated with cervical HPV infection (Table 2).

Cervical, oral, and anal genotype distribution

Most frequent cervical hrHPV genotypes observed were hrHPV58 (n=18, 8.4%), 52 (n=11, 5.1%), 16 (n=11, 5.1%) and 51 (n=11, 5.1%) (Figure 1, Table 3). HrHPV 52 (n=3, 1.4%) was the most frequent oral hrHPV infection. Other orally observed hrHPV infections were only present once (Figure 1, Table 3). Most frequent anal hrHPV genotypes were hrHPV51 (n=20, 9.3%), 58 (n=19, 8.9%), 16 (n=15, 7.0%) and 18 (n=15, 7.0%) (Figure 1, Table 3). Table 2 summarizes to which extent the observed genotypes were covered by the 2-or 4-valent HPV vaccine. Cervical, oral, and anal hrHPV genotype distribution is presented in Figure 1 and Table 3.

Predictors of oral and anal HPV

We found no predictors of overall oral HPV infection (Supplementary file 2). Overall anal HPV infection was associated with cervical HPV infection (adjusted OR per year 4.47 (95%CI 2.25-8.89)) (Table 4). In adjusted analyses, we found no predictors of anal hrHPV (data not shown).

Discussion

In this multicentre, cross-sectional cohort study of WLWH in Denmark, more than half of WLWH were concurrently cervical and anal HPV positive, and a large proportion presented with multiple anogenital HPV infections. A correlation between cervical and anal hr- and lrHPV was observed and cervical HPV infection predicted anal HPV infection. Non-16/18 hrHPV genotypes were

predominant at all anatomical sites. Almost half the present hrHPV genotypes would have been covered by the 9-valent HPV vaccine.

Cervical HPV prevalence

Cervical HPV prevalence was 50.5% overall with a hrHPV prevalence of 28.0%, which is substantially higher than found amongst women participating in the Danish cervical screening program (hrHPV prevalence between 9.4-16.2% dependent on the assay used) [42].

Oral HPV prevalence

Little is known about the natural history of oral HPV infections [14,43]. However, subclinical persistent oral HPV infection is likely to precede OPC [43]. We found an overall oral HPV prevalence of 5.6% (hrHPV prevalence: 3.7%), which is somewhat lower than that found in similar studies of PLWH where HPV and hrHPV prevalence has been reported at 20-45% and 12-26%, respectively [14]. In comparison, a recent review of the HIV-negative population found the overall oral HPV prevalence to be an average of 7.5% (range 2.5-20%) [43]. In general, less oral HPV have been reported in women, which may reflect reduced HPV seroconversion rates among men versus women following genital HPV infection, resulting in greater protection against subsequent oral HPV infections in women [13].

Anal HPV prevalence

Anal HPV and hrHPV prevalence was 63.1% and 39.3%. The higher prevalence in WLWH of anal compared with cervical hrHPV, is similar to other reports [23,44]. Moreover, anal hrHPV prevalence is higher in WLWH compared with HIV-negative women [45,46]. In WLWH, studies

have found an overall anal HPV and hrHPV prevalence of 75.3- 83.15% [44,45] and 47.6-65.0%, respectively [23,44,45]. Moreover, a third of WLWH presented with multiple anal HPV infections, which is finding consistent with previous research [21,23]. The clinical impact of multiple HPV infections is still debatable and the causal attribution of specific genotypes in multiple infections is difficult to assess. One study found that multiple hrHPV infections could identify women with persistent cervical low-grade squamous intraepithelial lesion and CIN grade 1 [47]. The effect of multiple infections on anal intraepithelial neoplasia (AIN) is not well described, though a recent meta-analysis notes that single infections with hrHPV16 caused over 85% of AC cases amongst HIV-negative, while in PLWH only about 70% of HPV-positive cases harboured hrHPV16 and a third of these had multiple infections [16]. In comparison, studies on men who have sex with men (MSM) infected with HIV, have found an even higher overall anal HPV prevalence ranging from 86-100% [48-50] and detection of hrHPV in 85-94% [48,49].

Cervical, oral, and anal concordance

We found no genotype concordance between oral and anal HPV, which is consistent with previous studies [51,52]. The lack of concordance is suggested to be caused by independent infection events, different predilection of the two anatomical sites to various HPV types and/or different modes of clearance [14,52]. However, anal overall, hr- and lrHPV prevalence, number of genotypes, having all genotypes present targeted by the 9-valent HPV vaccine and presence of ≥ 1 genotypes targeted in the 2-, 4- and 9-valent HPV vaccines were positively correlated with being cervical HPV positive. The association between concurrent anal and cervical HPV infection supports previous reports [21,45,46].

HPV genotype distribution

Cervical hrHPV distribution has previously been published for the entire cohort [18], most frequent cervical hrHPV genotypes were hrHPV58, 52, 16 and 51. Though numbers were small, hrHPV52 was the most frequent oral HPV infection. HrHPV16, which was found orally in only one patient (0.5%), is otherwise the most commonly detected oral hrHPV genotype in PLWH with a reported prevalence around 2–6% and involved in 90-95% of HPV-related OPCs [14]. As in the present study, where predominant anal hrHPV genotypes were hrHPV51, 58, 16 and 18, Kost *et al.* [45] and de Pokomandy *et al.* [44] found the most prevalent anal hrHPV genotypes in WLWH to be hrHPV51, 16, 31 and 18 and hrHPV16 and 51, respectively. Whereas hrHPV16 and to some extent hrHPV18 are the predominant strains amongst women <35 years of age, other hrHPV genotypes becomes more prevalent amongst the >35 years old women [53]. Adding to this, we and others have previously reported that differences in genotype distribution between WLWH and women from the general population can to some extent be affected by African migrants presumably infected with HPV strains predominating in Africa before migrating to Europe [22,54].

Predictors of oral and anal HPV

We were unable to study predictors of oral HPV due to few prevalent cases. Previously, oral HPV has been associated with HIV infection, smoking, recent tooth-brushing, and more lifetime tongue-kissing, and/or oral sex partners [55]. Like others [21,23,45,46], we found an increased risk of overall anal HPV infection in WLWH with cervical HPV infection. Previously, prevalent anal hrHPV infection have been associated with CD4 count <350/ μ L and concurrent cervical lesions [23]. Predictors of cervical hrHPV infection in the present cohort have previously been reported [18].

Strengths and limitations

Strengths include the well-characterized cohort and the use of nationwide registries. Furthermore, HPV analyses were performed routinely in a high throughput, quality controlled and quality assured clinical laboratory using a well-characterized HPV assay. Limitations include the rather high number of inadequate samples. One study found that oral rinse samples were significantly more sensitive than self-collected swabs in order to obtain analytically sufficient oral samples [55]. However, the use of cytobrushes, as done in the present study, allows for retrieval of cells from specified anatomical locations in the oral cavity [24]. Moreover, as persistence of HPV infection is required for development of intraepithelial neoplasia, more than a single positive sampling should be obtained with a defined time interval between to establish whether the infection is indeed persistent rather than transient. Finally, though prophylactic HPV vaccines in PLWH appear safe and immunogenic [56] the clinical impact of HPV vaccination in this population is still uncertain.

Implications for guideline development.

Regarding primary prevention in the form of vaccine, between 6.7-17.9% of hrHPV infections at all three anatomical sites would have been covered by childhood/adolescent vaccination using 2-or 4-valent HPV vaccine (targeting hrHPV16 and 18), and 42.9-50% of observed hrHPV genotype infections would be covered by the 9-valent HPV vaccine (targeting hrHPV16, 18, 31, 33, 45, 52 and 58). These data supports the new EACS guidelines [46] recommending a three-dose regimen of preferably the 9-valent HPV vaccine in WLWH through age 26, which generates hope for WLWH in future HPV vaccinated cohorts. European AIDS Clinical Society (EACS) guidelines recommend screening for CC every 1-3 years and AC every 1-3 years with digital rectal exam \pm anal cytology in MSM and persons with HPV-associated dysplasia [57]. The evidence of benefit for AC screening is however unknown [57] and no data on the efficacy of any type of AC screening

technique exists [45]. Strategies for AC screening and treatment of AIN are currently under investigation in randomized controlled studies [58]. Current evidence for OPC screening in asymptomatic adults is insufficient [59].

Conclusion

Systematically generated evidence of HPV infection in cohorts of PLWH can help shape primary and secondary HPV related cancer prevention. Here we present data from a Danish cohort of WLWH, demonstrating that more than half had cervical and anal HPV infection with a large proportion presenting with multiple, concurrent anogenital HPV infections. Non-16/18 hrHPV genotypes were predominant, which renders the 2- and 4-valent HPV vaccines less effective than the 9-valent HPV vaccine. Regarding secondary prevention, evidence of benefit is still insufficient regarding OPC and AC screening, but these data support continued focus on CC screening in WLWH.

Authors' contributions

KT contributed to conception and design of the study, included patients, performed interviews and gynaecological examinations, analysed and interpreted data, and drafted the manuscript. MS contributed to conception and design of the study, included patients, performed interviews and gynaecological examinations, and critically reviewed the manuscript. TLK contributed to conception and design of the study, included patients, performed interviews and gynaecological examinations, and critically reviewed the manuscript. SL, designed the bioinformatics analyses with KT and JB and critically reviewed the manuscript. FR included patients, performed interviews

and gynaecological examinations, and critically reviewed the manuscript. ISJ contributed to conception and design of the study, included patients, performed interviews and gynaecological examinations, and critically reviewed the manuscript. GP contributed to conception and design of the study, included patients, performed interviews, and critically reviewed the manuscript. LNN included patients and performed interviews, and critically reviewed the manuscript. AG contributed in interpretation of data, drafting and revising of the manuscript. JB was in charge of the analyses of HPV, was involved in data structuring, the interpretation of data, and writing the manuscript. AML, principal investigator, contributed to conception and design of the study, included patients and performed interviews and gynaecological examinations, was involved in analysis and interpretation of data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Ethical approval

The study and the DHCS were approved by the Danish Data Protection Agency (2015-231-0126, 2012-58-0004 and 2012-41-0005). The study was approved by the Danish Regional Committee on Health Research Ethics (approval numbers: H-3-2010-119 and H-2-2014-102).

Conflict of interests

KT has received research funding from Abbott, a travel grant from Janssen-Cilag and honoraria from Janssen-Cilag, BMS and GlaxoSmithKline/Viiv. MS has received an unrestricted grant from Gilead. TLK has received research funding and/or honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline/Viiv, Abbott, Gilead, and Janssen-Cilag. Since the paper in question was initiated, SL, has taken up a position in Novo Nordisk A/S working within the insulin franchise. For this paper SL is affiliating Clinical Research Centre, Copenhagen University Hospital, Hvidovre. JB attended meetings with various HPV device manufacturers. JB used to serve as a paid advisor to Roche and Genomica, and has received honoraria from Hologic/Gen-probe, Roche, Qiagen, Genomica, and BD Diagnostics for lectures, and is the principal investigator on projects funded by BD Diagnostics, Genomica, and Qiagen. AML has received travel grant and/or honoraria from Bristol-Myers Squibb, Gilead and GlaxoSmithKline. SL, FR, IJ, GP, LNN, AG discloses no conflicts of interest.

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ACCEPTED MANUSCRIPT

Reference List

1. Parkin DM, Bray F: **Chapter 2: The burden of HPV-related cancers.** *Vaccine* 2006, **24 Suppl 3**: S3-11-S3/25.
2. Brickman C, Palefsky JM: **Human Papillomavirus in the HIV-Infected Host: Epidemiology and Pathogenesis in the Antiretroviral Era.** *Curr HIV/AIDS Rep* 2015, **12**: 6-15.
3. Taylor S, Bunge E, Bakker M, Castellsague X: **The incidence, clearance and persistence of non-cervical human papillomavirus infections: a systematic review of the literature.** *BMC Infect Dis* 2016, **16**: 293.
4. Palefsky J: **Human papillomavirus-related disease in people with HIV.** *Curr Opin HIV AIDS* 2009, **4**: 52-56.
5. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM: **Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis.** *Lancet* 2007, **370**: 59-67.
6. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA: **Risk of human papillomavirus-associated cancers among persons with AIDS.** *J Natl Cancer Inst* 2009, **101**: 1120-1130.
7. Rocha-Brischiliari SC, Gimenes F, de Abreu AL, Irie MM, Souza RP, Santana RG *et al.*: **Risk factors for cervical HPV infection and genotypes distribution in HIV-infected South Brazilian women.** *Infect Agent Cancer* 2014, **9**: 6.
8. McKenzie ND, Kobetz EN, Hnatyszyn J, Twigg LB, Lucci JA, III: **Women with HIV are more commonly infected with non-16 and -18 high-risk HPV types.** *Gynecol Oncol* 2010, **116**: 572-577.
9. Denslow SA, Rositch AF, Firnhaber C, Ting J, Smith JS: **Incidence and progression of cervical lesions in women with HIV: a systematic global review.** *Int J STD AIDS* 2014, **25**: 163-177.
10. Engsig FN, Gerstoft J, Kronborg G, Larsen CS, Pedersen G, Pedersen C *et al.*: **Head and neck cancer in HIV patients and their parents: a Danish cohort study.** *Clin Epidemiol* 2011, **3**: 217-27. doi: 10.2147/CLEP.S19875. Epub; 2011 Jul 21.: 217-227.
11. Park LS, Tate JP, Sigel K, Rimland D, Crothers K, Gibert C *et al.*: **Time trends in cancer incidence in persons living with HIV/AIDS in the antiretroviral therapy era: 1997-2012.** *AIDS* 2016, **30**: 1795-1806.
12. Legarth R, Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C *et al.*: **Anal carcinoma in HIV-infected patients in the period 1995-2009: a Danish nationwide cohort study.** *Scand J Infect Dis* 2013, **45**: 453-459.
13. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C: **Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma.** *J Clin Oncol* 2015, **33**: 3235-3242.

14. Wang CC, Palefsky JM: **Human papillomavirus-related oropharyngeal cancer in the HIV-infected population.** *Oral Dis* 2016, **22 Suppl 1**: 98-106.
15. Frisch M: **On the etiology of anal squamous carcinoma.** *Dan Med Bull* 2002, **49**: 194-209.
16. Lin C, Franceschi S, Clifford GM: **Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis.** *Lancet Infect Dis* 2017.
17. Tugizov SM, Herrera R, Chin-Hong P, Veluppillai P, Greenspan D, Michael BJ *et al.*: **HIV-associated disruption of mucosal epithelium facilitates paracellular penetration by human papillomavirus.** *Virology* 2013, **446**: 378-388.
18. Thorsteinsson K, Storgaard M, Katzenstein TL, Ladelund S, Ronsholt FF, Johansen IS *et al.*: **Prevalence and distribution of cervical high-risk human papillomavirus and cytological abnormalities in women living with HIV in Denmark - the SHADE.** *BMC Cancer* 2016, **16**: 866.
19. Konopnicki D, Manigart Y, Gilles C, Barlow P, de MJ, Feoli F *et al.*: **High-risk human papillomavirus genotypes distribution in a cohort of HIV-positive women living in Europe: epidemiological implication for vaccination against human papillomavirus.** *AIDS* 2016, **30**: 425-433.
20. Delory T, Ngo-Giang-Huong N, Rangdaeng S, Chotivanich N, Limtrakul A, Putiyanun C *et al.*: **Human Papillomavirus infection and cervical lesions in HIV infected women on antiretroviral treatment in Thailand.** *J Infect* 2017, **74**: 501-511.
21. Hessol NA, Holly EA, Efird JT, Minkoff H, Weber KM, Darragh TM *et al.*: **Concomitant anal and cervical human papillomavirusV infections and intraepithelial neoplasia in HIV-infected and uninfected women.** *AIDS* 2013, **27**: 1743-1751.
22. Thorsteinsson K, Storgaard M, Katzenstein TL, Ladelund S, Ronsholt FF, Johansen IS *et al.*: **Prevalence and distribution of cervical high-risk human papillomavirus and cytological abnormalities in women living with HIV in Denmark - the SHADE.** *BMC Cancer* 2016, **16**: 866.
23. Heard I, Poizot-Martin I, Potard V, Etienney I, Crenn-Hebert C, Moore C *et al.*: **Prevalence of and Risk Factors for Anal Oncogenic Human Papillomavirus Infection Among HIV-Infected Women in France in the Combination Antiretroviral Therapy Era.** *J Infect Dis* 2016, **213**: 1455-1461.
24. Richter KL, van Rensburg EJ, van Heerden WF, Boy SC: **Human papilloma virus types in the oral and cervical mucosa of HIV-positive South African women prior to antiretroviral therapy.** *J Oral Pathol Med* 2008, **37**: 555-559.
25. Marais DJ, Passmore JA, Denny L, Sampson C, Allan BR, Williamson AL: **Cervical and oral human papillomavirus types in HIV-1 positive and negative women with cervical disease in South Africa.** *J Med Virol* 2008, **80**: 953-959.

26. Ciccarese G, Herzum A, Rebora A, Drago F: **Prevalence of genital, oral, and anal HPV infection among STI patients in Italy.** *J Med Virol* 2017, **89**: 1121-1124.
27. Chuang E, Lim E, Milne C, Zhu X, Agsalda M, Killeen J *et al.*: **Human Papillomavirus at Multiple Sites Associated with Anal Squamous Intraepithelial Lesions in HIV-Seropositive Individuals.** *Ann Clin Cytol Pathol* 2016, **2**.
28. Menezes LJ, Poongulali S, Tommasino M, Lin HY, Kumarasamy N, Fisher KJ *et al.*: **Prevalence and concordance of human papillomavirus infection at multiple anatomic sites among HIV-infected women from Chennai, India.** *Int J STD AIDS* 2015.
29. Statistics Denmark. <http://www.dst.dk/da/Statistik/emner/befolkning-og-valg/befolkning-og-befolkningsfremskrivning/folketal>. Accessed on April 27th 2017. Webpage in Danish. 11-8-2016. 27-4-2017.

Ref Type: Internet Communication

30. Statens Serum Institut. HIV infection and AIDS. <http://www.ssi.dk/Service/Sygdomsleksikon/H/AIDS%20-%20HIV.aspx>. Accessed on April 27th 2017. Webpage in Danish. 27-4-2017. 27-4-2017.

Ref Type: Internet Communication

31. Obel N, Engsig FN, Rasmussen LD, Larsen MV, Omland LH, Sorensen HT: **Cohort profile: the Danish HIV cohort study.** *Int J Epidemiol* 2009, **38**: 1202-1206.
32. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H: **Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.** *MMWR Recomm Rep* 2009, **58**: 1-207.
33. Screening of cervical cancer - recommendations 2007. The Danish National Board of Health. Available from: http://sundhedsstyrelsen.dk/publ/Publ2007/PLAN/Kraeft/Anbef_screen_livmoderhals.pdf. Article in Danish. Summary in English. Accessed on 22nd may 2015. 22-5-2015. 22-5-2015.

Ref Type: Internet Communication

34. Thorsteinsson K, Ladelund S, Storgaard M, Ronsholt FF, Johansen IS, Pedersen G *et al.*: **Sexually transmitted infections and use of contraceptives in women living with HIV in Denmark - the SHADE cohort.** *BMC Infect Dis* 2016, **16**: 81.
35. Lauritsen JM & Bruus M. EpiData (version 3.1). A comprehensive tool for validated entry and documentation of data. The EpiData Association, Odense, Denmark, 2003-2005. 11-2-2015.

Ref Type: Generic

36. Pedersen CB: **The Danish Civil Registration System.** *Scand J Public Health* 2011, **39**: 22-25.

37. Bonde J, Rebolj M, Ejegod DM, Preisler S, Lyng E, Rygaard C: **HPV prevalence and genotype distribution in a population-based split-sample study of well-screened women using CLART HPV2 human papillomavirus genotype microarray system.** *BMC Infect Dis* 2014, **14**:413. doi: 10.1186/1471-2334-14-413.: 413-414.
38. Zeier MD, Botha MH, Engelbrecht S, Machezano RN, Jacobs GB, Isaacs S *et al.*: **Combination antiretroviral therapy reduces the detection risk of cervical human papilloma virus infection in women living with HIV.** *AIDS* 2015, **29**: 59-66.
39. Marks MA, Gupta S, Liaw KL, Tadesse A, Kim E, Phongnarisorn C *et al.*: **Prevalence and correlates of HPV among women attending family-planning clinics in Thailand.** *BMC Infect Dis* 2015, **15**: 159.
40. Heard I, Cubie HA, Mesher D, Sasieni P: **Characteristics of HPV infection over time in European women who are HIV-1 positive.** *BJOG* 2013, **120**: 41-49.
41. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>. Accessed June 24th 2015. 24-6-2015. 24-6-2015.

Ref Type: Internet Communication

42. Rebolj M, Bonde J, Preisler S, Ejegod D, Rygaard C, Lyng E: **Human Papillomavirus Assays and Cytology in Primary Cervical Screening of Women Aged 30 Years and Above.** *PLoS One* 2016, **11**: e0147326.
43. Wood ZC, Bain CJ, Smith DD, Whiteman DC, Antonsson A: **Oral human papillomavirus infection incidence and clearance: a systematic review of the literature.** *J Gen Virol* 2017, **98**: 519-526.
44. de PA, Kaufman E, de CC, Mayrand MH, Burchell AN, Klein M *et al.*: **The EVVA Cohort Study: Anal and Cervical Type-Specific Human Papillomavirus Prevalence, Persistence, and Cytologic Findings in Women Living With HIV.** *J Infect Dis* 2017, **216**: 447-456.
45. Kost BP, Hofmann J, Stoellnberger S, Bergauer F, Blankenstein T, Alba-Alejandre I *et al.*: **Prevalence of human papillomavirus infection of the anal canal in women: A prospective analysis of high-risk populations.** *Oncol Lett* 2017, **13**: 2495-2501.
46. Stier EA, Sebring MC, Mendez AE, Ba FS, Trimble DD, Chiao EY: **Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review.** *Am J Obstet Gynecol* 2015, **213**: 278-309.
47. De BL, Pellegrini B, Moretti ST, Carraro DM, Soares FA, Rocha RM *et al.*: **Infections with multiple high-risk HPV types are associated with high-grade and persistent low-grade intraepithelial lesions of the cervix.** *Cancer Cytopathol* 2017, **125**: 138-143.
48. Patel P, Bush T, Kojic EM, Conley L, Unger ER, Darragh TM *et al.*: **Prevalence, incidence, and clearance of anal high-risk human papillomavirus (HPV) infection among HIV-infected men in the SUN Study.** *J Infect Dis* 2017.

49. Supindham T, Chariyalertsak S, Utaipat U, Miura T, Ruanpeng D, Chotirosniramit N *et al.*: **High Prevalence and Genotype Diversity of Anal HPV Infection among MSM in Northern Thailand.** *PLoS One* 2015, **10**: e0124499.
50. Mendez-Martinez R, Rivera-Martinez NE, Crabtree-Ramirez B, Sierra-Madero JG, Caro-Vega Y, Galvan SC *et al.*: **Multiple human papillomavirus infections are highly prevalent in the anal canal of human immunodeficiency virus-positive men who have sex with men.** *BMC Infect Dis* 2014, **14**: 671.
51. Parisi SG, Cruciani M, Scaggiante R, Boldrin C, Andreis S, Dal BF *et al.*: **Anal and oral human papillomavirus (HPV) infection in HIV-infected subjects in northern Italy: a longitudinal cohort study among men who have sex with men.** *BMC Infect Dis* 2011, **11**: 150.
52. Steinau M, Gorbach P, Gratzler B, Braxton J, Kerndt PR, Crosby RA *et al.*: **Concordance between Anal and Oral Human Papillomavirus (HPV) Infections Among Young Men Who Have Sex with Men.** *J Infect Dis* 2017.
53. Kjaer SK, Munk C, Junge J, Iftner T: **Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ASCUS/LSIL, HSIL, or cervical cancer: what is the potential for prevention?** *Cancer Causes Control* 2014, **25**: 179-189.
54. Konopnicki D, Manigart Y, Gilles C, Barlow P, de MJ, Feoli F *et al.*: **High-risk human papillomavirus genotypes distribution in a cohort of HIV-positive women living in Europe: epidemiological implication for vaccination against human papillomavirus.** *AIDS* 2016, **30**: 425-433.
55. Read TR, Hocking JS, Vodstrcil LA, Tabrizi SN, McCullough MJ, Grulich AE *et al.*: **Oral human papillomavirus in men having sex with men: risk-factors and sampling.** *PLoS One* 2012, **7**: e49324.
56. Toft L, Tolstrup M, Storgaard M, Ostergaard L, Sogaard OS: **Vaccination against oncogenic human papillomavirus infection in HIV-infected populations: review of current status and future perspectives.** *Sex Health* 2014, **11**: 511-523.
57. EACS Guidelines version 9.0 October 2017. Available from: http://www.eacsociety.org/files/guidelines_9.0-english.pdf . Accessed on November 21th 2017. 21-11-0017. 21-11-2017.

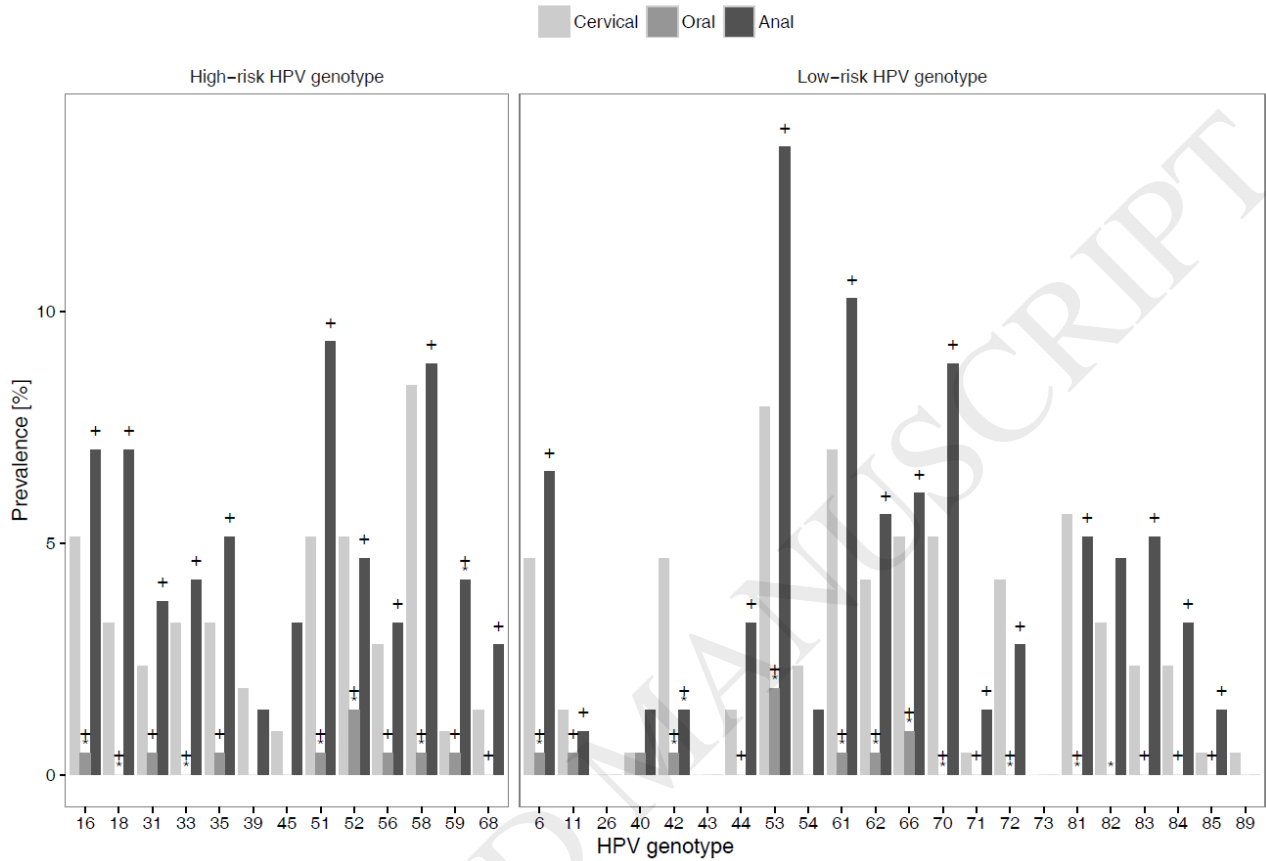
Ref Type: Internet Communication

58. Gosens KC, Richel O, Prins JM: **Human papillomavirus as a cause of anal cancer and the role of screening.** *Curr Opin Infect Dis* 2017, **30**: 87-92.
59. Moyer VA: **Screening for oral cancer: U.S. Preventive Services Task Force recommendation statement.** *Ann Intern Med* 2014, **160**: 55-60.

Caption:

Figure 1.

Comparison of the cervical, oral, and anal human papillomavirus genotype distribution in women living with HIV in Denmark (n=214).



+ = Statistically significant positive correlation with cervical HPV infection.

* = Statistically significant difference in prevalence from cervical HPV infection.

Table 1.
Characteristics of women living with HIV (WLWH) in the study cohort

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Number of individuals	214
Duration of HIV (years), median (IQR)	11.0 (5.3-17.1)
Follow-up time, total (person-years)	2,412
Age at inclusion (years), median (IQR),	42.9 (36.3-48.4)
Race, n(%) White Asian Black Other (missing)	97 (46.0) 27 (12.8) 84 (39.8) 3 (1.4) (3)
Place of HIV transmission, n(%) Denmark Europe + US Africa Asia Other (missing)	75 (38.9) 19 (9.8) 78 (40.4) 21 (10.9) 0 (0) (21)
Mode of transmission, n(%) Heterosexual IDU Other (missing)	189 (90.9) 11 (5.3) 8 (3.8) (6)
CD4 count at inclusion in SHADE (cells/ μ L), n(%) <200 200-350 >350 (missing)	9 (4.6) 32 (16.4) 154 (79.0) (19)
ART at inclusion), n(%) Yes No (missing) On ART with HIV RNA<40 copies/mL), n(%) Yes No (missing) HPV vaccination prior to inclusion, n(%) Yes (4-valent HPV vaccine) Yes (2-valent HPV vaccine) Yes (do not know name of vaccine) No (missing)	204 (95.3) 10 (4.7) (0) 154 (80.6) 37 (19.4) (13) 3 (1.4) 0 (0) 1 (0.5) 210 (98.1) (0)
Age at sexual debut (years), mean (range) Lifetime sexual partners, n(%) <5 5-14 15-25 >25 (missing)	17.1 (6-37) 68 (31.8) 82 (38.3) 28 (13.1) 36 (16.8) (0)

IDU = intravenous drug user, SHADE = Study on HIV, cervical Abnormalities and infections in women in Denmark, ART = combined antiretroviral therapy, HPV=Human papillomavirus.

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Table 2

Prevalence of cervical, oral, and anal human papillomavirus (HPV) in women living with HIV (WLWH) with sufficient DNA for analyses at all three anatomical sites (n=214)

	Cervical	Oral	Anal	p-value comparing cervical and oral HPV prevalence	p-value for correlation between cervical and oral HPV infection	p-value comparing cervical and anal HPV prevalence	p-value for correlation between cervical and anal HPV infection
HPV sample result, n(%)							
Overall							
Positive	108 (50.5)	12 (5.6)	135 (63.1)	<0.0001 ¹	0.13 ²	0.0021 ¹	<0.0001 ³
Negative	106 (49.5)	202 (94.4)	79 (36.9)				
High-risk HPV							
Positive	60 (28.0)	8 (3.7)	84 (39.3)	<0.0001 ¹	0.22 ²	0.0013 ¹	<0.0001 ³
Negative	154 (72.0)	206 (96.3)	130 (60.7)				
Low-risk HPV							
Positive	85 (39.7)	7 (3.3)	99 (46.3)	>0.0001 ¹	0.12 ²	0.12 ¹	0.0011 ³
Negative	129 (60.3)	207 (96.7)	115 (53.7)				
Number of genotypes, mean (range)	1.1 (0-9)	0.1 (0-6)	1.5 (0-14)	<0.0001 ⁴	0.13 ⁵	0.0003 ⁴	<0.0001 ⁵
Multiple (>1) infections, n(%)							
Yes	58 (27.1)	3 (1.4)	73 (34.1)	<0.0001 ¹	0.18 ²	0.055 ¹	<0.0001 ³
No	156 (72.9)	211 (98.6)	141 (65.9)				
All high-risk HPV genotypes present targeted by the 2-or 4-valent HPV vaccine ¹ , n(% of women being high-risk HPV-positive at the specific anatomic location)							
Yes	4 (6.7)	1 (12.5)	15 (17.9)	-. ⁶	-. ⁶	0.16 ¹	0.068 ²
No	56 (93.3)	7 (87.5)	69 (82.1)				
All high-risk HPV genotypes present targeted by the 9-valent vaccine ² , n(% of women being high-risk HPV-positive at the specific anatomic location)							
Yes	30 (50.0)	4 (50.0%)	36 (42.9)	-. ⁶	0.33 ²	0.25 ¹	0.0089 ²
No	30 (50.0)	4 (50.0%)	48 (57.1)				
Presence of ≥1 high-risk HPV genotypes from the 2- or 4-valent HPV vaccine, n(% of women being high-risk HPV-positive)							
Positive	16 (26.7)	1 (12.5)	29 (34.5)	-. ⁶	-. ⁶	0.48 ¹	0.0004 ²
Negative	44 (73.3)	7 (87.5)	55 (65.5)				

Presence of ≥ 1 high-risk HPV genotypes from the 9-valent HPV vaccine, n(% of women being high-risk HPV-positive)							
Positive	44 (73.3)	5 (62.5)	58 (69.1)	- ⁶	0.25 ²	1.00 ¹	<0.0001 ²
Negative	16 (26.7)	3 (37.5)	26 (30.9)				

¹ McNemar's test, ² Fisher's test,

³ Chi-square test, ⁴ Wilcoxon rank sum test,

⁵ Kendall's Tau-b test, ⁶ Cannot be estimated.

Table 3

Comparison of cervical, oral and, anal HPV genotype distribution (n=214)

HPV genotype	Cervical HPV genotype distribution n(%)	Oral HPV genotype distribution n(%)	Anal HPV genotype distribution n(%)	Comparison of cervical and oral HPV infection <i>p</i> -value	Comparison of cervical and anal HPV infection <i>p</i> -value
hrHPV58	18 (8.4)	1 (0.5)	19 (8.9)	<0.0001	1.00
hrHPV52	11 (5.1)	3 (1.4)	10 (4.7)	0.021	1.00
hrHPV51	11 (5.1)	1 (0.5)	20 (9.3)	0.0020	0.093
hrHPV16	11 (5.1)	1 (0.5)	15 (7.0)	0.0063	0.45
hrHPV35	7 (3.3)	1 (0.5)	11 (5.1)	0.070	0.34
hrHPV33	7 (3.3)	0 (0)	9 (4.2)	0.016	0.69
hrHPV18	7 (3.3)	0 (0)	15 (7.0)	0.016	0.057
hrHPV56	6 (2.8)	1 (0.5)	7 (3.3)	0.063	1.00
hrHPV31	5 (2.3)	1 (0.5)	8 (3.7)	0.13	0.51
hrHPV39	4 (1.9)	0 (0)	3 (1.4)	0.13	1.00
hrHPV68	3 (1.4)	0 (0)	6 (2.8)	0.25	0.38
hrHPV59	2 (0.9)	1 (0.5)	9 (4.2)	1.00	0.0016
hrHPV45	2 (0.9)	0 (0)	7 (3.3)	0.50	0.13
lrHPV53	17 (7.9)	4 (1.9)	29 (13.6)	0.0024	0.058
lrHPV61	15 (7.0)	1 (0.5)	22 (10.3)	0.00012	0.17
lrHPV81	12 (5.6)	0 (0)	11 (5.1)	0.00049	1.00
lrHPV70	11 (5.1)	0 (0)	19 (8.9)	0.00098	0.057
lrHPV66	11 (5.1)	2 (0.9)	13 (6.1)	0.012	0.75
lrHPV42	10 (4.7)	1 (0.5)	3 (1.4)	0.012	0.039
lrHPV6	10 (4.7)	1 (0.5)	14 (6.5)	0.012	0.42
lrHPV72	9 (4.2)	0 (0)	6 (2.8)	0.0039	0.45
lrHPV62	9 (4.2)	1 (0.5)	12 (5.6)	0.0078	0.58
lrHPV82	7 (3.3)	0 (0)	10 (4.7)	0.016	0.61
lrHPV84	5 (2.3)	0 (0)	7 (3.3)	0.063	0.73
lrHPV83	5 (2.3)	0 (0)	11 (5.1)	0.063	0.11
lrHPV54	5 (2.3)	0 (0)	3 (1.4)	0.063	0.73
lrHPV44	3 (1.4)	0 (0)	7 (3.3)	0.25	0.22

lrHPV11	3 (1.4)	1 (0.5)	2 (0.9)	0.50	1.00
lrHPV89	1 (0.5)	0 (0)	0 (0)	1.00	1.00
lrHPV85	1 (0.5)	0 (0)	3 (1.4)	1.00	0.50
lrHPV71	1 (0.5)	0 (0)	3 (1.4)	1.00	0.50
lrHPV40	1 (0.5)	1 (0.5)	3 (1.4)	1.00	0.63
lrHPV73	0 (0)	0 (0)	0 (0)	1.00	1.00
lrHPV43	0 (0)	0 (0)	0 (0)	1.00	1.00
lrHPV26	0 (0)	0 (0)	0 (0)	1.00	1.00

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Table 4
Unadjusted and adjusted odds ratios for predictors of overall anal human papillomavirus (HPV) infection (n =214)

Predictors of anal HPV ¹	HPV-positive group (n=135)	HPV-negative group (n=79)	Unadjusted odds ratios	p-value	Adjusted odds ratios ²	p-value
Age at 1 February 2011 (inclusion), n(%)						
18-29 years	12 (8.9)	2 (2.5)	1.00	-	1.00	-
30-50 years	93 (68.9)	63 (79.8)	0.25 (0.05-1.14)	0.073	0.25 (0.05-1.36)	0.11
≥50 years	30 (22.2)	14 (17.7)	0.36 (0.07-1.82)	0.21	0.36 (0.06-2.29)	0.28
(missing)	(0)	(0)		0.14		0.21
Combined p-value						
Race, n(%)						
White	65 (49.6)	32 (41.6)	1.00	-	1.00	-
Asian	14 (10.7)	13 (16.9)	0.53 (0.22-1.26)	0.15	0.66 (0.24-1.84)	0.43
Black	52 (39.7)	32 (41.6)	0.80 (0.43-1.47)	0.47	1.12 (0.49-2.55)	0.80
(missing)	(4)	(2)				
Combined p-value				0.35		0.59
Sexual debut, n(%)						
< 16 years of age	47 (34.8)	21 (26.6)	1.00	-	1.00	-
≥ 16 years of age	88 (65.2)	58 (73.4)	0.68 (0.37-1.25)	0.21	0.77 (0.35-1.69)	0.51
(missing)						
ART duration, (years)						
Median (IQR)	7.57 (2.59-12.02)	7.54 (3.93-10.64)	0.98 (0.93-1.04)	0.56	1.03 (0.95-1.11)	0.52
(missing)						
AIDS prior to inclusion, n(%)						
Yes	20 (14.9)	15 (19.2)	1.00	-	1.00	-
No	114 (85.1)	63 (80.8)	1.37 (0.65-2.84)	0.42	2.18 (0.92-5.15)	0.076
(missing)	(1)	(1)				
Smoking status, n(%)						
Never smoker	70 (51.9)	53 (67.1)	1.00	-	1.00	-
Current smoker/ Ex-smoker	65 (48.1)	26 (32.9)	1.89 (1.06-3.37)	0.031	1.91 (0.87-4.19)	0.11
(missing)	(0)	(0)				
Number of lifetime sexual partners at inclusion, n(%)						
<5	39 (28.9)	29 (36.7)	1.00	-	1.00	-
≥5	96 (71.1)	50 (63.3)	1.43 (0.79-2.58)	0.22	0.92 (0.44-1.93)	0.85
(missing)	(0)	(0)				
Use of hormonal contraceptives, n(%)						
Yes	7 (5.2)	8 (10.1)	1.00	-	1.00	-
No	128 (94.8)	71 (89.9)	2.06 (0.72-5.92)	0.18	2.03 (0.53-7.83)	0.31
(missing)	(0)	(0)				
Cervical HPV infection, n(%)						
No	52 (38.5)	54 (68.3)	1.00	-	1.00	-
Yes	83 (61.5)	25 (31.7)	3.45 (1.92-6.20)	<0.0001	4.47 (2.25-8.89)	<0.0001
(missing)				1		
CD4 count at inclusion in SHADE (cells/μL),						
<200	4 (3.3)	5 (6.6)	1.00	-	1.00	-
200-350	24 (20.2)	8 (10.5)	3.75 (0.81-17.48)	0.092	4.14 (0.72-23.74)	0.11
>350	91 (76.5)	63 (82.9)	1.81 (0.47-6.99)	0.39	2.13 (0.46-9.91)	0.34
(missing)	(16)	(3)				
Combined p-value				0.15		0.21

ART = combined antiretroviral therapy, SHADE = Study on HIV, cervical Abnormalities and infections in women in Denmark.

¹Two models are shown in the table: Age, race, sexual debut, smoking status, number of lifetime sexual partners and use of hormonal contraceptives were included in both models, whereas ART duration and AIDS prior to inclusion were included in the first model and replaced by CD4 at inclusion in the second model. We only presented the ORs of the CD4 count from the second model; ² The validity of the model was tested using the Hosmer and Lemeshow Goodness-of-Fit Test.