Human papillomavirus (HPV) genotypes and associated cervical disease in an anti-retroviral setting in Accra, Ghana

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Abstract

Background

The vast majority of women diagnosed with HIV/AIDS are found in the Sub-Saharan African region. These women have a high chance of being infected with human papillomaviruses (HPV), which causes cervical cancer and precursor lesions. Early initiation of HAART coupled with a high HAART compliance may reduce disease burden, but in Ghana, little is known about the distribution of HPV infections and epithelial changes in this vulnerable group.

Methods

This work was carried out to establish the distribution of genital HPV genotypes among women living with HIV attending a special HIV outpatient clinic at the Korle-Bu Teaching hospital Accra, Ghana. Pap smears were performed for 538 selected women. A highly sensitive nested multiplex PCR (NMPCR) assay was conducted for the detection and typing of human papillomavirus (HPV) genotypes. These included, 6/11, 16,18, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 56, 58, 59, 66, and 68. Cervical smears were examined for cytologic abnormalities by two cytologists and verified by a pathologist.

Results

Coverage of HAART in this population was 84%. HPV DNA was detected in 280 out of the 538 individuals studied, 52.0% (95%CI 47.7–56.3). Out of these 129 (46.1%, 95%CI 40.1–52.1) had multiple HPV infections and 151 (53.9%, 95%CI 47.9–59.9) had single infections. The prevalence of LR HPV was 10.2% (95% CI: 11.3–17.6). while that of HR HPV was 29.7% (95% CI: 27.4–35.7). The commonest HR types were, 35 ,18 ,58 ,52 and 45 in descending order. The frequency of HPV 16 was 2.4%. Cytologically, 2.8% had ASCUS, 3.9% LGSIL and 2.8% HGSIL, none of the women was found to have atypical glandular cells or adenocarcinoma. The commonest HPV genotypes detected among women with ASCUS were HPV-18 (25% of all ASCUS cases), 52 (25% of all ASCUS cases) and 68 (25% of all ASCUS cases). Among women with LSIL most prevalent were HPV-52 (66.5% of all LSIL cases), HPV-18 (22.2% of all LSIL cases) and HPV 45 (22.2% of all LSIL cases). HPV-16, 52 and 42 were each found in 50% of all High-grade lesions., being the top three in that order for high grade intraepithelial/severe dysplasia lesions

Conclusions

There is a high burden of HPV infection in women living with HIV attending clinic at the KBTH. Given the high prevalence of HIV-HPV coinfection despite the high coverage of HAART, associated cervical lesions represent a major public health burden. These results show that currently available prophylactic vaccines have the potential to be useful in the primary prevention of HPV infections among immunocompromised

women. This study also found a cross-sectional association between early age at first sex and the presence of precancerous cervical lesions. Efforts to make vaccines available to young girls before sexual debut should be prioritized along with education on safe sexual habits.

Background

The trend of HIV in Africa is on the rise among women due to cultural and heterosexual activities (Awofala & Ogundele, 2018). In 2015, approximately 390,000 new infections of HIV were recorded among young women between the ages of 15 to 24 representing about 60% of all new HIV infection all over the world in this age group (HIV/AIDS, 2018). Unfortunately, when these women are not mapped to proper healthcare and fail to achieve viral suppression, the risk of opportunistic infections increase and may result in a poor prognosis.

Both human papillomaviruses (HPV) and human immunodeficiency viruses (HIV) have a common transmission route and are often found together in human populations exhibiting high-risk sexual behaviour (Adams et al., 2019; Clifford et al., 2006; Park et al., 2014). Characteristically, low- and middle-resource countries which have not implemented robust pap testing strategies and where women have been hit hardest by the AIDS epidemic, also have a very high prevalence of HPV infection and its sequelae of precancerous lesions (Franceschi & Jaffe, 2007). Vulnerable women living with HIV, especially those having low CD4 T-cell counts and often beyond the reach of healthcare services are most likely to be infected with human papillomaviruses (Denny et al., 2012; Sinayobye et al., 2014).

The immunocompromised state of women living with HIV predisposes them to a higher rate of infection with high-risk HPV types. Reduced ability to clear HPV may result in multiple HPV infections with aggressive HPV types and a higher tendency for viral persistence (Akarolo-Anthony et al., 2013; Burd, 2003; Clifford et al., 2006; Odida et al., 2011; Strickler et al., 2005). As a result of this synergy, HIV infection may increase the risk of developing cervical squamous intraepithelial neoplasia (CIN) and gynaecological cancers among women (Sinayobye et al., 2014). In addition, persistent HPV genotypes harboured by these women could spill-over into the general population if unchecked.

Antiretroviral therapy (ART) for WLHIV provides a golden opportunity to increase cervical screening through the integration of ART services with frequent screening of women for cervical cancer (Torre et al., 2016). Ghana does not have a national cervical cancer screening program presently and therefore Pap smears are routinely ordered for differential diagnosis in cases of unusual vaginal bleeding rather than as part of a routine gynaecologic investigation or screening program (Donkoh et al., 2019; Handlogten et al., 2014). As such, data on cervical intraepithelial neoplasia and invasive cancer among women living with HIV and enrolled/unenrolled on HAART is routinely not available.

Cervical cancer and precancer takes a great toll on women globally. In Sub Saharan Africa about 500,000 new cases of cervical cancer are recorded annually resulting in 270,000 deaths (Cancer, 2012; Torre et al., 2015). HIV-infected women remain at a continued substantial risk for cervical cancer, even if they receive ART because these treatment programs improve the women's survival long enough for undetected

precursor lesions to progress to invasive cancer (Mbulaiteye et al., 2006; Sinayobye et al., 2014). To prevent this, other strategies for prevention are urgently needed (Ghebre et al., 2017). Aside the highly effective pap test, a number of vaccines have been developed and evaluated for efficacy in preventing HPV infection especially when given to young girls before sexual debut. So far, these have been shown to be safe and efficacious in most large-scale trials (Arbyn et al., 2011; FDA, 2014 ; Petrosky et al., 2015; WHO/ICO, 2010). Nevertheless an important prerequisite for universal vaccination programmes is the need for reliable data on the epidemiology of HPV types especially among women with HIV coinfection. Genotyping studies will allow for the estimation of the total burden attributable to vaccine preventable HPV types and by extension, the impact of vaccination in the general population. The paucity of literature in this population especially in the HAART era motivated this study.

Methods

Study population and demography of study site

A cross-sectional observational study was undertaken among women living with HIV with the objective to characterize cytological lesions and the epidemiology of human papillomaviruses (HPV) in this population. Women 18 years and above presenting to the HIV clinic at the Korle-Bu Teaching Hospital (KBTH) with a verifiable diagnosis of HIV infection were qualified to be included in the study. Women who had undergone hysterectomy, had Pap smear result in the last 6 months or could not undergo an interview or a speculum examination were excluded from the study. The HIV Clinic at the KBTH is located in the Fever's Unit under the Department of Medicine has been providing ART services to PLHIV since December 2003 from the capital city of Ghana. Currently the KBTH HIV Clinic has 24-beds and the largest register of HIV patients in Ghana. About 20,000 patients attend the clinic each year. The hospital runs the HIV Clinic three days in a week (Mondays, Wednesdays and Fridays) and operates an institutionalized electronic database which stores all clinic visits as well as medications, laboratory investigations and other patients' data.

Selection of study participants

In all, 538 women were randomly selected from the clinic register and scheduled for interviews. The minimum required sample size was calculated using the formula $N = z^2 p(1-p)/d^2$ at 95% confidence interval. In this equation, N = desired sample size, z = the standard normal deviation (set at 1.96 corresponding to the 95% CI), d = precision or degree of accuracy desired (set at 0.05) and p = the proportion in the target population estimated to have the outcome of interest. In previous studies in sub-Saharan Africa, HPV prevalence rates have ranged from 40–86% in women living with HIV (Menon et al., 2016; Yar et al., 2015); the prevalence of high-risk HPV infection in this population was established at 23% (Donkoh, 2015) and the prevalence of Pap smear abnormalities among women attending reproductive health services was 44% (Dames et al., 2009). Sample size was calculated using StatCalc application of EpiInfo 3.5.3.

On clinic days, lists of scheduled clients were obtained and a sample size of 10/day was selected by computer generated random digit numbers. A maximum of 10 clients per clinic day was agreed to afford the clinic staff adequate time for sampling within clinic hours. Unique code numbers of previously seen patients were excluded from subsequent sampling frames.

Ethics

After recruitment, patients were taken through the consent process and sampled only after satisfying the study inclusion/selection criteria. The study was approved by the Korle Bu Teaching Hospital Ethical Committee and the College of Health Sciences ethics review board. Study participants were sufficiently briefed on the reasons, nature, processes, risks and dangers of the procedure. Importance was placed on anonymity, secrecy and the right to opt-out of the study any time without any consequences to their right to care at the clinic. Written informed consent was obtained from all women recruited for this study. Recruited patients who did not satisfy the inclusion/selection criteria or who refused to take part in the study on any particular study day were not replaced: the enrolment procedure continued until the sample size estimated was reached. A total of 109 clinic days were used for the recruitment of study participants.

Data collection tools: pretesting and administration

An in-depth, semi-structured, interviewer-administered questionnaire (Appendix 1) was previously developed and pre-tested in a non-study area. Feedback from the pre-test was used to restructure the format and presentation of interview guides and questionnaire for optimum achievement of study aims and benefits. The questionnaire, which was in English, was administered in Twi by the investigator in the presence of clinic nurses as required. Participants were encouraged to ensure they understood the questions first before providing answers. Information was sought on demographics and socioeconomic characteristics.

Clinical examination, sample collection

Cervical swabs were available for 538 eligible women. To ensure that the best specimens were collected for analysis, standard procedure for collecting cervical samples was followed [12, 13]. Cervical epithelial cells were obtained using the Pap Pak® cytology kit (Medical Packaging Corporation, Camarillo, CA, USA) according to the manufacturer's instructions. Cervical smears were taken by gynaecologists with experience in taking Pap smears. Exfoliated cervical cells were recovered by washing into pre-labelled tubes containing DNA Guard (Biometrica, San Diego, USA), to preserve cellular genetic material at room temperature until HPV-DNA detection.

Staining and screening of cytological slides

The modified Papanicolaou method employing a standard nuclear stain, hematoxylin and two cytoplasmic counterstains (Orange-G-6 & Eosin Azure was used for the staining of cervical cytology slides (Koss & Melamed, 2006). Slides were examined independently by two experienced cytotechnologists at the Pathology Department, KBTH. All positive cases, unsatisfactory smears and 10%

random selection of all negative cases were reviewed by a pathologist for final interpretation, reporting and quality control.

HPV-DNA extraction, detection and genotyping

HPV-DNA detection and identification of the genotypes was carried out by nested multiplex PCR (NMPCR) as previously described (Awua et al., 2016). Briefly, DNA was extracted with a commercial kit (Qiagen Ltd, Maryland, USA) according to the manufacturer's instructions. A single consensus forward primer (GP-E6-3F) and two consensus back primers (GP-E7-5B and GP-E7-6B) were used for the general primer PCR. The PCR reaction mix of 50µl contained 10X PCR buffer, 2.5 mM MgCl₂ 200µM of each of the four deoxyribonucleoside triphosphates (dNTP), 15pmols of each E6/E7 consensus primers and 1.25 units of Taq polymerase enzyme. Four microlitres (4µl) of DNA extracts was used as template for the amplification reactions on a thermal cycler (BIOER GenePro thermocycler, BIOER Co., USA). In the second round PCR, 2µl of first round PCR product, 15pmols of forward and reverse primers for genotyping were used. Primers for the identification of high-risk genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 and low-risk genotypes 6/11, 42, 43, and 44 were used. The amplification products were analysed by gel electrophoresis on 2% agarose gel and stained with 0.5µg/ml ethidium bromide as described (Awua et al., 2016).

Data management and analyses

Data from questionnaires was checked for accuracy and processed in Microsoft® Excel® (Microsoft Corporation, Redmond Campus, Washington DC, USA) computer software. Data was analysed and managed using SYSTAT 12 for Windows (2007) (SYSTAT Software Inc., Florida, USA) and GraphPad Prism 5.31 for Windows (2007) (GraphPad Software, San Diego California USA).

All HPV types were classified as low or high risk for high-grade cervical disease or as uncharacterized. HPV assignments were as described elsewhere (Munoz et al., 2003). HPV types grouped within the high-risk category included 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. HPV types grouped within the low-risk category included 6/11, 42, 43, 44 and 66. Women with multiple HPV types were considered to be in each risk category on the basis of the detection of any 1 of the high-risk or low-risk, HPV types. Analyses were not restricted to women with only single HPV infections.

The goals of the statistical analysis were to describe the relationship of sex history and age to the detection of high-risk, low-risk, and uncharacterized HPV types, as well as to evaluate additional subject characteristics for their association with the detection of these 2 HPV groups after controlling for sex history and age. Sex history included number of lifetime sex partners, number of sex partners in the past year, age at first intercourse, number of years since first sexual intercourse, and sex history of the current sex partner. Additional subject characteristics included age, ethnicity, marital status, education level, age at menarche, parity, smoking history, history of use of condoms, and birth control pills. The relationships among variables of HPV detection, sex history, and age were depicted graphically and with simple contingency tables. In initial analysis, categorical variables were compared using Chi square test and student t-test was used for quantitative variables. For hypotheses comparing frequencies among groups,

X² tests were performed; comparisons of subgroups (e.g., gender, race) was assessed by logistic regression.

Results

This study investigated the association of selected demographic and behavioural characteristics with the detection of 18 genital human papillomavirus (HPV) genotypes in women recruited at the KBTH for cervical screening. Cervical samples were obtained from 538 women aged 20 to 69 years. The mean age of the participants was 40.7 years (SD = 8.4years). The four major ethnic groupings in Ghana were represented in the study as follows: Akan (48.8%), Mole-Dagbani (16.9%), Ewe (19.5%) and Ga (19.3%) (Table 1). Coverage of formal education was 76.2%: most women had completed primary school (57.4%), fewer (4.6%) had completed tertiary level education. Married women (38.3%) and widows (23.4%) formed the majority of the population. With regards to employment, majority of the women were involved in non-formal work, mostly petty trading (78.8%).

Table 1
Socio-demographic characteristics of study population

Variable	Frequency	Percentage	Valid responses
Age (years)			538
< 25	6	1.1	
25–34	118	21.9	
35–44	248	46.1	
45–54	137	25.5	
55–64	29	5.4	
Formal education			538
None	128	23.8	
Primary	309	57.4	
Secondary	76	14.1	
Tertiary	25	4.7	
Occupation			538
Civil servant	35	6.5	
Unemployed	79	14.7	
Non-formal work	424	78.8	
Marital status			538
Divorced	96	17.8	
Married	206	38.3	
Single	110	20.5	
Widowed	126	23.4	
Ethnicity			532
Akan	230	43.2	
Ewe	105	19.7	
Ga	104	19.5	
Mole-Dagbani	91	17.1	
HIV duration (months)			535
< 48	118	22.1	

Variable	Frequency	Percentage	Valid responses
48–71	119	22.2	
72–95	104	19.4	
96–119	106	19.8	
> 119	88	16.4	
ART enrolment			511
Yes	429	84.0	
No	82	16.0	
ART duration (months)			424
< 30	148	35.0	
30–59	95	22.4	
60–89	128	30.2	
> 89	53	12.5	

Prevalence of Cervical Cytology Abnormalities

Out of the 538 women for whom a Pap smear was available for evaluation, 433 (80.5%) were negative for intraepithelial lesion or malignancy and 26 were unsatisfactory for evaluation due to various reasons. Included among the 433 negative smears were 27 slides with no transformation zone components but no dyskaryosis or intraepithelial lesion seen (Table 2). Fifteen women (2.8%) showed atypical squamous cells of undetermined significance (ASCUS), 21 (3.9%) low-grade squamous intraepithelial lesions, and 15 (2.8%) high-grade squamous intraepithelial lesions. None of the women was suspected to have invasive squamous cell carcinoma and none was found to have atypical glandular cells or adenocarcinoma.

Table 2
Prevalence of cervical abnormalities among WLHIV

	Frequency (N)	Percentage (%)
NILM*	433	80.5
ASCUS	15	2.8
ASC-H	1	0.2
LGSIL	21	3.9
HGSIL	15	2.8
No TZC	27	5.0
Unsatisfactory	26	4.8
Total	538	100.0
Cytology results according to Bethesda system. NILM: Negative for intraepithelial lesions or malignancy, ASCUS: Atypical squamous cells of unknown significance, ASC-H: Atypical squamous cells, cannot rule out HSIL, LGSIL: Low-grade squamous intraepithelial lesions, HGSIL: high-grade squamous intraepithelial lesions.		

Prevalence of HPV Genotypes among Unscreened Women Living with HIV

Cervical swabs were obtained from 538 HIV-positive women with no history of Pap smear screening and analysed for 18 HPV types. Table 3 shows the prevalence of HPV types detected in smears from these women. The prevalence of low-risk HPV (LR-HPV), types 6/11, 42, 43, 44 and 66, and high-risk HPV (HR-HPV), types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are shown in Figs. 1 and 2. The occurrence of HPV DNA was 52.0% (280/538 women, 95% CI: 47.7–56.3). The prevalence of LR-HPV without taking note of other types was 22.3% (120/538 women; 95% CI 18.8–26.1) while that of HR HPV without accounting for other types was 41.8% (225/538 women; 95% CI 37.6–46.1). LR HPV only infection was seen in 10.2% (55/538 women, 95%CI 7.8–13.1). HR HPV only infection was seen in 29.7% (160/538 women, 95% CI 25.9–33.8). Both HR and LR were seen in 12.1% (65/538 women, 95%CI 9.4–15.1).

Table 3
Prevalence of human papillomavirus (HPV) in WLHIV.

Parameter	Frequency	Percentage
HPV present (N = 538)		% ^a
Yes	280	52.0
No	258	48.0
Type of HPV detected (N = 280)		% ^b
HR HPV only	160	57.1
LR HPV only	55	19.6
Both HR & LR HPV	65	23.2
Number of HPV genotypes detected (N = 280)		% ^b
Single	151	53.9
Multiple	129	46.1
^a Percentages calculated using total number of cases (N = 538) as common denominator.		
^b Percentages calculated using number of positive cases (N = 280) as common denominator.		
^α Women infected with only LR HPV. Low-risk HPV types include 6/11, 42, 43, 44 and 66.		
^β Women infected with only HR HPV. High-risk HPV types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.		

All 18 HPV genotypes screened were detected as shown in Figs. 1 and 2. The most common HR-HPV types were HPV-35 with 14.1% (76 out of 538 women, 95%CI 11.3–17.4), HPV-18 (13.0%; 70 out of 538 women, 95%CI 10.3–16.1), HPV-58 (7.4%; 40 out of 538 women, 95% CI 5.4–10.0), HPV-52 (7.2%; 39 out of 538 women), and HPV-45 (4.8%; 26 out of 538 women, 95% CI 3.2–7.0). HPV 42 with 7.8% (39 out of 538 women, 95% CI 5.2–9.8) was the commonest LR-HPV type detected. The frequency of HPV 16 (the main HR-HPV type linked with cervical cancer worldwide) was 2.4% (13 out of 538 women, 95%CI 1.3–4.1) (Supplementary file: S1 Table).

Distribution of HPV genotypes according to cytology outcome

The HPV type distribution in WLHIV stratified according to cytological outcome (presence or absence of cervical cytology abnormality) is shown in Table 4. The majority of women 86.2% (464/538 women, 95% CI 83.0–89.0) had normal cervical findings. Only 9.7% (52/538 women, 95% CI 7.3–12.5 (9.7%) had a concurrent abnormal Pap smear result. Among women who had abnormal cervical results, the prevalence of HPV infection was 50.0% (26/52 women, 95% CI 35.8–64.2) compared to 51.5% (239/464 women, 95%CI 46.8–56.1) who had normal cytology results ($\chi^2 = 0.04$, df = 1, P = 0.84). Women who had abnormal Pap smear findings did not have a disproportionate prevalence of HR-HPV infection ($\chi^2 = 0.01$, df = 1, P = 0.91). The prevalence of HR HPV infection was 80.8% among women with abnormal simultaneous pap result compared to 79.9% among women with normal Pap smear findings. The distribution of LR-HPV infections according to cytology outcome was not statistically significant ($\chi^2 = 0.51$, df = 1, P = 0.47). Again, women with atypical pap smears did not show a greater tendency to harbour multiple HR-HPV infections compared to women with normal pap smears ($\chi^2 = 0.57$, df = 1, P = 0.45). Multiple infections were more likely to be associated with HR-HPV genotypes than with LR-HPV infection ($\chi^2 = 122.3$, df = 2, P = 0.00).

Table 4

HPV type distribution in women living with HIV stratified according to concurrent cytology outcome and number of detected HPV genotypes

Pap test									
Normal			Abnormal			Total			
HPV type	Single	Multiple	count (% ^{a,b})	Single	Multiple	count (% ^{c,d})	Single	Multiple	Total (%)
			n = 464 (86.2)			n = 52 (9.7)			n = 538
HPV negative			225 (48.5 ^a)			26 (50.0 ^c)			251 (46.7 ^e)
HPV positive	129	110	239 (51.5 ^a)	12	14	26 (50.0 ^c)	141	124	265 (49.3 ^e)
HR HPV positive ^α	81	110	191 (79.9 ^b)	8	13	21 (80.8 ^d)	89	123	212 (75.7 ^f)
LR HPV positive ^β	48	54	102 (42.7 ^b)	4	9	13 (50.0 ^d)	52	63	115 (41.1 ^f)
^α All women harbouring at least one HR HPV infection. Cases with more than one HR infection are counted once.									

^β All women harbouring at least one LR HPV infection. Cases with more than one LR infection are counted once.

%^a: out of 464 women with normal cytology

%^b: out of 239 HPV positive cases with normal cytology

%^c: out of 52 women with abnormal cytology

%^d: out of 26 HPV positive cases with abnormal cytology

%^e: out of 538 WLHIV

%^f: out of 280 HPV positive WLHIV, not excluding 22 unsatisfactory pap smears absent from Table 4

There were 22 unsatisfactory slides out of which 17 had HPV infection: 7 had multiple HPV infections and 10 had single HPV infections (the distribution of HR- and LR-HPV in rejected slides are given in Supplementary file: S2 and S3 Tables).

Prevalence of high-risk HPV according to cytology outcome

The present study investigated the relationship between detection of HPV genotypes and cytology outcome in women living with HIV at the Korle-Bu teaching hospital, Accra. Table 5 presents the distribution of all types of HPV, low risk and high-risk HPVs and the corresponding diagnostic category for these women. Prevalence of HPV infection ranged from 25.9% (95% CI 11.1–46.3) among women with no TZC to 56.3% (95% CI 32.3–83.7) among women with ASC and 65.4% (95% CI 44.3–82.8) in women with unsatisfactory smears. The cross-tabulation procedure in SPSS helps to evaluate differences in distribution of various cytology outcomes and the prevalence of low risk, high risk and any type HPV among these women. In this regard, no significant difference in distribution of cases was noted for the HPV infection in general, high-risk HPV, or low-risk HPV and Pap smear outcome (Table 5).

Table 5: Distribution of low risk, high risk and any type HPV in concurrent cervical cytology outcomes

Characteristic	No. (% [#])	Prevalence of HPV, %*		
		Any HPV ^a	High-risk HPV	Low-risk HPV
No TZC	27 (5.0)	7 (25.9)	5 (18.5)	2 (7.4)
NILM	433 (80.5)	230 (53.1)	184 (42.5)	99 (22.9)
ASCUS	15 (2.8)	9 (60.0)	9 (60.0)	2 (13.3)
LSIL	21 (3.9)	9 (42.9)	6 (28.6)	7 (33.3)
ASC-H	1 (0.2)	1 (100.0)	1 (100.0)	0 (0.0)
HSIL	15 (2.8)	7 (46.7)	5 (33.3)	4 (26.7)
Unsatisfactory	26 (4.8)	17 (65.4)	15 (57.7)	6 (23.1)
(χ ² , df=5, P-value)		10.2; 0.12	4.91; 0.56	8.36; 0.21

[#] Percentage fraction of respondents.

* Row percentages are computed to show within-group HPV prevalence estimates.

^a Prevalence of HPV (any type) varies significantly across categories (Pearson χ^2 test).

The commonest HPV genotypes detected among women with ASCUS were HPV-18 (20% (95%CI 4.3–48.1) of all ASCUS cases), 35 (20% (95%CI 4.3–48.1) of all ASCUS cases) and 31, 39, 45, 51, 52, 58, 68 (6.7% (95%CI 0.2–31.9) of all ASCUS cases each) (Supplementary file: S4 Table). Among women with LSIL most

prevalent were HPV-52 (28.6% (95%CI 11.3-52.2) of all LSIL cases), HPV-35 (14.3% (95%CI 3.0-36.3) of all LSIL cases), and HPV 16,18, 58,39 (9.5% (95%CI 1.2-30.4) of all LSIL cases). HPV-52, 35 (20% (95%CI 4.3-48.9) of all HSIL cases) and 58,45 (13.3% (95%CI 1.7-40.5) of all HSIL cases) were top three in that order for high grade intraepithelial/severe dysplasia lesions.

HPV-35 (14.8% (95%CI 11.6-18.5) of all normal cases), HPV-18 (13.2% (95%CI 10.1-16.7) of all normal cases), HPV-52 (7.6% (95%CI 5.3-10.5) of all normal cases), HPV-58 (7.2% (95%CI 4.9-10.0) of all normal cases) and HPV-68 (5.8% (95%CI 3.8-8.4) of all normal cases) was more commonly detected in women without any precancerous lesions.

Discussion

HIV infection is known to be an important independent risk factor for development of precursor lesions and cervical cancer following high-risk HPV acquisition (Getinet et al., 2015). The present study provides data on the burden of cervical cancer and precancerous lesions among women living with HIV and attending specialized care in Accra, Ghana. Abnormal smears detected among women were characteristic of LSIL (3.9) and HSIL (2.8%). No cases of squamous cell carcinoma or adenocarcinoma were detected in this population and equivocal smears (ASC-) accounted for approximately 3% of women (Table 2).

The overall prevalence of cervical epithelial abnormalities (9.3%) in this population is higher than what has previously been reported in the general population in Ghana (Donkoh, 2015; Handlogten et al., 2014; Odida et al., 2011) and other countries with an absence of universal screening programs, such as Cameroun (HIV/AIDS, 2018), South Africa (Fonn et al., 2015) and India (Burd, 2003). High-resource populations with well-established screening programs and lower HIV endemicity, often have lower rates of epithelial cell abnormality (ECA). Lower rates of ECA have been reported among Australian (Soccio et al., 2015), Italian (Meloni et al., 2014) and Chinese women (Tao et al., 2014).

In general, precancerous cervical lesions and cervical tissue neoplasm in the cervical area are prevalent among WLHIV in Sub-Saharan Africa (Getinet et al., 2015). Separate studies conducted in Zambia, Rwanda, Ethiopia and Kenya reported higher diagnostic frequencies of cervical epithelial abnormalities among women infected with HIV (Getinet et al., 2015; Kayumba, 2014; Lehtovirta et al., 2008; Memiah et al., 2012). A systematic review and meta-analysis conducted among HIV positive women in sub-Saharan Africa showed that the prevalence of precancerous cervical lesions ranged from 2.9–76% (Strickler et al., 2005). Furthermore, the pooled prevalence of precancerous cervical lesions among HIV-positive women in sub-Saharan Africa was 25.6%. The trend is replicated in other developing nations: cervical cytology was abnormal in 19.0% of women recruited from an antiretroviral therapy (ART) clinic in Mumbai (Isaakidis et al., 2013). Among HIV-infected women attending Pusan National University Hospital in Korea, HIV-infected women had tenfold higher odds of abnormal cervical cytology and a prevalence of 18.3% (vs 1.8%) (Park et al., 2014). In addition, studies in Cambodia (25.0%) (Marie-Eve et al., 2009), the Bahamas (44.0%) (Dames et al., 2009), among women attending HIV clinics also report an elevated prevalence of precancerous lesions than has been reported by this study.

Early initiation of HAART and sustained adherence for viral control is likely to reduce incidence and progression of SIL and ultimately incidence of invasive cervical cancer (Akarolo-Anthony et al., 2013; Memiah et al., 2012). The lower threshold of cervical precancer/SIL in the presence of HPV infections among women living with HIV may reflect the high coverage of HAART in this population (84%). Even though data on the length of ART was not available, it is expected to be high among women recruited from HIV clinics such as this (Massad et al., 2016; Minkoff et al., 2010). Several African studies (Chaturvedi, 2010; Doorbar et al., 2012; Zeier et al., 2012) provide indication that earlier initiation and effective HAART over a prolonged duration can prevent cervical lesion progression and promote regression. Recent evidence from two systematic reviews and meta-analyses of studies in African populations and the world over have concluded that early initiation of HAART coupled with a high HAART compliance may be the defining reason for lower-than-expected prevalence of precancerous and cancerous lesions in hospital-based studies among women with HIV (Akarolo-Anthony et al., 2013).

This work has confirmed previous reports in both local and overseas settings that women living with HIV have a greater prevalence of precancerous lesions by demonstrating a similar trend in a population of women from the largest Ghanaian HIV clinic. Access to reliable cervical cancer screening must be considered to be a priority for high-risk populations. It is recommended that focus must be given to treating women with precancerous lesions to prevent their progressing to cervical cancer and death.

Although the Pap Smear test has a very good specificity for malignancy and precursor lesions, it suffers a corresponding low sensitivity at the same time (Saslow et al., 2012). The large number of ambiguous cytology reports in the atypical squamous cells (ASC) category shows that a number of positive cases may be missed with adverse clinical implications. The most effective way to manage this outcome is a matter of concern for healthcare services. Recent guidelines recommend that, following two initial normal Pap-smears at a 6-month interval, all HIV-positive women should undergo annual cervical cytologic examination. In addition, it is recommended that all immunosuppressed women with atypical squamous cells undergo colposcopy (Yar et al., 2016). In well-endowed settings, cervical cancer screening strategies integrating HPV testing have been proven to improve disease detection and afford longer screening cycles (Saslow et al., 2012) and could be explored in high-stakes patient populations such as this. This approach benefits from the HPV test's greater sensitivity in diagnosing women with CIN3+ (Arbyn et al., 2006). In more advanced cytology screening settings, the practice has been to perform reflex HPV testing for all ambiguous cytology reports (ASCUS) and onward colposcopic evaluation in the event of a positive HPV screen. Another way is to perform cytology and HPV testing simultaneously (Wright et al., 2014). Both approaches have been shown to improve the clinical performance of cytology in other settings.

Cervical cancer caused by persistent infection with high-risk human papillomaviruses is a defining condition of HIV/AIDS (Denny et al., 2012) In the present era of type-specific vaccines and HAART, there is a lot of interest regarding the prevalence and distribution of HPV among women living with HIV. In this study, the overall prevalence of HPV infection was 52.0% (high-risk HPV: 41.8%) (Table 3). Among women on ART the overall prevalence of high-risk HPV infection was 80.3% against 91.7% in those not enrolled on ART. Concordant estimates have been reported in several studies from sub-Saharan Africa (Akarolo-

Anthony et al., 2014; Whitham et al., 2017). Elevated rates of HPV infection among vulnerable women have been reported in Ghana (Adams et al., 2019; Donkoh, 2015; Obiri-Yeboah et al., 2017; Yar et al., 2015, 2016) and in other major cities in Africa (Weldegebreal & Worku, 2019; Whitham et al., 2017). In many of these studies, the ART status of participating women was undisclosed and could underscore the higher rates reported. In one study elevated CD4 count and prolonged HAART use were significantly associated with lower prevalence of high-risk HPV infection (Gasparini & Panatto, 2009).

HIV-infected women are more likely than those without HIV infection to have persistent HPV (Adler et al., 2015; 2014). In general, the higher HPV prevalence among HIV-positive women can be attributed to increased susceptibility or decreased ability to clear infection which may be due to factors directly related to immunosuppression and frequent reactivation of latent infection associated with immunosuppression (Khan et al., 2005). The destruction of CD4 cells by HIV may increase the likelihood of HPV establishing infection (Mbulaiteye et al., 2011). The evidence also suggests that immunosuppression leads to higher probability of HPV reactivation, potentially due to incomplete clearance of HPV DNA (Humans et al., 2007).

Variability in the distribution of HPV genotypes in HIV positive women compared to the general population introduces the potential for HPV genotypes to spill-over from this population into the general population and has implications for cancer prevention efforts in the general population (Krings et al., 2019). In this study, HIV positive women had multiple HR-HPV genotypes other than HPV 16 and 18. HPV 16 and 18 accounted for the majority of HPV types in cervical cancer tissue (Denny et al., 2014). This finding shows that although HPV 16 and 18 are underrepresented in precancerous lesions compared to other genotypes (Supplementary file: S2, S3 Tables), they are better at evading the host immune system and are less impacted by HIV-associated immunosuppression. Consequently, vaccines with expanded genotype coverage may be more beneficial than those containing only HPV 16 and 18 genotypes in preventing precancerous lesions in this population. It is also clear that cervical screening will continue to play a role in cancer prevention in this population.

High-risk HPV infections were frequently detected in women living with HIV infection (Tables 4 and 5). Vaccine preventable HPVs were significantly associated with squamous intraepithelial lesions, suggesting that this population follows an epidemiological pattern in common with other HPV-infected women, who are at high risk for cervical neoplasia from high risk, vaccine preventable genotypes. High-risk HPV 16, 18, 31, 33, 45, 52 and 58 targeted by licensed preventive HPV vaccines are the most common genotypes found in invasive cervical cancer even among HIV positive women (Denny et al., 2014). However, the present data reveals that a large number of women may harbour other HR-HPV genotypes not targeted by the currently available HPV vaccines: there was a high prevalence of non-vaccine HPV types such as HPV-35, 39 and 68 among women with ambiguous and high grade squamous intraepithelial lesions. These vaccines could be less effective and leave women open to risk for invasive cancer if used in isolation. Early vaccination may protect women who eventually develop vaccine-preventable HPV types but for best results, regular screening of women and colposcopic management of HIV-positive women will continue to be justified for preventing the excess morbidity from non-vaccine

types found here. Moreover, in the future, any preventive HPV vaccine(s) should contain more HR-HPV genotypes based on ongoing genotype surveillance.

Conclusions

The prevalence of precancerous cervical lesions was lower than what has been reported among other cohorts of HIV-infected women in similar settings. However, the data strongly confirms that HIV-infection is highly convergent with high-risk HPV infection and development of a cervical precancerous lesions and has implication for the management of HIV women attending specialized healthcare in the country especially in the era of sustainable HAART. Additionally, the risk from high-risk HPV infection suggests that prompt initiation of HAART through an early enrolment into care is essential.

Declarations

Competing interests

All the authors have no interests to declare.

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Figures

Figure 1

Prevalence of high-risk human papillomavirus (HPV) Genotypes

Figure 2

Prevalence of low-risk human papillomavirus (HPV) Genotypes

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