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High-risk human papillomavirus genotype distribution among women living with and at risk for HIV in Africa

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Objective: Cervical cancer is a common preventable cancer among African women living with HIV (WLWH). Molecular diagnostics for high-risk human papillomavirus (HR-HPV) genotypes are standard components of cervical cancer screening in resource-rich countries but not in resource-limited settings. We evaluated HR-HPV genotypes among women with and without HIV in four African countries to inform cervical cancer preventive strategies.

Methods: The African Cohort Study (AFRICOS) enrolled participants with and without HIV at 12 clinics in Tanzania, Kenya, Uganda, and Nigeria. Cervical cytobrush specimens from women were genotyped for 14 HR-HPV types using the multiplex Seegene Anyplex real-time PCR assay. Robust Poisson regression was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) for factors associated with HR-HPV in WLWH.

Results: From January 2015 to March 2020, 868 WLWH and 134 women living without HIV (WLWoH) were tested for HR-HPV with prevalence of 50.9 and 38.1%, respectively ($P = 0.007$). Among WLWH, 844 (97.4%) were antiretroviral therapy (ART)-experienced and 772 (89.7%) virally suppressed 1000 copies/ml or less. The most frequent HR-HPV types among WLWH were HPV-16 (13.5%), HPV-52 (9.5%), and HPV-35 (9.3%). HR-HPV infection was more common among Tanzanian WLWH (adjusted RR: 1.23, 95% CI 1.05–1.44, $P = 0.012$). Also, WLWH with $CD4^+$ T cells of less than 200 cell/μl had 1.51-fold increased risk of having HR-HPV (95% CI 1.23–1.86, $P < 0.001$).

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Conclusion: HR-HPV was common in WLWH in four African countries, particularly among women with low $CD4^+$ cell count. Scale up of HPV vaccines and development of vaccines with broader activity against less common HR-HPV types may improve cervical cancer prevention in Africa.

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Introduction

Cervical cancer is the leading cause of cancer-related death among women globally, with the majority of cases occurring in low-income and middle-income countries (LMICs), especially in Africa [1]. Almost all cervical cancer cases are caused by persistent high-risk human papillomavirus (HPV) infections, with carcinogenic types 16 and 18 being linked to 70% of cervical cancer cases worldwide [2]. HPV16 and HPV18 infections are largely preventable by vaccination, but such vaccines are not widely available in much of Africa [3–5].

In Africa, where HIV is often co-prevalent, 85% of women with cervical cancer are also living with HIV [6]. In fact, women living with HIV (WLWH) are at multifold increased risk of acquiring and having a persistent high-risk HPV infection, and as a consequence developing cervical cancer, compared with their counterparts without HIV [6–8]. Regular HPV-based screening has been shown to reduce cervical cancer incidence and mortality by up to 70% [9–11]. Thus, although not operational in most countries, the WHO currently recommends HPV DNA detection as the primary screening test for women (aged ≥30 years) to prevent cervical cancer [12]. Through the cervical cancer elimination initiative, WHO is aiming for 70% of women to be screened, and to effectively treat 90% of those with a positive screening test or a cervical lesion by 2030 [12]. Recognizing a high burden of HPV disease in WLWH, the US President's Emergency Plan for AIDS Relief (PEPFAR) has so far supported the integration of cervical cancer screening and precancerous treatment into PEPFAR-supported HIV care and treatment clinics in 12 African countries with high HIV prevalence [13].

Although vaccines can prevent infection with some of the most common high-risk HPV types, only 15 African countries currently include HPV vaccination in their national immunization programs [14]. Uganda, Tanzania and Kenya added HPV vaccination to their national routine immunization schedules in 2015, 2018 and 2019, respectively; while in Nigeria, HPV vaccination is still being piloted and yet to be introduced into the country's routine immunization program [14–16].

There is geographical variation in the distribution of some of the less common high-risk HPV types. For example, although HPV-35 is only linked to about 2% of global cervical cancer cases, it is more prevalent in Africa, where it occurs in about 10% of precancerous and cervical cancer cases [2,17–22]. In a recent study in East Africa, HPV-35 was the second most frequent HPV type in precancerous lesions and was still detected in 11% of cervical cancer cases in WLWH. However, HPV-35 typically occurred together with other high-risk HPV types in cervical cancer, making it difficult to understand its contribution to cancerogenesis in infected women [23]. This may have implications on the effectiveness of vaccination strategies in HPV-35 prevalent regions, as the existing HPV vaccines do not target HPV-35.

Understanding the distribution of HPV genotypes among WLWH and factors associated with high-risk HPV genotype infection and persistence in various regions is crucial for evaluating, improving, and developing cervical cancer prevention initiatives. Herein, we report on the distribution of high-risk HPV infections among WLWH attending PEPFAR-supported HIV clinics in four African countries, using a simple real-time PCR-based detection method that differentiates all 14 high-risk HPV genotypes.

Material and methods

Study population and data collection

The African Cohort Study (AFRICOS) is an ongoing multi-site observational study that enrols adults living with and without HIV aged 18 years and older at 12 PEPFAR-supported clinical care sites in Uganda, Kenya, Tanzania and Nigeria, as previously described [24]. Medical history and physical examination is conducted for every participant at enrolment and every 6 months thereafter. For individuals with HIV, assessment of $CD4^+$ cell count, HIV-1 plasma viral load and ART history is performed. Measurements for $CD4^+$ cell count, HIV-1 plasma viral load were done using platforms previously detailed in [25]. HIV-1 drug resistance genotyping has previously been performed for some participants as described in [26]. Additionally, demographic and clinical

data including sex, age, education level, comorbidities and self-reported sexual behaviour are also collected for each participant, by using extensive questionnaires. From 2015 onward, high-risk HPV testing was offered annually as an additional optional procedure to all women participating in AFRICOS, with the test being rolled out in Tanzania first in 2015, followed by Kenya, Uganda and Nigeria in 2018. This analysis included WLWH and women living without HIV (WLWoH) enrolled in AFRICOS with HPV genotyping data.

Collection of endocervical cells

Cervical cells were collected by experienced nurses, by applying a cytobrush (Solann, Sundbyberg, Sweden) into the endocervical wall and gently rotating the brush 360°. Specimens were then stored in 5 ml PreservCyt cell collection media (Roche, Vorna Valley, South Africa). Cytobrush specimens from Tanzania were directly taken to National Institute for Medical Research-Mbeya Medical Research Center (NIMR-MMRC) HPV reference laboratory in Tanzania while those from Uganda, Kenya and Nigeria were temporarily stored at −20 or −80 °C before their transportation to Tanzania for HPV genotyping. Upon the specimens' arrival, cells were thoroughly dislodged from the cytobrush, aliquoted and short-term (−20 °C) or long-term (−80 °C) stored prior to HPV genotyping.

Human papilloma virus genotyping

DNA was extracted from cervical cells using QIAamp DNA mini kit (Qiagen, Hilden, Germany), followed by HPV genotyping using the Anyplex II HPV HR detection test (Seegene, Seoul, Korea) with the CFX96 Real-time PCR System (Bio-Rad, Hercules, California, USA) as per manufacturer's instructions. The assay detects 14 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), which are regarded as carcinogens. HPV infection was defined as the presence of at least one high-risk HPV genotype in the tested samples. To monitor the quality of NIMR-MMRC laboratory in HPV genotyping, the laboratory has been participating in WHO HPV genotyping proficiency testing since 2013. Of note, accuracy of the Seegene Anyplex II HPV HR detection assay at NIMR-MMRC was 100% in the most recent (2020) WHO proficiency panel.

Statistical analyses

Stata version 14 (StataCorp, College Station, Texas, USA) and Prism version 9 (GraphPad Software, San Diego, California, USA) were used for statistical analyses. Two-sided Fisher's exact test (or wherever applicable, Pearson's chi-squared test) was used to compare the differences in the frequency of individual HPV genotypes between groups of interest. Robust (modified) Poisson regression model was used to estimate relative risk (RRs) and associated 95% confidence intervals (CIs) for factors potentially associated with high-risk HPV in WLWH. Akaike information criteria (AIC) was used to select variables to be included in the model. The model with the lowest AIC was selected. Statistical significance was defined as P less than 0.05 for all analyses except for multiple comparison between country of residence and high-risk HPV, where Bonferroni corrections were used to adjust for the P value. High-risk HPV genotype-specific analyses included all women with data who were infected with the respective high-risk HPV genotype, meaning that women with multiple high-risk HPV infections were included in more than one of the compared groups.

Ethical consideration

All women were fully briefed on the study procedures and provided written informed consent prior to their enrolment. The study was approved by the institutional review boards of the Walter Reed Army Institute of Research (#1897) and ethics committees from all collaborating institutions. Research was performed in accordance with the Declaration of Helsinki.

Results

Study population

Between January 2015 and March 2020, a total of 1712 women were enrolled in AFRICOS and were eligible for HPV testing. Among them, there were 1002 (58.5%) women with median age of 40.8 years [interquartile range (IQR) 34.2–47.4 years] who had their endocervical specimens collected for high-risk HPV testing (Table S1, http://links.lww.com/QAD/C721). About 41.5% of eligible women opted not to participate in HPV typing. Reasons for refusal to undergo HPV testing were primarily because of invasive nature of the procedure, time limitations because of other long study procedures, participants reporting to have already received annual cervical cancer screening, menstruation, or if participants were virgo intacta. Generally, WLWH who consented to HPV testing and were included in the analyses were older (Table S1, http://links.lww.com/QAD/C721). In Tanzania, WLWH who were HPV-tested were more likely to be on ART, have $CD4^+$ T-cell counts of above 200 cells/μl and viral load of 1000 copies/ml or less compared with those not tested (Table S2, http://links.lww.com/QAD/C722).

Table 1 details the characteristics of the 1002 AFRICOS participants who were genotyped for high-risk HPV. Of these, 98 (9.8%) were from Uganda, 554 (55.3%) from Kenya, 230 (22.9%) from Tanzania and 120 (12.0%) from Nigeria. Among 868 WLWH (86.6%), 844 (97.3%) were on ART and 772 (89.7%) had a viral load 1000 copies/ml or less (Table 1). Overall, WLWH had a median $CD4^+$ nadir of 216 (IQR: 108–352) cells/μl, median $CD4^+$ at the time of specimen collection of 538 (IQR: 376–732) cells/μl and median HIV-1 RNA of 0 (IQR: 0–40) copies/ml. High-risk HPV was more common among women with HIV than without (50.9 vs. 38.1%,

Table 1. Characteristics of the African Cohort Study women who received high-risk human papilloma virus genotyping ($n = 1002$).

Characteristic	*n* (column %)	High-risk HPV not detected [*n* (column %)]	High-risk HPV detected [*n* (column %)]	*P value
Age (years)				0.329
18–24	50 (5.0%)	19 (3.7%)	31 (6.3%)	
25–39	430 (42.9%)	221 (43.4%)	209 (42.4%)	
40–49	347 (34.6%)	178 (35.0%)	169 (34.3%)	
≥50	175 (17.5%)	91 (17.9%)	84 (17.0%)	
Site, country				0.143
Kayunga, Uganda	98 (9.8%)	56 (11.0%)	42 (8.5%)	
South Rift Valley, Kenya	447 (44.6%)	237 (46.6%)	210 (42.6%)	
Kisumu West, Kenya	107 (10.7%)	58 (11.4%)	49 (9.9%)	
Mbeya, Tanzania	230 (22.9%)	103 (20.2%)	127 (25.8%)	
Abuja, Nigeria	62 (6.2%)	26 (5.1%)	36 (7.3%)	
Lagos, Nigeria	58 (5.8%)	29 (5.7%)	29 (5.9%)	
Education				0.962
No formal education	36 (3.6%)	19 (3.7%)	17 (3.4%)	
≤Primary	256 (25.5%)	131 (25.7%)	125 (25.3%)	
≥Secondary	710 (70.9%)	359 (70.5%)	351 (71.2%)	
Age at 1st sexual intercourse				0.293
≤18	701 (71.0%)	349 (69.4%)	352 (72.6%)	
>18	287 (29.0%)	154 (30.6%)	133 (27.4%)	
Missing	14	6	8	
Number of lifetime sexual partners				0.541
No partner	323 (32.4%)	164 (32.3%)	159 (32.4%)	
One partner	595 (59.6%)	307 (60.6%)	288 (58.7%)	
Multiple (≥two) partners	80 (8.0%)	36 (7.1%)	44 (9.0%)	
Missing	4	2	2	
HIV status				**0.007**
Women living without HIV	134 (13.4%)	83 (16.3%)	51 (10.3%)	
Women living with HIV	868 (86.6%)	426 (83.7%)	442 (89.7%)	
HIV-associated parameters (among WLWH only)				
On ART				**0.010**
Yes	844 (97.3%)	420 (98.8%)	424 (95.9%)	
No	23 (2.7%)	5 (1.2%)	18 (4.1%)	
Missing	1	1	0	
$CD4^+$ cell count (cells/μl)				**<0.001**
≤200	57 (6.7%)	14 (3.4%)	43 (9.9%)	
201–500	311 (36.7%)	142 (34.2%)	169 (39.0%)	
>500	480 (56.6%)	259 (62.4%)	221 (51.0%)	
Missing	20	11	9	
HIV viral load (copies/ml)				**0.010**
≤1000	772 (89.7%)	391 (92.4%)	381 (87.0%)	
>1000	89 (10.3%)	32 (7.6%)	57 (13.0%)	
Missing	7	3	4	

*P values were calculated using Pearson's chi-squared test. Statistically significant *P* values ($P < 0.05$) are in bold.

$P = 0.007$). Among WLWH, high-risk HPV was more common among those not on ART, with lower $CD4^+$ counts, and with higher viral loads (Table 1). Of note, ART exposure, $CD4^+$ T-cell counts and viral suppression in WLWH differed by country, with Tanzania having significantly more women who were off ART and viraemic than other countries (Fig. S1, http://links.lww.com/QAD/C720 and Table S3, http://links.lww.com/QAD/C723).

Distribution of high-risk HPV genotypes

The most frequent high-risk HPV genotypes among WLWH were HPV-16 (13.5%), HPV-52 (9.4%) and HPV-35 (9.3%), whereas HPV-52 (6.7%), HPV-16 (6.0%) and HPV-31 (5.2%) were the most common HPV genotypes among WLWoH (Fig. 1a). Despite 97.4% being on ART, HIV was associated with a higher overall prevalence of infection with any high-risk HPV genotype ($P = 0.007$, Fig. 1a). Also, when compared with WLWoH, WLWH had higher prevalence of high-risk HPV genotypes covered by the bivalent and quadrivalent vaccine (HPV-16 and/or HPV-18) and those targeted by the nonavalent vaccine (HPV-16/18/31/33/45/52/58). Specifically, as compared with WLWoH, a higher proportion of WLWH had HPV-16 (13.5 vs. 6%, $P = 0.011$) and infection with the nonvaccine HPV-35 was more frequent in WLWH compared with WLWoH (9.3 vs. 3.7%, $P = 0.030$, Fig. 1a). When stratified by country of residence, a significant association between HIV and high-risk HPV was particularly observed for Tanzanian women (Fig. 1b).

Of 442 WLWH with high-risk HPV infections, 252 (57.0%) had single high-risk HPV infection and 190 (43.0%) had two or more high-risk HPV genotypes (Fig. 2a). On the contrary, the proportion of WLWoH with multiple high-risk HPV genotypes was only 21.6%

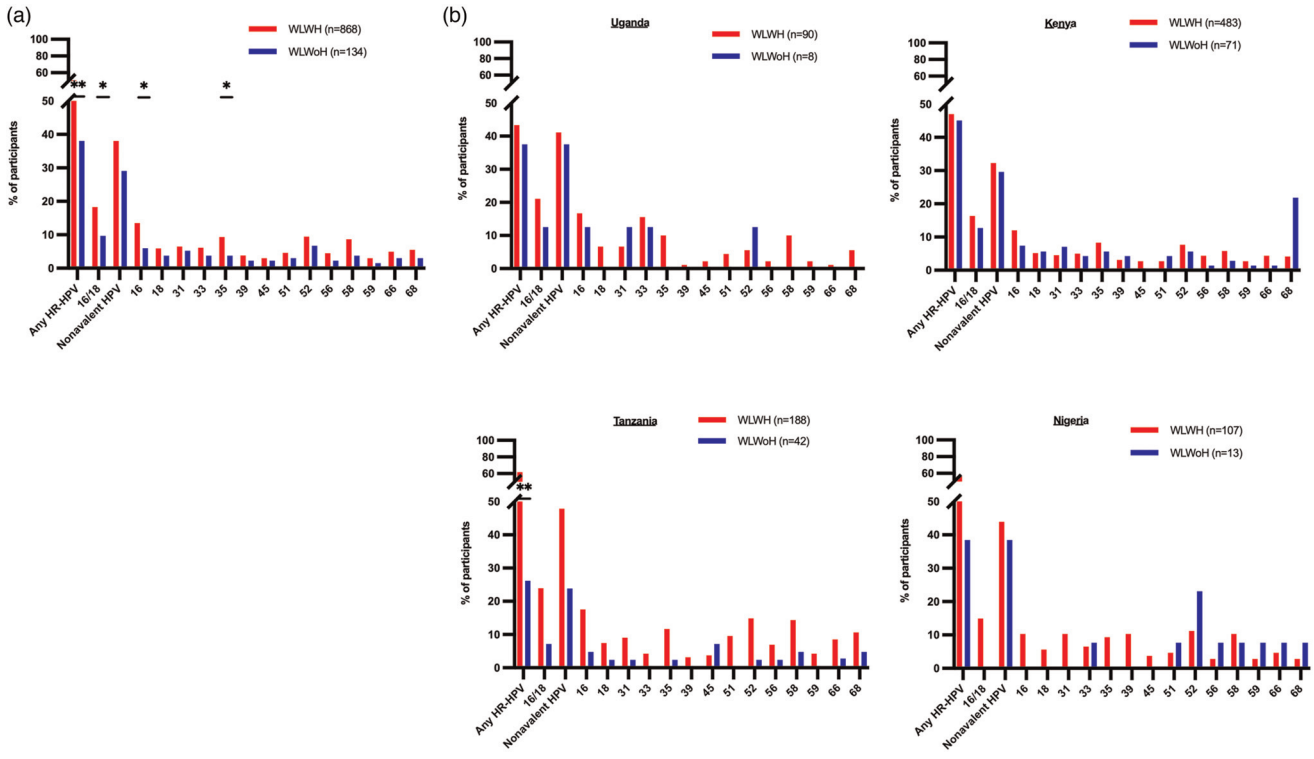

Fig. 1. Distribution of high-risk human papilloma virus genotypes in women living with HIV and women living without HIV in the African Cohort Study. (a) Comparison of the frequency of each high-risk HPV genotype (shown in *y*-axis) between WLWH (red bars, $n = 868$) and WLWoH (blue bars, $n = 134$). Country-specific comparison of the frequency of each high-risk HPV genotype between WLWH and WLWoH is shown in (b). Fisher's exact test was used for comparison. Asterisks denote different *P* values: $^{*}P < 0.05$, $^{**}P < 0.005$. *P* values less than 0.05 are considered significant for (a) whereas *P* values after the results corrections (<0.003) are considered significant for (b). HPV, human papilloma virus; WLWH, women living with HIV; WLWoH, women living without HIV.

(Fig. 2b) and significantly lower than that of WLWH ($P = 0.010$, chi-squared test). Of 252 women with a single high-risk HPV infection, HPV-16 was the most frequent single infecting genotype, $n = 41$ (16.3%) followed by HPV-35, $n = 28$ (11.1%) and HPV-52, $n = 27$ (10.7%) (Fig. 2c). The proportion of women with multiple high-risk HPV co-infections varied for each HPV genotype. Although 78.4% of women with HPV-18 were also co-infected with other high-risk HPV genotypes, 57.1% of women with HPV-31 had multiple high-risk HPV genotypes (Fig. 2d).

HIV-1 subtype information was available for 155 of 442 WLWH with high-risk HPV infection, of whom 68 (42.8%) had subtype A, 32 (20.1%) had C, 17 (10.7%) had D, 12 (7.5%) had G, 12 (7.5%) had CRF02_AG, whereas 18 (11.3%) had other circulating recombinant forms. The distribution of specific HIV subtypes in WLWH with detected high-risk HPV types is further detailed in Fig. S2, http://links.lww.com/QAD/C720.

Women with $CD4^+$ T-cell counts below 200 cells/μl were more frequently infected with a high-risk HPV type compared with those with $CD4^+$ counts of 201–500 or greater than 500 cells/μl, especially with: HPV-16 (24.6 vs. 13.8 and 12.1%, $P = 0.042$), 18 (14 vs. 6.8 and 4.6%, $p = 0.018$) and 33 (17.5 vs. 6.1 and 4.8%, $P = 0.003$; Fig. 3a). Of note, the following high-risk HPV genotypes, which are not covered by the available HPV vaccines, were also significantly associated with $CD4^+$ T-cell counts less than 200 cells/μl: HPV-35 (24.6 vs. 10.3 and 6.7%, $P < 0.001$), 39 (15.8 vs 3.9 and 2.5 and 2.5%, $P < 0.001$), 59 (5.3 vs. 4.5 and 1.7%, $P < 0.025$) and 66 (14 vs 5.1 and 3.5%, $P < 0.006$; Fig. 3a). The association of $CD4^+$ levels with high-risk HPV genotype infections varied by country, with HPV-35 being more frequent in Tanzanian WLWH with less than 200 cells/μl $CD4^+$ T cells (Table S4, http://links.lww.com/QAD/C724).

Similarly, a greater proportion of WLWH with plasma HIV-1 viral load of more than 1000 copies/ml were infected with high-risk HPV compared with WLWH with a viral load of 1000 copies/ml or less, as follows: HPV-18 (12.4 vs. 5.2%, $P = 0.014$), HPV-56 (10.1 vs. 3.9%, $P = 0.014$), HPV-58 (16.9 vs. 7.8%, $P = 0.008$) and HPV-59 (6.7 vs. 2.6%, $P = 0.045$, Fig. 3b). This difference was also observed for nonvirally suppressed women when stratified by country, but not to a significant level when statistically adjusted (Table S5, http://links.lww.com/QAD/C725).

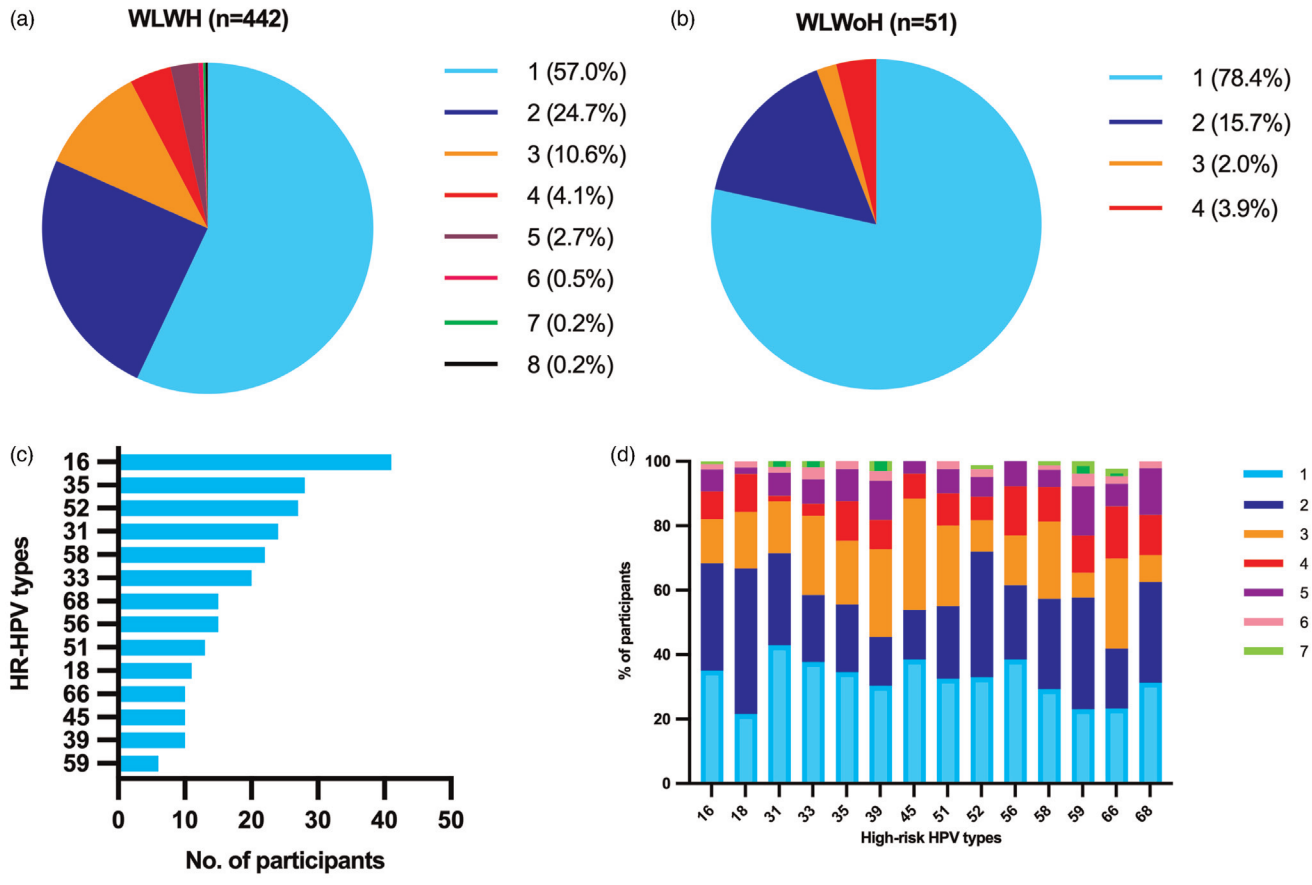

Fig. 2. Prevalence of multiple high-risk human papilloma virus infections in women living with HIV and women living without HIV with high-risk human papilloma virus infections in the African Cohort Study. Proportions of number of detected HPV infections in WLWH and WLWoH diagnosed with high-risk HPV are shown in (a) and (b), respectively. (c) the distribution of high-risk HPV genotypes among WLWH with single high-risk HPV infection is shown. (D)The proportion of single and multiple HPV infections in each HPV type is shown. Colours correspond with the number of detected high-risk HPV genotypes as indicated on the legend. HPV, human papilloma virus; WLWH, women living with HIV; WLWoH, women living without HIV.

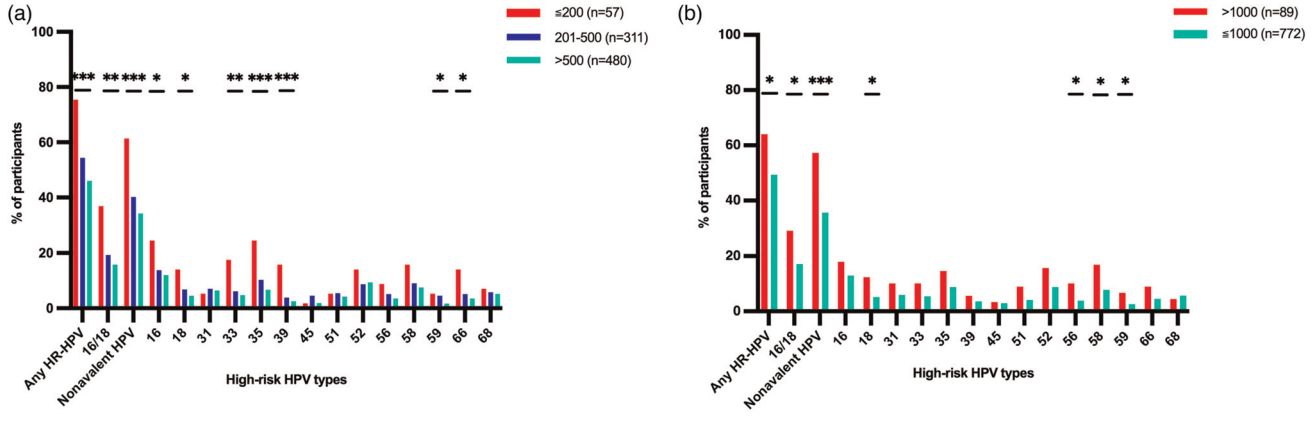

Fig. 3. Distribution of high-risk human papilloma virus genotypes in women living with HIV in the African Cohort Study stratified by HIV-related parameters. The frequency of each HPV genotype is shown for women with: (a) $CD4^+$ T-cell counts of 200 cells/μl or less (red bars, $n = 57$), 201–500 cell/μl (blue bars, $n = 311$) and greater than 500 cell/μl (green bars, $n = 480$); and (b) HIV viral load of 1000 copies/ml or less (green bars, $n = 772$) and greater than 1000 copies/ml (red bars, $n = 89$). Statistical analysis was performed using Fisher's exact test. Asterisks denote different P values: $^*P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.001$

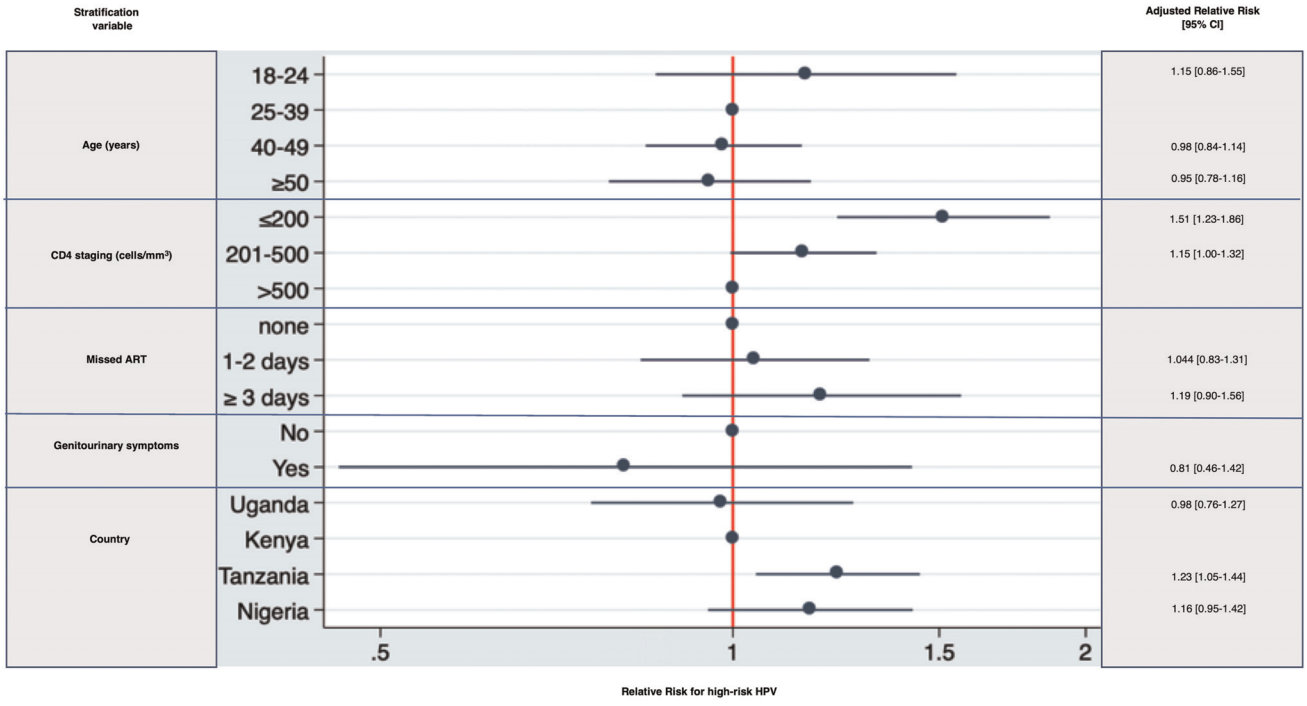

Fig. 4. Factors associated with high-risk human papilloma virus among women living with HIV in the the African Cohort Study. Robust Poisson regression model with the number of high-risk HPV infections as a dependent variable for AFRICOS women living with HIV, adjusting for age (18–24 vs. 25–39, 40–49 and ≥50 years), $CD4^+$ staging (≤200 vs. 201–500 and >500 cell/μl), ART adherence (none vs. 1–2 days and ≥3 days of missed ART dose), genitourinary symptoms (no vs. yes) and women's country of residence (Uganda vs. Kenya, Tanzania and Nigeria). The individual risk factors are indicated on the *y*-axis; adjusted relative risk and 95% confidence intervals (CI) are shown on the *x*-axis. Actual 95% CI are shown on the right side of the graph. AFRICOS, the African Cohort Study; ART, antiretroviral therapy.

Factors associated with high-risk human papilloma virus among women living with HIV in the African Cohort Study

As high-risk HPV was a common outcome, Robust (modified) Poisson regression model was used to estimate RR associated with high-risk HPV [27]. A model showed that WLWH with $CD4^+$ cell count less than 200 cells/μl and 201–500 cells/μl had a 58% (95% CI 1.31–1.91, $P < 0.001$) and 17% (95% CI 1.01–1.34, $P = 0.030$) increased RR of having high-risk HPV, respectively (Fig. 4). Moreover, residence in Tanzania was associated with an increased risk of having high-risk HPV infection in WLWH compared with Kenya (adjusted RR: 1.25, 95% CI 1.07–1.46, $P = 0.004$, Fig. 4).

Discussion

This study evaluated the distribution of clinically relevant high-risk HPV infections among WLWH attending PEPFAR-supported HIV clinics in four African countries. WLWH from this multicountry study were almost all (>97%) on ART, yet they still were more frequently infected with high-risk HPV genotypes compared with WLWoH. Women with HIV not only had a high prevalence of oncogenic HPV-16 but were also burdened with less common and moderate high-risk HPV genotypes, in particular 35 and 52. Of note, high-risk HPV infection was more common among Tanzanian WLWH. Nonetheless, high-risk HPV infection was less frequent in 'immunocompetent' and virally suppressed WLWH, irrespective of country of residence, emphasizing that adherence to treatment and viral suppression has a beneficial effect thereby probably increasing clearance of infection and hence reducing the risk of HPV disease progression in WLWH.

Our findings are similar to previous studies, which reported higher frequencies of HPV infection in WLWH than WLWoH [28,29], even though over 97% of women in this study were on ART. Consistent with previous findings [17,30,31], HPV-16 was the most frequently detected high-risk HPV genotype in WLWH, with infection prevalence being significantly higher in WLWH than WLWoH.

Interestingly, the high prevalence of high-risk HPV in WLWH from the studied population was in part driven by WLWH from Tanzania. This may be explained by the fact that, of the four studied countries, Tanzania had the highest proportion of WLWH who were treatment-naive, immunocompromised and viremic, perhaps

because HPV testing within AFRICOS was introduced earliest in Tanzania (in 2015) before the 'test and treat' era [32]. This suggests that more advanced HIV disease progression in many Tanzanian study participants may contribute to the elevated prevalence of high-risk HPV infection (and persistence) and hence higher risk for cervical cancer.

Recent studies have linked HPV-35, which is currently not targeted by any of the available HPV vaccines, with cervical carcinogenesis in women of African ancestry [33]. Indeed, the prevalence of HPV-35 is higher in some African countries compared with other regions and has been detected in 4–10% of precancerous and cervical cancer cases [2,17–22]. In the present study, HPV-35 was also frequent in WLWH, where the proportion of WLWH with HPV-35 infection ranged from 8 to 11% across all countries. We and others have previously studied HPV-35 infections in WLWH with precancerous or cervical cancer [17,30,34]. Of note, in our recently published study, HPV-35 infections occurred frequently in women with precancerous lesions (27% of WLWH with such lesions), typically in the presence of other high-risk HPV genotypes with a similar pattern, yet at a lower frequency (11%) observed in cervical cancer cases [23]. In contrast, HPV-16/18 and also HPV-45 were often detected as single infections in cancers in the same study [23]. Hence, the RR of HPV-35 infections to cause cervical cancer progression in WLWH should be studied more in detail. Nonetheless, given its reported occurrence and potential contribution to cervical cancer cases in Africa, including HPV-35 in vaccines may prove beneficial, especially for African WLWH.

Infection with HPV-52 is linked to 3% of reported invasive cancer cases worldwide [2]. In our study, HPV-52 infections were prevalent in both women with and without HIV. In particular, Tanzanian WLWH had a six-fold higher prevalence of HPV-52 than WLWoH. Although HPV-52 is targeted by the nonavalent vaccine, most African countries including Tanzania use the bivalent or quadrivalent vaccine [15], which only covers the highest risk HPV genotypes 16 and 18 [2]. Robust, longitudinal research describing the persistence of high-risk HPV infections with non-HPV-16/18 genotypes, their associated risk of disease and progression to cancer will be necessary to optimize diagnostic algorithms for WLWH. Furthermore, cost-effectiveness studies on implementation of nonavalent vaccines in these settings should be considered.

Consistent with previous reports [23,31,35], we found that infections with multiple high-risk HPV genotypes were common in WLWH. We and others have also shown a predominance of multiple high-risk HPV infections in WLWH with precancerous lesions, whereas WLWH with cervical cancer often had single high-risk HPV genotype infections, especially of HPV-16, 18 and 45 [23,30]. Moreover, women aged 30 years and above with persistent high-risk HPV infection, have a high risk of developing precancerous cervical lesions and cervical cancer [36,37]. Lack of capacity for cytohistological diagnosis during our current study limited investigation of high-risk HPV genotypes associated with HPV disease in the studied WLWH. Nonetheless, the identified WLWH, with HPV-16, HPV-18 and/or HPV-45 in this study (about 18% of WLWH) could benefit from follow-up HPV testing to identify those at greatest risk for HPV disease, and thus refer them for intensive evaluation with cytohistological analyses. Importantly, prior work has similarly shown an increased risk of multiple anal HPV infections also in men living with HIV as compared with those without HIV [38].

In this study, infections with particular vaccine (16, 18 and 33) and non-vaccine (35, 39, 59 and 66) HPV genotypes were most frequent in WLWH with advanced immunosuppression. Women with less than 200 cell/μl $CD4^+$ T cells had 1.5 increased risk of having high-risk HPV infections. These results are consistent with previous results showing that low $CD4^+$ T-cell counts increase the risk of high-risk HPV infection, precancerous lesions and progression to cervical cancer compared with those with higher $CD4^+$ T cells [7,29,39–44]. Low $CD4^+$ cell counts and detectable HIV viremia in WLWH correlate with depletion of high-risk HPV-specific T-cell responses [45], which may constitute a mechanism of the increased risk for high-risk HPV persistence and associated cancerogenesis in these women [45].

Importantly, those who consented to high-risk HPV genotyping and were included in the analysis were also more likely to be on ART and be aviraemic. We would, therefore, expect that those who did not participate to have even higher risk for high-risk HPV infections compared with those included in the study, particularly in Tanzania.

One major limitation of this study is the missing cytohistological diagnosis of cervical lesions and cancer in these women. Visual inspection with acetic acid (VIA) was performed on some women as part of their cervical cancer screening procedures, but systematic interpretation of VIA results in this analysis was difficult because of methodological challenges. The AFRICOS study procedures closely reflect national cervical cancer screening and treatment algorithms for WLWH. It is, therefore, evident that more advanced cytohistological investigation for detection of precancerous lesions is typically not performed in WLWH in the participating clinical sites, preventing the possibility of early intervention in these women. Smart molecular diagnosis of high-risk HPV genotypes, which was relatively simple in this study, could, therefore, help to pre-select women with high-risk HPV infection (in particular, those above 30 years of age and with persistent infection) for referral to specialized care and treatment centres, for more advanced diagnostic

work-up that require specialized medical resources (like pathologists and obstetrician/gynaecologists). Also, uptake of HPV testing was relatively low in this cohort and could be improved by increasing community awareness on the importance of cervical cancer screening, dispelling myths about cervical cancer and HPV, and introducing HPV self-collection, which has been shown to be highly acceptable among African women [46–50].

In conclusion, this study not only confirms a high prevalence of carcinogenic HPV-16 in WLWH from the four studied African countries but provides evidence of high prevalence of less common high-risk HPV genotypes 35 and 52 in these populations. Although HPV-35 is not covered in any of the currently licensed vaccines, HPV-52 is also not targeted by the currently distributed bivalent and quadrivalent vaccines in these countries, which may have implications on the effectiveness of ongoing HPV vaccination strategies in the region. Further studies should focus on better understanding the contribution of non-HPV-16/18/45 genotypes in cervical cancer development in African populations. Cost-effectiveness studies of switching to nonavalent HPV vaccines (that includes HPV- 52) in countries that have yet to introduce them at a large scale should also be considered, as this may improve cervical cancer prevention in Africa – home to the highest proportion of women burdened with cervical cancer and HIV in the world [6].

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analyses. C.G., M.H. and J.A.A. conceived/designed the study. All authors contributed to drafting, reading and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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