Cervical epithelial abnormalities and associated factors among HIV-infected women in Lagos, Nigeria: A cytology-based study

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Abstract

Introduction: As it may not be feasible to provide cervical cancer screening services to all HIV-infected women in most resource-limited settings, there is a need to identify those who are most at risk. We determined the prevalence, patterns, and associated factors of cervical cytological abnormalities among HIV-infected women in Lagos, Nigeria.

Methods: This descriptive cross-sectional study was conducted among HIV-infected women at the adult HIV treatment and colposcopy clinics of a university teaching hospital in Lagos, Nigeria

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between October 2018 to December 2019. A cervical sample was collected from each woman to detect cervical cytological abnormalities.

Results: Of the 593 enrolled women, cervical cytological abnormalities were present in 40 (6.7%). Most (37.5%) of the women with cytological abnormalities had atypical squamous cells of undetermined significance (ASCUS). Age at coitarche (<20 versus 20 years: adjusted odds ratio, 2.42; 95% confidence interval, 1.21–4.83, P=0.01) was the only factor that was independently associated with cervical epithelial abnormalities.

Conclusion: The prevalence of cervical cytological abnormalities in our study is lower than most previous reports in Africa. Sexual debut at an early age was significantly associated with cytological abnormalities. It is necessary to confirm the findings of this study through a well-designed and adequately powered longitudinal study.

Introduction

Human papillomavirus (HPV) infection is a well-established cause of cervical cancer [1]. Women who are infected with HIV, even while on antiretroviral therapy [2], are more likely to have persistent high-risk HPV infections [3] that lead to precancerous squamous intraepithelial lesions (SIL) of the cervix [4], [5] which if left untreated may progress to invasive cervical cancer [5]. Sub-Saharan Africa accounts for about 80% of the global burden of cervical cancer [6] and is also the region most affected by the global HIV epidemic with an estimated 25 million cases [7]. Nigerian women currently bear the highest burden of cervical cancer in Africa, with an annual incidence of 14,089 new cases and 8,240 deaths [8].

To deliver and scale-up access to antiretroviral therapy (ART) many countries across the sub-Saharan Africa (SSA) region have successfully established dedicated HIV programmes in the past two to three decades to extend the lifespan of people living with HIV (PLVIV) [9], [10]. With a longer lifespan, HIV-infected women are now at increased risk of developing cervical precancer and cancer [3]. Integration of cervical cancer screening and treatment services into HIV treatment programmes is currently used in most settings in SSA including Nigeria to effectively control the unnecessarily high burden of cervical cancer in women living with HIV (WLHIV) [11], [12]. However, due to limited resources in most countries in the region, it may not be feasible to provide these screening services to all HIV-infected women and thus there is a need to identify those who are most at risk of developing cancer. There is currently limited access to diagnostic colposcopy compared to cervical cytology in most resource-limited settings due to a dearth of facilities and skilled manpower [1]. Furthermore, available data, suggest that Pap smear cervical cytology is a more sensitive and specific screening and diagnostic tool for cervical pre(cancer) than colposcopy in HIV-infected women [13]. We, therefore, aimed in this study to determine the prevalence, patterns and factors associated with cervical epithelial abnormalities using Pap

smear cytology among HIV-infected women attending the adult HIV treatment clinic of a university teaching in Lagos, Nigeria.

Patients and Methods

Study design and setting

This cross-sectional study involved HIV-infected women at the adult HIV treatment clinic of a university teaching hospital in Lagos, Nigeria who were enrolled in the "*Epigenetic Biomarkers of Cervical Cancer in Nigerian Women Study*" [14] between October 2018 to December 2019. The HIV treatment clinic provides comprehensive care for people living with HIV in Lagos and its surrounding states in Southwest Nigeria. The clinic also offers integrated reproductive health services to sexually active WLHIV such as routine cervical cancer screening with either a Pap smear, HPV DNA testing or visual inspection with acetic acid (VIA) depending on availability and affordability.

Study population and eligibility criteria

The study participants were consecutively enrolled HIV-infected women who attend care at the adult HIV clinic and consented to undergo cervical cancer screening using the Papanicolaou (Pap) test smear at the Colposcopy clinic of the hospital as part of the "*Epigenetic Biomarkers of Cervical Cancer in Nigerian Women Study*" [14]. Inclusion criteria at enrolment included sexually active HIV-infected women aged 25–65 years [15] while exclusion criteria were virgo intacta, suspicious cervical lesions, current pregnancy or childbirth within the past 6 weeks, previous hysterectomy, history of HPV DNA testing or Pap smear within the past 3-years, and history of cervical cancer or therapy for benign or malignant cervical lesions. Women who were confirmed as having invasive cervical cancer at any time during the study were also excluded and referred for treatment.

Sample size calculation

The primary study endpoint was the proportion of screened HIV-infected women with cervical cytological abnormalities. We calculated a sample size of 184 WLHIV by imputing an estimated prevalence of 12.2% for cervical cytological abnormalities [16], type I error and precision rates of 5% respectively, and a projected non-response or data recording error rate of 10%. We, however, included all the 593 women enrolled for Pap smear screening during the study period in the final data analyses.

Study procedure and data collection

Potentially eligible participants were enrolled by members of the study team using the consecutive sampling technique. Study intent and procedures were introduced, and informed consent was obtained before any study procedure. A data collection form created on REDCap software was used to collect information on socio-demographic variables, duration of HIV diagnosis and use of combination antiretroviral therapy (cART), and other relevant information aimed at evaluating the risk factors for cervical cancer [17]. Information on participants' immune status (the most recent values CD4+ cell counts, and HIV RNA viral load documented within ±8 weeks from the enrolment date) was extracted from the electronic medical records at the HIV clinic. All the participants then had a pelvic

examination and cervical smear sample collection by the study nurse at the Colposcopy clinic. The smear samples were sent to the hospital's Anatomic and Molecular Pathology laboratory for cytological examination using the conventional Pap smear. The presence or absence of cervical cytological abnormalities was determined and interpreted according to the revised 2014 Bethesda classification system [18]. Internal and external quality assurances were ensured by labelling the slides with the participant's unique identification code after which a unique laboratory identifier is assigned before being viewed by a third-year histopathology resident doctor. These are then reviewed by either of the two experienced pathologists in the study. Cases with cervical epithelial abnormalities were randomly selected and jointly reviewed by the two pathologists to have an agreement. In addition, the reviewed slides were scanned using a slide scanner and sent to a pathologist at Northwestern University in Chicago, Illinois after which virtual meetings were held to discuss discordant cases.

Statistical analyses

Statistical analyses were carried out using SPSS version 27.0 for Windows. We computed descriptive statistics for the women's sociodemographic, clinical and laboratory characteristics. Continuous variables were presented as mean and standard deviation if normally distributed or median and interquartile range if skewed while categorical variables were presented as frequencies and percentages. The associations between cervical cytological abnormalities and the women's characteristics were tested using the $\chi2$ test for categorical variables and the independent sample t-test, one-way analysis of variance or Mann-Whitney U test where applicable for continuous variables. Odds ratios (OR) and 95% confidence interval (CI) of cervical cytological abnormalities were estimated using multivariate binary logistic analyses for all the women's characteristics. The mean age at enrolment and coitarche as well as the median CD4+ cell count as reported in this study were used as the stratifying cut-off values in our models. Variables with P<0.20 such as participant's age, the CD4+ cells count, age at coitarche, and tobacco smoking were included in the adjusted multivariate model. We considered P<0.05 as statistically significant.

Results

The characteristics of women enrolled in the study are shown in Table 1. The participants' mean age at enrolment, BMI, duration of use of cART and age of sexual debut were 43.3 ± 8.0 years, 27.1 ± 5.2 kg/m2, 111.4 ± 49.1 months, and 20.0 ± 3.4 years respectively. The median time since HIV diagnosis was 11.0 (8.0–14.0) years, CD4+ cells count was 407.0 (265.0–583.0) cells/μL, and HIV viral load was 20.0 (0.0–52.0) copies/mL. The women were predominantly multiparous (n=510, 86.0%), married (n=372, 62.7%), and had at least a secondary level of education (n=497, 83.8%). Most of the participants had never previously used any form of hormonal contraceptive (n=407, 68.6%), had no previous STI (n=469, 79.1%), and had never smoked tobacco (n=571, 96.3%) nor consumed any alcoholic beverages (n=464, 79.2%). About four in five of the women have had at least two-lifetime sexual partners (n=487, 82.1%). Cervical cytological abnormalities were present in 40 (6.7%) of the 593 enrolled women.

As shown in Figure 1, of the 40 women with cervical cytological abnormalities, 15 (37.5%) had atypical squamous cells of undetermined significance (ASCUS), 10 (25.0%) had low-grade squamous intraepithelial lesions (LSIL), 4 (10.0%) had atypical squamous cells cannot exclude high-grade squamous intraepithelial lesions (ASC-H), and 11 (27.5%) had high-grade squamous intraepithelial lesions (HSIL). In Figure 2, an increasing but no significant difference in the mean ages of enrolled participants was recorded based on the types of cervical precancerous lesions (P=0.33) from LSIL to HSIL. The women were stratified into two groups based on the presence of cervical precancerous lesions in their cervical cytology samples and the associated factors were compared in Table 2.

Based on a predefined P<0.20, cervical precancer was found to be associated with the participant's age (P=0.09), the CD4+ cells count (P=0.35), and age at coitarche (P=0.02) and tobacco smoking (P=0.03). However, after adjustments for other factors in the final multivariate analysis, the age of coitarche (Adjusted OR=2.42, 95%CI: 1.21–4.83, P=0.01) was the only factor that was independently associated with the presence of cervical precancerous lesions in HIV-infected women [Table 3].

Discussion

This cross-sectional study conducted among HIV-infected women in Lagos, Nigeria determined the prevalence, patterns, and associated factors of cervical epithelial abnormalities using a cytology-based screening method. The prevalence of cervical epithelial abnormalities was 6.7% and this was relatively lower than the reported 8.7% by Liu et al in Dar es Salaam, Tanzania [10], 12.2% by Daniel et al in Jos, Nigeria [16], 17.8% by Getinet et al in East Gojjam, Northwest Ethiopia [19] and 29.4% by Branca et al in Rome, Italy [20] that utilized the same screening method among similar populations of WLHIV. The relatively lower prevalence of cervical epithelial abnormalities in our study may reflect the population of women enrolled as the study site is an HIV treatment centre where almost all clinic attendees are already on antiretroviral therapy. Furthermore, the prevalence of cervical cytological abnormalities reflects closely the burden of HIV reported in the geographical settings of these respective studies [21], [22]. The higher prevalence rates of cervical epithelial abnormalities in this study and others [16], [19], [23] compared to the figures reported in the general women population (3.5–4.1%) [24]–[26] comprising predominantly of HIV seronegative women are not unexpected as HIV-infected women are more likely to have persistent oncogenic HPV infections which predispose them to cervical precancers and cancer [2], [4].

There are variations in the patterns of cervical cytological abnormalities reported in this study and that of previous studies. Most of the cytological abnormalities reported in this study were ASCUS (37.5%) unlike in the studies by Daniel et al [16] and Liu et al [10] that reported LSIL as the commonest abnormalities. The higher prevalence of ASCUS in our study may be attributed mostly to the predominantly higher mean age (43.3±8.0 years) of this study cohort who are prone to having atrophic cervix and vagina that largely mimic atypical epithelial changes as commonly found in postmenopausal women [27]. The recorded patterns of cytological abnormalities are however the same as that of the cross-sectional study conducted by Getinet et al in 2014 among HIV-infected women attending

gynaecological examination in a cervical cancer screening centre at the Debre Markos referral hospital in Ethiopia [19].

The incidence of cervical precancer and cancer is only marginally affected by the introduction of effective antiretroviral therapy in WLHIV [28] unlike that of other AIDS-defining cancers such as non-Hodgkin's lymphoma and Kaposi's sarcoma. This is largely supported by data from HIV/AIDS cohorts in developed countries [28], [29] and thus this reinforced the need to identify women that are mostly at risk of developing cervical precancer and cancer for targeted evidence-based screening in an integrated HIV treatment and reproductive health setting. There are varying results reported in previous studies that examined the association between age and cervical cytological abnormalities among WLHIV. In similarity to our study, findings from the study by Daniel et al in Jos, Nigeria [16] and Kafuruki et al in Mwanza-Tanzania [30] reported no association between age and cervical cytological abnormalities while others conducted by Ononogbu et al in Abuja, Nigeria [31], Kassa et al in Amhara Region, Northwest Ethiopia [32] found that age was a significant predictor for cervical epithelial changes. The variations reported across these various studies including the current study concerning the association between age and cervical epithelial abnormalities could therefore be attributed to the residual effects of other confounding factors which may or may not be adequately controlled for during statistical analyses. CD4+ cell count is a marker of HIV-induced immunosuppression and viral replication and correlates inversely with the risk of acquisition and persistence of high-risk HPV infection, cervical precancer and progression to cancer [23], [33]. This has also been corroborated in several studies conducted among HIV-infected women in sub-Saharan Africa [10], [31], [32]. However, in converse to this proven belief, our current study and the study by Daniel and colleagues [16] conducted in Southwest and North central regions of Nigeria found no association between CD4+ cell counts and cervical precancerous lesions. This, therefore, shows that the interaction effects of HIV immunosuppression and genital high-risk HPV infection on the development of cervical precancer and cancer still deserve further examination, especially in the context of cART.

In similarity to our study, tobacco smoking was not associated with the risk of developing cervical cytological abnormalities in the study conducted by Guarisi et al among a cohort of women in Campinas, Brazil [34]. However, when Guarisi and colleagues restricted their analysis to women with high-grade CIN only, smoking significantly increased the probability of developing the disease [34]. Among behavioural factors weakening the immune system, smoking appeared to strongly increase the risk of cervical precancer and cancer [35]–[37], however, there is an interplay of multiple factors concerning smoking and cervical carcinogenesis, especially by direct local carcinogenic effect and local immunosuppression [32]. It is therefore almost always difficult to isolate the epidemiologic contribution of smoking to cervical carcinogenesis as confirmed in our current study and other recent studies that found no independent correlation between smoking and cervical precancer and/or cancer [16], [32]. Nonetheless, smoking should always be considered in clinical practice and research concerning cervical precancer and cancer.

The mean age at coitarche reported in our study (20.0±3.4 years) is higher than the average age recorded in most industrialized parts of the world [38], [39]. The later age of coitarche

recorded in our study may be attributed mostly to the societal premium placed on delaying sexual intercourse before marriage among most ethnic groups in Nigeria. Furthermore, in agreement with the study conducted by Getinet et al in East Gojjam, Northwest Ethiopia that identified earlier initiation of first sexual contact before age 15 years as a significant risk factor for the development of epithelial cervical abnormalities [19], our study also illustrated that women whose age was less than 20 years at their first sexual intercourse were 2.42 times more likely to have precancerous cervical lesions compared to those whose age at first sexual intercourse was at or after 20 years of age. This is probably because women who experience sexual debut very early in life may be at greater risk of exposure to high-risk HPV infection [32]. This finding was, however, at variance with the studies conducted in various parts of Africa by Daniel et al in Jos, Nigeria [16], Ononogbu et al in Abuja, Nigeria [31], Liu et al in Dar es Salaam, Tanzania [10] and Kassa et al in Amhara, Ethiopia [32].

We have a few limitations in this study. First, as this was a cross-sectional study, it was not possible to infer any cause-and-effect relationships. Secondly, there was a chance that some women did not divulge accurate information about their sexual behaviour due to the inherent social desirability bias in society. Thirdly, as this is a cytology-based study, we did not include data on the gold standard diagnosis of cervical precancerous lesions using biopsy and histology that could have confirmed the results of the Pap smear cytological abnormalities. Finally, the study site is an HIV treatment centre where all the enrolled women were on combination ART and thus our findings in the study may not be representative of HIV-infected women who are not on therapy or those who are HIV-negative. However, this study is the first step in generating the hypothesis for a well-designed and adequately powered longitudinal study necessary to confirm the findings of this study.

Conclusions

We found a relatively lower prevalence of cervical precancerous lesions among HIV-infected women in this study compared to results from some other studies conducted within and outside the country. In addition, we found that the initiation of sexual intercourse at an early age was associated with higher odds of cervical precancerous lesions. It is, however, necessary to further confirm the findings of this study through a well-designed and adequately powered longitudinal study using histology as the gold standard diagnostic method for cervical precancerous lesions. Meanwhile, as resources are mostly limited with reduced capacity to provide cervical cancer prevention services to all HIV-infected women in settings such as ours, greater efforts should be made in the interim to identify and scale up screening services in women who initiated sexual intercourse at a relatively younger age.

Acknowledgements

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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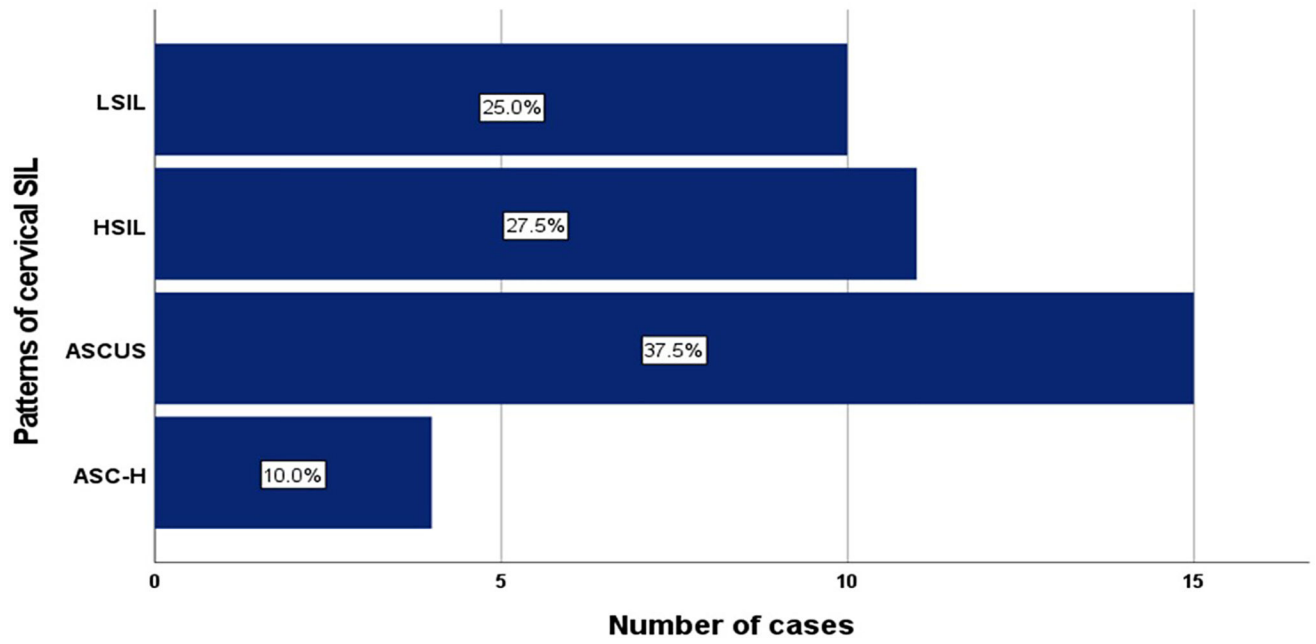
Figure 1:
Patterns of cytological abnormalities among HIV-infected women with cervical squamous intraepithelial lesions (SIL).
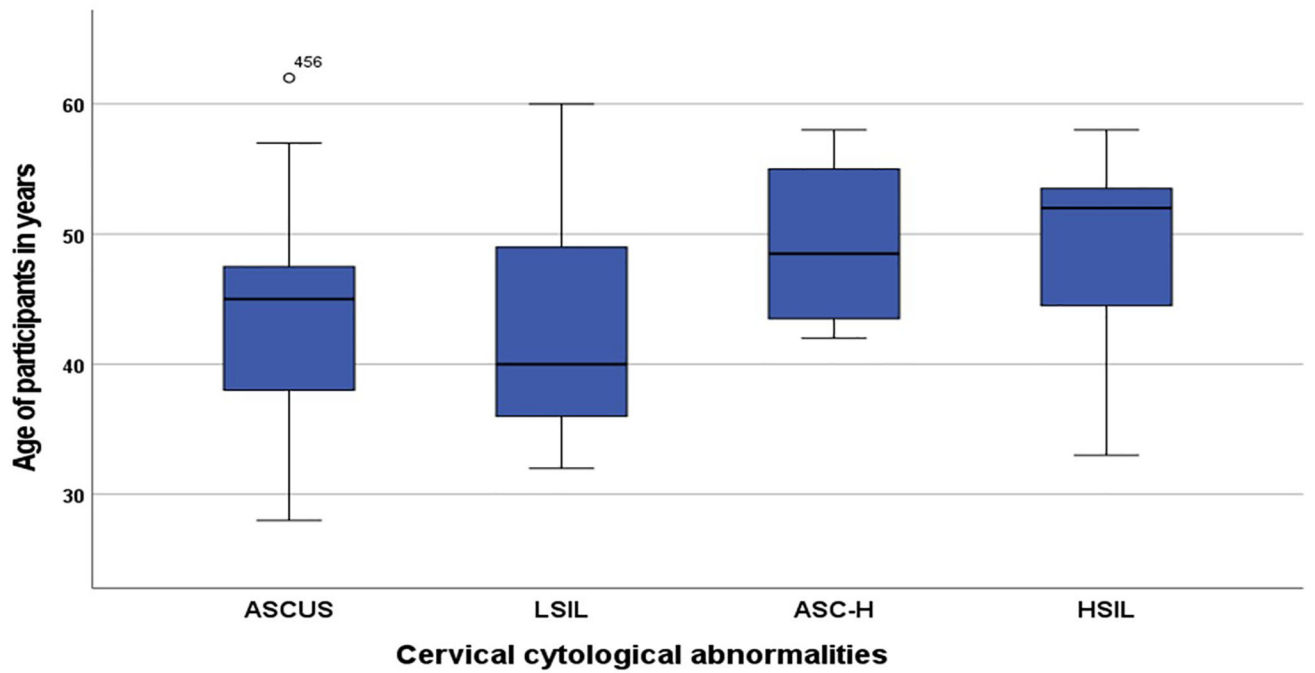
Figure 2:
Box plot showing the mean ages of HIV-infected women with ASCUS (43.6±8.8 years), LSIL (43.0±9.6 years), ASC-H (49.3±7.2 years), and HSIL (48.4±7.6 years).

Table 1:

Characteristics of study participants (n=593)[a]

Characteristics	Frequency (%)
Mean age at enrolment (± SD) in years	43.3 ± 8.0
Mean BMI (± SD) in kg/m ^{2}	27.1 ± 5.2
Median overall time since HIV diagnosis (IQR) in years	11.0 (8.0–14.0)
Mean duration of cART use (± SD) in months	111.4 ± 49.1
Median CD4+ cells count (IQR) in cells/µL	407.0 (265.0–583.0)
Median HIV viral load (IQR) in copies/mL	20.0 (0.0–52.0)
Mean age at coitarche (± SD) in years	20.0 ± 3.4
Parity	
Nulliparity	83 (14.0)
Multiparity	510 (86.0)
Marital status	
Married	372 (62.7)
Unmarried	221 (37.3)
Educational level	
Uneducated	19 (3.2)
At least primary education	77 (13.0)
At least secondary education	293 (49.4)
At least tertiary education	204 (34.4)
Use of hormonal contraceptive	
Yes	186 (31.4)
No	407 (68.6)
Number of lifetime sexual partners	
One	106 (17.9)
More than one	487 (82.1)
Previous STI	
Yes	124 (20.9)
No	469 (79.1)
Tobacco smoking	
Yes	22 (3.7)
No	571 (96.3)
Consumption of alcoholic beverages	
Yes	129 (21.8)
No	464 (79.2)
Cervical cytological abnormalities	
Yes	40 (6.7)
No	553 (93.3)

Abbreviations: cART, combination antiretroviral therapy; BMI, body mass index; IQR, interquartile range; SD, standard deviation; STI, sexually transmitted infections

[a]Values are given as mean ± SD, median (interquartile range), or frequency (percentage) unless indicated otherwise.

Table 2:

Bivariate analyses of study participants by Pap smear cytology results (n=593).[a]

Characteristics	Abnormal Pap smear		P-value
	Yes (n=40)	No (n=553)	
Age at enrolment (± SD) in years	45.3 ± 8.6	43.2 ± 7.9	0.09
BMI (± SD) in kg/m^2	27.9 ± 4.4	27.0 ± 5.3	0.31
Overall time since HIV diagnosis (IQR) in years	11 (8.0 – 15.0)	11 (8.0 – 13.0)	0.62
Duration of ART use (± SD) in months	116.9 ± 55.5	111.0 ± 48.6	0.46
CD4+ cells count (IQR) in cells/μL	369.0 (148.0 – 521.0)	414.0 (266.0 – 591.5)	0.15
Viral load (IQR) in copies/mL	20.0 (0.0 – 182.7)	20.0 (0.0 – 51.0)	0.35
Age at coitarche (± SD) in years	18.8 ± 3.1	20.1 ± 3.4	0.02
Parity			
Nulliparity	3 (3.6)	80 (96.4)	0.22
Multiparity	37 (7.3)	473 (92.7)	
Marital status			
Married	23 (6.2)	349 (93.8)	0.48
Unmarried	17 (7.7)	204 (92.3)	
Educational level			
Uneducated	1 (5.3)	18 (94.7)	0.73
At least primary education	7 (9.1)	70 (90.9)	
At least secondary education	17 (5.8)	276 (94.2)	
At least tertiary education	15 (7.4)	189 (92.6)	
Use of hormonal contraceptive			
Yes	11 (5.9)	175 (94.1)	0.57
No	29 (7.2)	376 (92.8)	
Number of lifetime sexual partners			
One	6 (5.7)	100 (94.3)	0.62
More than one	34 (7.0)	453 (93.0)	
Previous STI			
Yes	7 (5.6)	117 (94.4)	0.58
No	33 (7.0)	436 (93.0)	

Characteristics	Abnormal Pap smear		*P*-value
	Yes (n=40)	No (n=553)	
Tobacco smoking			
Yes	4 (18.2)	18 (81.8)	0.03
No	36 (6.3)	535 (93.7)	
Consumption of alcoholic beverages			
Yes	10 (7.8)	119 (92.2)	0.61
No	30 (6.5)	434 (93.5)	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; SD, standard deviation; STI, sexually transmitted infections

[a]Values are given as mean ± SD, median (interquartile range), or frequency (percentage) unless indicated otherwise.

Table 3:

Multivariate logistic regression of cervical cytological abnormalities and associated factors

Factors	Presence of cervical cytological abnormalities		*P*-value
	Adjusted OR	**95%CI**	
Age at enrolment in years			
40	1.43	0.69 – 2.96	0.33
<40	1.00	Reference	
CD4+ cells count in cells/μL			
400	0.73	0.38 – 1.42	0.35
<400	1.00	Reference	
Age at coitarche in years			
<20	2.42	1.21 – 4.83	0.01
20	1.00	Reference	
Tobacco smoking			
Yes	2.34	0.73 – 7.57	0.16
No	1.00	Reference	

Abbreviations: CI, confidence interval; OR, odds ratio