



Prevalence of Human Papilloma Virus DNA in HIV Positive Women in Lagos University Teaching Hospital (LUTH) Lagos, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author IGN conceived and designed the study, collected sample, procured the kits, did statistical analysis and contributed in the manuscript preparation. Authors AAFB and FBA contributed to the design and managed the analyses. Author VUN contributed in the manuscript preparation. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Introduction: HIV-infected women have a high prevalence of Human Papilloma virus (HPV) infection and are more likely to be infected with high risk genotypes with the potential of progressing to cervical cancer. There is paucity of data regarding the prevalence of sexually transmitted HPV infection among HIV positive women in Nigeria.

Aims: The objective of this cross-sectional prospective study was to determine the prevalence of high risk HPV among HIV positive and negative women in LUTH, Lagos, Nigeria and to relate HPV genotypes in the study population to commercially available HPV vaccine types that would be or not be appropriate for implementation of vaccination programs in Lagos State.

Place and Duration of Study: AIDS Prevention Initiative In Nigeria (APIN) clinic as well as the Gynecologic outpatient clinic of LUTH, Lagos between August 2011 and August 2012.

Methodology: A combination of PCR and flow through hybridization method was used in the genotyping of HPV from samples obtained from 98 HIV positive and 97 HIV negative women. Data was analyzed using Epi info 3.5.6. Non parametric variables were compared

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with chi-square or Fisher exact test as appropriate. The differences in mean for parametric variables were compared using student T test. P value <0.05 were considered significant.

Results: The prevalence of HPV among HIV positive women was 44.9% while the prevalence of high risk types was 37.5%. The commonest high risk types seen were types 31, 52, 53 and 35. The prevalence of HPV among the HIV negative women was 11%. The commonest high risk types seen were types 18, 16, 52 and 56.

Conclusion: In view of the high prevalence and diversity of HPV genotypes among the HIV positive women, adequate screening protocols should be put in place for screening this category of women. Studies should also be carried out to determine the efficacy of existent HPV vaccines on this group of patients.

Keywords: Prevalence; HPV genotypes; HIV positive women; Lagos.

1. INTRODUCTION

Cervical cancer which theoretically is a preventable disease is the second most common cancer among women worldwide [1]. Its incidence has been shown to vary across regions of the world from over 30 per 100,000 women per year in Africa to under 10 per 100,000 women per year in developed countries [2]. In Nigeria, the most populous country in sub-Saharan Africa, it is the second most common cancer (after breast cancer) where it has been estimated that of the 14,550 women who are diagnosed with the disease, 9659 die from it annually [3].

Human Papilloma virus (HPV) is a well established causal agent of cervical cancer [1]. Current estimate also show that about 23.7% of women in Nigeria harbor cervical HPV infection at any given time [3]. HPV is a double stranded DNA virus made up of 7900 base pairs [4]. Over 100 known types have been identified of which 40 infect the female genital tract. Of these, 15 high risk (HR) types cause approximately 95% of cervical cancers [5]. Other types classified as low risk (LR) cause low-grade lesions including 75% to 95% of genital warts (condylomata acuminata) [6]. In Human Immunodeficiency Virus (HIV) negative women, the majority of HPV infections are cleared within 8-10 months following infection [7]. However some infections evade the immune system through a complicated cascade of events and become persistent. Persistence is arbitrarily defined as two or more positive HPV tests within one year. It is the first step toward the development of high grade squamous intraepithelial lesions (HSIL/CIN2-3) and cancer [7]. The status of the immune system may determine the development of persistence after primary infection. HIV positive patients have an impaired immune system which permits a high viral load. They are more frequently infected with multiple HPV types and are more at risk of developing cervical squamous intraepithelial lesions (SIL) and cervical cancer [8]. Due to this impaired immunity, HIV positive women with severe immunosuppression are 5 times more likely than HIV negative women to have lower genital tract neoplasia. Treatment failure and recurrence also occur more frequently in HIV positive women. This underscores the importance of routine screening of HIV positive women for lower genital tract neoplasia and cancer [9].

Prior to the introduction of antiretroviral therapy in 1996 a lot of HIV positive women living in low resource countries had limited survival time after being diagnosed. However an increasing number of women from these regions are now accessing antiretroviral therapy with an increase in life span and a paradoxical increased risk of developing cancers in particular invasive squamous cell carcinoma of the cervix [9].

Current US guidelines recommend that women diagnosed with HIV should go for cervical screening at 6 monthly intervals until two Pap tests have been documented negative then annually afterwards [10]. The developing world has a lot of challenges in establishing population-level screening programmes [11]. In populations where cytology programmes are either not in place or are not efficient especially in resource constrained nations, HPV testing is being considered as an alternative test for primary screening [1]. Women with normal Pap smears are at increased risk of developing squamous intraepithelial lesion when high risk HPV DNA is detected in the uterine cervix [4]. Equally when HPV DNA is detected in women with low grade squamous intraepithelial lesion (LSIL) the risk of developing cervical cancer is increased (4). Prevention of exposure to high risk HPV types through vaccination may prove to be the most efficient and logistically feasible preventive measure [1].

The aim of this study was to determine the prevalence of genital Human Papilloma virus infection among HIV positive women at the Lagos University Teaching Hospital (LUTH) Lagos, Nigeria, West Africa and to relate HPV genotypes in the study population to commercially available HPV vaccine types that would be or not be appropriate for implementation in vaccination programs in Lagos State.

2. MATERIALS AND METHODS

The study was undertaken at the AIDS PREVENTION INITIATIVE (APIN) in Nigeria clinic and the Gynecologic out-patient Clinics of the Lagos University Teaching Hospital Idi Araba, Lagos. Lagos state is situated in South West geopolitical zone of Nigeria. The APIN clinic caters for over 3000 HIV positive patients with an average of twenty new cases seen on a daily basis. LUTH is the biggest tertiary institution in Lagos state and its environs and provides specialist healthcare services to the people of Lagos and its neighboring states.

2.1 Study Type

The study design was a comparative cross-sectional analytic observational study.

2.2 Study Population

The study populations are divided into two groups; comprising HIV positive women on antiretroviral therapy and HIV negative controls. A total of 100 HIV positive females within reproductive age were recruited into this study from the APIN clinic. They were pooled from those undergoing daily blood sampling for CD4 and viral load estimations. For the control subjects, the study population was pooled from HIV negative women coming for routine cervical cancer screening test.

2.3 Sampling Technique

Systematic random sampling technique was used for selection of study subjects. For the HIV positive cohorts, since an average of thirty women were bled daily in APIN clinic, then the total number of patients to be bled over two weeks will be 300. The sampling interval given as Total Population (300)/Sample size (100) was set at 3. The second subject was selected by balloting among the first three patients that was bled; subsequently the 5th, 8th, 11th etc subjects were selected. Similar technique was applied in selecting the control population.

2.4 Eligibility Criteria

Consenting HIV positive and HIV negative females 18 years and above. All participants gave informed consent. For those who were not literate, consent was obtained by interpretation in their local dialect.

2.5 Exclusion Criteria

The exclusion criteria included females who were menstruating or pregnant, those who have had hysterectomies performed on them and those who declined HIV testing.

2.6 HIV Test Methodology

HIV testing was done by ELISA method for all the participants and confirmatory testing was done using Western Blot for the HIV positive population. Blood samples from the HIV positive cohorts were also collected for CD4 count and viral load assessments.

2.7 HPV Test Collection

Cervical samples (exfoliated cells from the ectocervix and endocervix) were collected from each patient by a Senior Obstetrics and Gynaecology resident. These samples were for HPV testing. The samples were collected using a disposable cervical specimen collection kit (HybriBio Biochemical Company Limited China). The samples were immediately transferred to the department of Anatomic and Molecular Pathology of the College of Medicine University of Lagos where they were stored at -20 degree Celsius.

All participants also had VIA (visual inspection with Acetic acid) performed on them by the generous application of 4% freshly prepared acetic acid on the ectocervix using soaked cotton wool swabs and a minute later the cervix was evaluated for the presence of acetowhite areas.

Participants with abnormal findings at VIA were referred free of charge to the Gynaecology department of LUTH, Lagos for colposcopy examination and when necessary biopsy and treatment.

2.8 HPV Serotyping

The samples were screened for HPV infections using HPV GenoArray test kits (HybriBio Biochemical Company Limited, China). These kits use the combination of both polymerase chain reaction and flow through hybridization technology for qualitative detection and the determination of specific HPV types present by genotyping 21 types of HPV DNA in cervical specimens. This process involved DNA extraction, PCR amplification, Flow-through hybridization and result interpretation.

In the DNA extraction phase, aliquots of cervical samples were repeatedly centrifuged at 14,000 rounds per minute for 3 times each lasting for 5 mins. Supernatant were discarded each time and solutions I, II, III added respectively with 1ml of sample pipetted for PCR amplification.

During the amplification phase all the PCR reagents were spun and a mixture of PCR mastermix and DNA Taq polymerase was prepared per PCR reaction tube. One microlitre of DNA template was added to each PCR tube. The solution was centrifuged for a few seconds and placed in the thermal cycler for DNA amplification.

Flow-through Hybridization was commenced by denaturing the sample by heating for 5 mins at 95 degrees Celsius. The denatured DNA was then placed into sample wells containing 0.5mls of 45 degrees pre-warmed hybridization solution upon thin membranes. It was thereafter incubated for 20 mins and blocking solution added. Enzyme conjugate was added and the solution rinsed in distilled water. The solution membranes were then dried on absorbent paper and the results interpreted by colour visualization observed on the membrane.

The basis for a positive result was determined by the localization of specific probes on the Hybrimem HPV-21 membrane. For quality, positive and negative controls were included in the GenoArray test kit in every PCR analysis as well as during the hybridization process. The positive control was needed to demonstrate the efficiency and specificity of the PCR while a negative control would indicate if the PCR reagents were contaminated. Certain processes were also employed to reduce contamination in the laboratory such as sterilizing all the equipments before use with ionizing radiation and maintaining a unidirectional laminar flow.

2.9 Data Collection Instruments and Analysis

Each participant was administered with a questionnaire with closed and open-ended questions which was used to gather demographic information as well as information on known risk factors associated with HPV infections. Data were processed using Epi info version 3.5.6. statistical software package.

2.10 Presentation and Test Statistics

Results were presented in frequency tables. The Chi-square test and Fisher's exact test were used as appropriate to compare differences between proportions. Student t-test was used for comparison of the differences in means of numerical variables. P values <0.05 was considered significant.

2.11 Ethical Considerations

Ethical clearance was obtained from the ethical committee of the Lagos University Teaching Hospital.

3. RESULTS

The full participation rates for the study subjects were 98 (98%) and 97 (97%) for the HIV positive and negative groups respectively. The mean ages of the participants were 36.8±9.0 years and 43.8±10.5 years for the test and control groups respectively. Majority (83.5%) of the control subjects attained tertiary level of education compared to 40.8% of the HIV positive subjects. Details of the tribes, nationality, religious preferences were as presented in Table 1

Table 1. Socio-demographic characteristics of the study population

AGE GROUP	HIV positive Frequency (%)	HIV negative Frequency (%)	P value
<25	2 (2.00)	2 (2.10)	
25-34	38 (38.80)	17 (17.50)	
35-44	38 (38.80)	23 (23.70)	
45-54	12 (12.20)	43 (44.30)	
55+	5 (5.10)	12 (12.40)	
Not stated	3 (3.10)	0 (0.00)	
Mean ± SD	36.8±9.0	43.8±10.5	P<0.0001
Nationality			
Nigerian	97 (99.00)	97 (100.00)	
Others	1 (1.00)	0 (0.00)	*p=1.00
Marital status			
Single	26 (26.50)	9 (9.30)	
Married	51 (52.00)	77 (79.40)	
Divorced	3 (3.10)	1 (1.00)	*p=0.0002
Widowed	13 (13.30)	10 (10.30)	
Separated	5 (5.10)	0 (0.00)	
Tribe			
Ibo	43 (43.90)	25 (25.80)	
Hausa	3 (3.10)	2 (2.10)	
Yoruba	34 (34.70)	54 (55.70)	*P=0.02
Others	18 (18.30)	16 (16.40)	
Religion			
Christianity	86 (87.80)	86 (88.70)	*p=1.00
Islam	11 (11.20)	11 (11.30)	
Others	1 (1.00)	0 (0.00)	
Education			
None	1 (1.00)	0 (0.00)	
Primary	13 (13.30)	4 (4.10)	*P=0.00
Secondary	43 (43.90)	12 (12.40)	
Tertiary	40 (40.80)	81 (83.50)	
Not stated	1 (1.00)	0 (0.00)	
Total	98 (100.00)	97 (100.00)	

3.1 Sexual and Reproductive History of Participants

Only 5.20% and 10.20% of the control and the HIV positive groups respectively had their sexual debut before the age of sixteen years. Majority of the subjects in both the HIV positive population and control groups had less than five sexual partners within the last year (96.90% each). Only 1% of the participants in the HIV positive group had greater than 10 sexual partners in the last year.

Majority of those with 5-10 lifetime sexual partners were HIV positive (23.50%) compared to the control subjects (11.30%). There was statistically significant difference in lifetime number of sexual partners among both groups of women ($p=0.0024$). Details of sexual and reproductive history are presented in Table 2.

Table 2: Sexual and reproductive history of participants

Variable	HIV positive	HIV negative	P value
Menarche	Frequency (%)	Frequency (%)	
A.<13	19 (19.40)	22 (22.70)	
B.13+	78 (79.60)	73 (75.30)	*P=0.65
Not stated	1 (1.00)	2 (2.10)	
Sexual debut			
A.<16	10 (10.20)	5 (5.20)	
B.16+	87 (88.80)	92 (94.80)	
Not stated	1 (1.00)	0 (0.00)	*P=0.24
Sexual partners in past year			
A.<5	95 (96.90)	94	
B.5-10	1 (1.00)	1 (1.00)	
C.>10	1 (1.00)	0 (0.00)	*P=1.00
Not stated	1 (1.00)	2 (2.10)	
Lifetime sexual partners			
A.<5	68 (69.40)	84 (86.60)	
B.5-10	23 (23.50)	11 (11.30)	
C.>10	6 (6.10)	0 (0.00)	*P=0.0024
Not stated	1 (1.00)	2 (2.10)	
Total	98 (100.00)	97 (100.00)	
Pregnancies			
A.<3	33 (33.70)	31 (32.00)	
B.3+	65 (66.30)	62 (63.90)	*0.16
Not stated	0 (0.00)	4 (4.10)	
Birth control			
None	32 (32.70)	46 (47.40)	
Barrier	61 (62.20)	17 (17.50)	
Abstinence	0 (0.00)	5 (5.20)	
Injectable	1 (1.00)	2 (2.00)	
IUCD	2 (2.00)	18 (18.60)	*P=0.00
Others	0 (0.00)	1 (1.00)	
Natural Method	0 (0.00)	1 (1.00)	
Oral contraceptive	2 (2.00)	7 (7.20)	
Total	98 (100.00)	97 (100.00)	

3.2 Social History

Fifty-five (56.70%) of the control group had ever taken alcohol as compared to thirty-seven (38.70%) of the HIV positive population. Majority of the participants who were HIV positive (62.20%) had never taken alcohol. There was also statistically significant difference in the two groups with respect to alcohol intake, $p=0.01$ (as shown in Table 3). Most of the participants in both the study population and the controls have never used tobacco (96.90% and 98.90% respectively). Similarly most of the participants in both groups also reported not to have used marijuana (96.90% and 99.00% in the HIV positive and control groups respectively).

Table 3: Showing frequency of intake of alcohol with the use of tobacco and marijuana

Variable	HIV positive	HIV negative	P value
ALCOHOL INTAKE	Frequency (%)	Frequency (%)	
Never	61 (62.20)	42 (43.30)	
Ever	37 (37.80)	55 (56.70)	*P=0.01
Total	98 (100.00)	97 (100.00)	
TOBACCO USE			
Never	95 (96.90)	96 (98.90)	
Ever	3 (3.10)	1 (1.00)	*P=0.62
Total	98 (100.00)	97 (100.00)	
MARIJUANA USE			
Never	95 (96.90)	96 (99.00)	
Ever	3 (3.10)	1 (1.00)	*P=0.62
Total	98 (100.00)	97 (100.00)	

3.3 Visual inspection with Acetic acid (VIA)

The exocervix in HIV-positives and controls failed to stain with acetic acid solution in 94.9% and 90.7% of the cases, respectively. There were no statistically significant differences ($p=0.28$) between the two groups of women.

3.4 HPV Test Result

A total of 19 different HPV types were identified from 45 (44.90%) HIV positive females of which 37 (37.75%) were infected with the high risk types. Eleven women (11.20%) had multiple high risk HPV infections involving between two and seven HPV types. The commonest high risk type detected in the HIV positive group were types 31 (16.80%), 52 (15.20%), 53 (9.10%) and 35 (7.60%). Five females (5.10%) were positive for the low risk groups with types 6 and 11 being equally prevalent (3.0%) each followed by type 44 (1.5%). Overall, single genotypes were found in 27 females (27.55%) while both high and low risk genotypes were found in 4 females (4.0%).

In the control group, 11 females (11.34%) tested positive for HPV infections. All HPV infections detected from this group were of the high risk types with 3 females (3.0%) testing positive for multiple HPV types. The commonest high risk type detected was type 18 (23.10%) followed by 16, 52 and 56 (15.40%) each. (Fig. 1)

3.5 Indices of HIV Positive Infection

3.5.1 CD4 counts

The mean CD4 lymphocyte count was 442cells/ml. Nine females had CD4 counts less than 200 cells/ml. Fifty-eight females had CD4 counts between 200 – 499 cells/ml, while 30 women had CD4 counts above 500cells/ml. There was no correlation between CD4 counts and HPV status in the HIV positive subjects.

3.5.2 Viral load

Only 16.30% of the HIV positive population had viral load above 1000 copies per ml. Majority (76.50%) had viral load between 200-399 copies per ml (Table 4).

Table 4. Showing the frequency of viral load in the HIV positive women

Viral load GRP	Frequency	Percent
>1000	16	16.30%
200-399	75	76.50%
400-1000	3	3.10%
Not Obtained	4	4.10%
Total	98	100.00%

4. DISCUSSION

This is the first report of the prevalence of cervical HPV among HIV-positive women attending the APIN clinic of LUTH, Lagos. The assumption was that due to the impaired immune status of HIV-positive women, they are likely to have higher rates of HPV infections than seen in the general population of this region.

The prevalence of HPV in this study among the HIV positive and negative women was 44.90% and 11.20% respectively. This figure is comparable with 57.10% of HIV positive but contrasts with the 35.50% of the HIV negative West African immigrants resident in Southern Italy, most of who were Nigerians [12]. A prevalence of 26.30% was also discovered among the general population in Ibadan, Nigeria [13]. The increased prevalence of HPVs among HIV positive women may be due to the fact that HPV replication may be more efficient in immunodeficient host which could result in increased detection rate as well as a higher chance of developing persistent HPV infection [14]. Previous HPV surveys in Sub-Saharan Africa have generally shown high HPV prevalence, with some variation depending on how the women were selected and how the HPV was tested for [13]. Studies carried out in Burkina-Faso showed a prevalence of 66.10% [15]. Studies also carried out in other parts of Africa like Zambia showed a HPV prevalence of as high as 97.2%. [6] This figure may be attributable to the exhaustive nature of the HPV detection strategy. Indeed studies have shown that with the use of a primer pair alone to detect HPV by PCR (MY09/MY11) certain HPV types such as 26, 35, 42, 45, 52, 54, 55, 59, 66, 68, 73 and 83 might be missed thereby underestimating the infection and thereby giving an erroneously low prevalence rate [15].

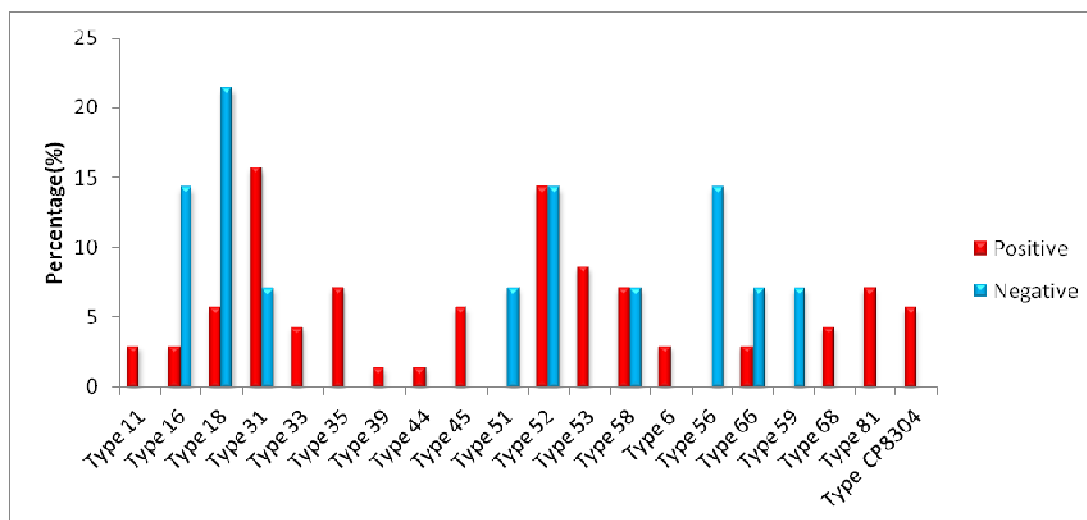


Fig. 1. showing the prevalence of the different HPV types in both HIV positive and negative populations

The commonest high risk HPV detected in our study among HIV positive women were types 31, 52, 53 and 35 in decreasing order of prevalence. This is also similar to the types found in other West African countries like Burkina-Faso (types 52, 35 and 58) [15] and other African countries like Zambia (53, 31, 51 and 45) [6]. This sharply contrasts with a worldwide prevalence rate of HPV 16 and 18; this was also found in our HIV-negative controls [16]. This finding has important implications in the eventual implementation of prophylactic HPV vaccines based on high risk types 16 and 18 [6]. If cross immunity is not induced across viral types by existing vaccines, this will limit their efficacy in immunosuppressed women in developing countries whose dominant high risk type may be other than 16 or 18 [6]. Among the HIV negative population in our study it was discovered that high risk type 18 was the commonest followed by 16, 52 and 56. This is not unusual as the behavioral and socioeconomic characteristics of HIV infected women may differ from women in the normal population [14].

The incidence of multiple HPV types among HIV positive females of 11% is also similar to the 12% discovered in a cohort of HIV positive women in the US [17]. This is much lower than the 45% seen in Brazilian HIV positive patients [18]. Studies in some African countries like Zambia also showed a prevalence of 78.6% [6]. These differences in prevalence may be due to variability in the genotype method used (14).

There were a number of socio-demographic factors that were predictive of high risk HPV status in the HIV positive population. Older females between the ages of 25-34 years were more likely to be infected with high risk HPVs than those less than 25 years and those 55 years and above. This is similar to what was discovered among HIV positive Rwandan women in whom prevalence peaked in those aged 25-34 years and declined in those greater than 55 years old [19]. This may be explained by the time taken for persistence to develop in the 25-34 years age range and the lower incidence of sexual activity in the >55 years age range. This picture contrasts with what was seen in the HIV negative population, where females in the 45-54 age range had two folds increased risk of being infected with high risk HPV than those in the 25-34 age range. A similar study carried out among the general

population of Ibadan, Nigeria showed a modest peak in HPV prevalence among women in the <25 years age range and a high prevalence among the middle aged and old women [13]. Part of the reasons that was adduced for this trend was that a fraction of the spouses of these women may continue to have multiple sexual contacts throughout their lives thereby reinfesting themselves and these women [13]. Similar studies carried out in other West African countries showed an increased prevalence of HPV among women who were less than 25 years of age [14,20].

There was no statistical relationship between lower educational level (primary) and high risk HPV as most of the participants had at least attained secondary education. The age of sexual debut as well as the lifetime no of sexual partners was not reliably predictive of high risk HPV infection since all the participants reported the age of sexual debut to be greater than 16 years with greater than 90% having less than 5 lifetime sexual partners.

5. CONCLUSION

In view of the diversity of HPV genotypes and high prevalence found among the HIV positive women, it is pertinent to reinforce the importance of adequate cervical cancer screening protocols, for this category of people by using polyvalent HPV vaccine [6]. This is especially important in our setting since we are yet to develop protocols for screening HIV positive women. It is noteworthy that in many developing countries, bilateral and multilateral donor assistance programmes such as AIDS Preventive Initiative In Nigeria is improving the availability of antiretroviral therapy. This study highlights the importance of linking such programmes with cervical screening strategies for HIV positive women. By so doing the burden of both HIV and cervical cancer would be reduced dramatically.

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CONSENT

Informed consent was obtained from all the participants and a copy is presented in the appendix.

ETHICAL APPROVAL

Ethical approval was obtained from the Lagos University Teaching Hospital ethical committee and a copy is attached.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX 1

ADM/DCST/HREC/159

5.2 INFORMED CONSENT

I, Dr Nweke I. G of the department of Morbid Anatomy of the Lagos University Teaching Hospital Idi-Araba, Lagos wishes to carry out a study on Prevalence of Genital Human Papillomavirus infection and cervical cytology abnormalities among retroviral positive women at LUTH, Lagos”.

The study is in partial fulfillment of the requirements for the Part II of the National Postgraduate Medical College of Nigeria Fellowship in the Faculty of Pathology. Any information that will be provided for this study will be treated as confidential and for the benefit of patients. This study is voluntary and you should feel free to participate or decline. Your declining will not affect the quality of care you receive in this hospital. This study also, would not attract any financial cost to you.

Any abnormality discovered will be communicated to you and intervention will be offered where necessary.

I initials (only) understand the purpose of this interview and I volunteer to participate in this study.

Signature:

Date:

Interviewer:

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