ORIGINAL RESEARCH ARTICLE

Epidemiology of Cervical Squamous Intraepithelial Lesions in HIV Infected Women in Kenya: a cross-Sectional Study

[1]Peter Memiah, [2]Violet Makokha, [3]Wangeci Mbuthia, [2] Grace Wanjiku Kiiru, [1]Solomon Agbor [2]Francesca Odhiambo, [2]Sylvia Ojoo, [4]Justice Mbizo, [5]Samuel Muhula, [2]Gabriel Mahasi and [6]Sibhatu Biadgilign*

[1]University of Maryland School of Medicine-Institute of Human Virology, Baltimore; [2]University of Maryland School of Medicine; Kenya; [3]Nazareth Hospital, Kenya; [4]University of West Florida, School of Allied Health and Life Sciences; [5]AMREF Kenya; [6]Independent Consultant

***For Correspondence:** *E-mail: pmemiah@gmail.com; Phone:+254 0734041071*

Abstract

Cervical cancer is the second most common cancer among women worldwide. Infection with the human immunodeficiency virus (HIV) and its related immunosuppression are associated with an increased risk of prevalent, incident, and persistent squamous intraepithelial lesions (SILs) of the cervix. The objective of the study was to describe the prevalence and predictors of high-risk HPV and cervical cancer to support the need for strengthening cervical cancer screening programs for HIV infected women in Kenya. A cross sectional study was conducted in a hospital in Central Kenya, Kiambu district. The study population constituted of HIV positive women attending the ART treatment clinic. A total of 715 HIV positive women initiated on Antiretroviral Therapy (ART) were enrolled in this study. About 359 (52.1%) were less than 40 years of age and 644 (90.3%) of the patients were widowed. About 642 (92.6%) of the HIV infected women were in follow-up period of ≥ 1 year. The outcome/prognosis of the patients undergoing ICC was 3 cured, 5 good and 4 poor respectively. In a multivariable ordinal logistic regression analysis showed that for a one-unit decrease of CD4, we expect 1.23 log odds of increasing the severity of cervical cancer (B=1.23, P<0.015), given that all of the other variables in the model are held constant. In conclusion screening of all HIV infected women, who are under HIV care and treatment, enrolling patients on HAART with higher CD4 counts is recommended to see the net effect of HAART response. *(Afr J Reprod Health 2013 (Special Edition); 19[1]: 133-139).*

Keywords: Cancer screening, ART, SILs, Women, CD4

Résumé

Le cancer du col est le deuxième cancer le plus fréquent chez les femmes à travers le monde. L'infection par le virus de l'immunodéficience humaine (VIH) et son immunosuppression associée sont liés à un risque accru de courants, incident, et lésions intra-épithéliales squameuses persistants (LIS) du col de l'utérus. L'objectif de l'étude était de décrire la prévalence et les facteurs prédictifs de VPH à haut risque et cancer du col pour soutenir la nécessité de renforcer les programmes de dépistage du cancer du col utérin pour les femmes séropositives au Kenya. Une étude transversale a été menée dans un hôpital Kenya Central, dans le district de Kiambu. La population d'étude comprenait de femmes séropositives qui fréquentaient la clinique de traitement de la TAR. Au total, 715 femmes séropositives initiées à la thérapie antirétrovirale (ART) ont été incluses dans cette étude. A peu près 359 (52,1%) avaient moins de 40 ans et 644 (90,3%) des patients ont été des veuves. A peu près 642 (92,6%) des femmes infectées par le VIH étaient en période de suivi d'un an ≥ 1. Le résultat / pronostic des patients suivaient le traitement par IPC était : guéri 3, 5 bon et 4 mauvais respectivement. Une analyse multivariée par la régression logistique ordinale a montré que pour une diminution d'une unité de CD4, nous nous attendons à 1,23 log odds d'accroître la gravité du cancer du col (B = 1,23, P <0,015), étant donné que tous les autres variables du modèle sont maintenus constants. En conclusion, nous préconisons le dépistage de toutes les femmes infectées par le VIH, qui reçoivent les soins et le traitement du VIH, l'inscription des patientes qui ont un CD4 plus élevé sous HAART afin de voir l'effet net de la réponse de la multithérapie. *(Afr J Reprod Health 2013 (Special Edition); 19[1]: 133-139).*

Mots-clés: dépistage du cancer, ART, Sils, femmes, CD4

Introduction

Cervical cancer is the second most common cancer among women worldwide; of the 274,000 deaths due to cervical cancer annually, 80% occur in developing countries[1]. Infection with the human immunodeficiency virus (HIV) and its related immunosuppression are associated with an

increased risk of prevalence, incidence, and persistent squamous intraepithelial lesions (SILs) of the cervix[2,3]. Invasive cervical carcinoma and its precursors are the most significant gynecologic manifestation of HIV infection and in 1993 cervical cancer was also included among the AIDS-defining conditions[4]. Cervical infection and persistence of human papillomavirus (HPV) infection are the major etiologic agent in most cervical neoplasms[5]. In sub-Saharan Africa, age-standardized incidence of cervical cancer is high, ranging from 29.3 (West Africa) to 42.7 (southern Africa) per 100,000 women[6]. The prevalence of squamous intraepithelial lesion (SIL) is higher among HIV-infected women compared with uninfected women[7]. In HIV-infected women, there is an increased risk of HPV infection and squamous intraepithelial lesions (SIL), the precursor of cervical cancer[8,9] . Highly active antiretroviral therapy (HAART) has been shown to decrease HIV viral loads, increase CD4 cell counts and decrease most opportunistic infections. Since the introduction of HAART there has been a decline in certain malignancies in HIV infected individuals[10,11] . Although some studies suggest that antiretroviral treatment may alter the course of HPV-induced cervical dysplasia among HIV-infected women by slowing progression and increasing regression of dysplasia[12] the incidence of invasive cervical cancer has not significantly decreased in the era of HAART[13]. The need for better understanding of the interactions between HIV and HPV in the context of HAART is therefore even more pressing as increasing numbers of HIV infected women are living longer with a persistent risk of ICC. Guidelines for prevention and treatment strategies for cervical cancer among HIV-infected women are largely based on limited evidence, or in the case of resource limited settings, are completely lacking[14]. As HIV-infected women continue to live longer with ART support, albeit in a moderately immunosuppressed state, they may be at increased risk for CIN and invasive cervical cancer[15,16]. So the objective of the study was to describe the prevalence and predictors of high-risk HPV and cervical cancer to support the need for strengthening cervical cancer screening programs for HIV infected women in Kenya.

Methods

Study setting

The study setting, subjects, and data collection methods have been previously described[17]. Briefly, data were collected in Kenya of which all consecutive HIV positive women attending the clinic between June 2009 and December 2010 were included for the study. The study site was a faith-based hospital offering comprehensive care and treatment to approximately 4,000 HIV infected patients. The study site was located in Central Kenya, Kiambu district that has a HIV prevalence of 4%. The study population constituted eligible women attending the ART treatment clinics. None of the patients had evidence of Kaposi sarcoma or non-Hodgkin lymphoma. Eligibility criteria included being aged 18-69 years, and having no current or past history of cervical disease. Women, eighteen years and older, who were on follow-up for their HIV positive status, were screened for cervical cancer using the Visual Inspection with Lugol's Iodine (VILI) technique.

Measurements

Data on socio-demographic status, sexual behavior, history of a sexually transmitted infection (STI), obstetrics and gynecology history (parity) was obtained from patient medical records as part of the routine quality improvement activities; CD4 count data and HAART status were also extracted from clinical records. Clients were referred to the clinician where a pelvic examination was conducted using a sterile speculum examination. Visual inspection with lugol's iodine (VILI) was used as the screening technique. A positive VILI test necessitated a cervical biopsy this was preserved in a sterile container using formalin as the fixative and the biopsies were then taken for histology.

The histology result upon biopsy would turn out to be either negative for Intra-epithelial Lesion (IEL), active/chronic cervicitis, pre-cancerous lesions (CIN I, CIN II or CIN III/ CIS) or cervical cancer (squamous cell or adenocarcinoma) which was either differentiated (well, moderately, poorly

differentiated) cervical cancer. The cervical cancer clients were clinically staged using the 1986 International Federation of Gynecology and Obstetrics (FIGO) architectural staging system[18].Their participation in the screening in no way affected access to, or provision of, comprehensive HIV/AIDS care, as this was a standard of care at the clinic.

Statistical analysis

Statistical analysis was carried out using STATA version 12. Descriptive statistics (medians and proportions) were used to characterize the variables. Bivariate (unadjusted) analysis was performed to identify factors significantly associated with the severity of CIN. $P<0.05$ was considered statistically significant. The parameter estimates, standard errors (SE), 95% confidence intervals (CI) and two-tailed p-values were calculated. Variables found to be statistically significant ($p<0.05$) on unadjusted analysis were included in a multivariable ordinal regression model. For the final model building, we use covariates found to be statistically significant ($p<0.05$) on unadjusted analysis and those variables that are considered to be scientifically/biological plausible evidence of CIN incidence and progression.

Results

Socio demographic and clinical characteristics

All the 715 HIV positive women attending the clinic between June 2009 and December 2010 were enrolled for this particular study. Concerning the age of the participants, 359 (52.1%) were less than 40 years of age. About 644(90.3%) of the patients were widowed. Regarding the parity, 300(50.7%) of the cases had less than 3 children. About 168(24.3%) of the participants were under WHO clinical stage of I and II. Pertaining to the baseline CD4 count, 200(45.1%) had a CD4 of less than 200 mm3. Similarly, 592(85.8%) of the study participants have most recent CD4 count of >200 mm3 greater. About 317 of participants with an age of less than 40 years (88.3%) had normal screening outcome. About 642 (92.6%) of the HIV-infected women were in follow-up period of ≥1 year. About 99 of the patients on ART (91.7%) had a normal screening outcome (Table1).

Table 1: Distribution of the characteristics of HIV+ women screened for cervical cancer at Nazareth Hospital

Characteristics	Normal	CIN I	CIN II	CIN III	ICC	P value
Age (n=689)						
Less than 40 years	317 (88.3)	18 (5.0)	11 (3.1)	10 (2.8)	3 (0.8)	0.762
≥ 40 years	297 (90.0)	15 (4.5)	7 (2.1)	7 (2.1)	4 (1.2)	
Marital Status (n=713)						
Widowed	572 (88.8)	31 (4.8)	19 (2.9)	15 (2.3)	7 (1.2)	
Married	46 (86.8)	4 (7.6)	1 (1.9)	2 (3.7)	-	0.983
Separated	10 (100.0)	-	-	-	-	
Single	6 (100.0)	-	-	-	-	
Parity (n=591)						
Less than 3	271 (90.3)	14 (4.7)	5 (1.7)	7 (2.3)	3 (1.0)	0.762
≥ 3	261 (89.7)	15 (5.2)	8 (2.7)	6 (2.1)	1 (0.3)	
CD4 at Baseline (n=621)						
Less than 200 mm3	246 (87.9)	11 (3.9)	11 (3.9)	9 (3.2)	3 (1.1)	0.112
≥ 200 mm3	308 (90.3)	20 (5.9)	4 (1.2)	6 (1.7)	3 (0.8)	
CD4 Most Current (n=690)						
Less than 200 mm3	80 (81.6)	4 (4.1)	7 (7.1)	5 (5.1)	2 (2.0)	0.008
≥ 200 mm3	534 (90.2)	30 (5.1)	12(2.0)	12 (2.0)	4 (0.7)	
WHO Most Current (n=692)						
WHO I and WHO II	148 (88.1)	8 (4.7)	5 (3.0)	7 (4.2)	-	0.326
WHO III and WHO IV	468 (89.3)	26 (5.0)	14(2.7)	10 (1.8)	6 (1.2)	
Time on ART (n=581)						
1-14 days	102 (87.2)	5 (4.3)	5 (4.3)	4 (3.4)	1 (0.8)	0.336

15-30 days	107 (89.2)	3 (2.5)	6 (5.0)	4 (3.3)	-	
≥ 31 days	305 (88.7)	21 (6.1)	8 (2.3)	5 (1.5)	5 (1.4)	
ART status (n=692)						
On ART	99 (91.7)	5 (4.6)	-	4 (3.7)	-	0.232
Pre-ART	511 (88.4)	29 (5.0)	19 (3.3)	13 (2.3)	6 (1.0)	
Abortion (n=714)						
None	543 (89.0)	30 (4.9)	17 (2.8)	13 (2.1)	7 (1.2)	
1	60 (90.9)	2 (3.0)	1 (1.5)	3 (4.6)	-	0.751
2	23 (82.1)	3 (10.7)	1 (3.6)	1 (3.6)	-	
3 and more	9 (90.0)	-	1 (10.0)	-	-	

Treatment and outcome of the treatment/prognosis

From the total patients undergoing screening, only 16 patients were treated on different modalities depending on the cases of the patients. From this, 6 patients were treated with total abdominal hysterectomy (TAH) from which the result of one of the patents were pending, 3 cases were referred to a tertiary hospital, 2 cases with Loop electrosurgical excision procedure (LEEP), 1 cases of lost to follow up and 2 cases on radio and chemotherapy, 1 on anti-TB medication. The outcomes/prognosis of the cases were 3 cured, 5 good and 4 poor respectively.

Predictors of increasing severity of CIN

We included the following variables in the model building development: WHO clinical stage, receiving HAART, marital status, month on HAART treatment, CD4 baseline and current, age of the respondents, parity, abortion history and frequency, duration of follow up and none of them were associated with increased severity of CIN in HIV infected women except current CD4 count. In unadjusted (bivariate) and adjusted/ multivariable ordinal logistic regression analysis, participants with greater odds of more severe CIN was current CD4 count. For a one unit decrease of CD4, we expect 1.23 log odds of increasing the severity of cervical cancer (B=1.23, P<0.015), given that all of the other variables in the model are held constant.

Discussions

In HIV-infected women, there is an increased risk of HPV infection and squamous intraepithelial lesions (SIL), the precursor of cervical cancer[8,9]. In our study only the current CD4 count of less than 200 was found to be an independent predictor for increasing the severity of CIN. Similar findings have been reported in other studies. According to Tirrum in Nigeria, they obtained a CD4 lymphocyte count of <200 cells/mm3 and an HIV-1 RNA viral load of<10,000 copies/mL were found to be significantly associated with cervical SIL[19]. Both CD4 lymphocyte count and HIV RNA viral load are independent predictors of the course of HIV/AIDS, and the frequency of occurrence and severity of cervical SIL in HIV-infected women[20]. Lower CD4+ cell counts have been shown to independently predict both incidence and progression of lesions[21] and higher and increasing CD4+ T-cell counts were associated with lower rates of HPV persistence[22] from a cohort in Spain of HIV-infected women with CD4+ cell counts >350 cells/mm3 and with no previous SIL, there was no significant difference in SIL incidence between groups receiving versus not receiving HAART. Other studies also documented similar result. The risk of SIL was significantly increased among women with CD4 cell count -200rmm multivariate odds ratio[23].

Multivariate analysis confirmed an independent association of CIN with CD4 T-lymphocyte count below 200 cells/mm^3[24] and CD4 counts <200 cells/mm as associated with a risk of recurrence of any CIN but not with a risk of recurrence of high-grade CIN in a Brazilian study[25]. In the same study with multivariate models the nadir CD4 count was significantly associated with cytological abnormalities. The odds ratio for having cytological abnormalities was 2.6 in those with a nadir CD4 count <200 cells/mm3 compared with those with a higher nadir CD4 count[26]. The relationship between CD4+ T-lymphocyte cell counts and the severity of cervical SIL was significant (P = 0.007) in Tanzania as well[27].(Table 2)

Table 2: Parameter estimates from ordinal regression model for predicting increasing disease severity of cervical cancer among HIV+ women at Nazareth Hospital

Variable	Unadjusted ordinal regression analysis			Multivariable ordinal regression analysis*		
	Estimate (95% CI)	SE **	P value	Estimate (95% CI)	SE	P value
Age						
> 40 years (ref: < 40 years)	-0.17(-0.65,0.31)	0.245	0.478	-0.23(-0.93,0.47)	0.358	0.518
Time on ART						
15-30 days (ref: 1-14 days)	-0.187(-0.98,0.60)	0.403	0.642	-0.26(-1.30,0.79)	0.53	0.630
> 31 days (ref: 1-14 days)	-0.162(-0.79,0.47)	0.324	0.617	-0.13(-1.00,0.75)	0.45	0.77
ART						
Not on ART (ref: On ART)	0.369(-0.36,1.10)	0.371	0.320	Not included	-	-
CD4 at Baseline						
> 200 mm3(ref: <200 mm3)	-0.28(-0.79,0.22)	0.258	0.276	0.50(-0.33, 1.33)	0.42	0.237
Most Current CD4 count						
> 200 mm3(ref: <200 mm3)	-0.78(-1.35,-0.20)	0.2945	0.008	-1.23(-2.21, -0.24)	0.504	0.015
Parity						
> 3 (ref: Less than 3)	0.06(-0.47,0.60)	0.274	0.820	-0.048(-0.74,0.64)	0.352	0.892
Marital Status						
Married (ref: Widowed)	0.17(-0.66,0.99)	0.423	0.691	0.60(-0.43,1.63)	0.52	0.255
Separated(ref: Widowed)	-12.52(-927.36,902.31)	466.76	0.979	-12.65(-2038.1, 2012.8)	1033.41	0.990
Single (ref: Widowed)	12.52(-1193.6,1168.5)	602.58	0.983	-12.86(-1988.35, 1962.63)	1007.92	0.990
Most Current WHO stage						
WHO III and WHO IV(ref: WHO I and WHO II)	-0.13(-0.67,0.41)	0.276	0.647	0.11(-0.78,1.00)	0.455	0.807
Abortion						
1 (ref: None)	-0.19(-1.07,0.68)	0.447	0.662	0.26(-1.37,0.85)	0.566	0.649
2 (ref: None)	0.52(-0.468,1.51)	0.503	0.301	0.30(-1.31,1.92)	0.825	0.711
3 and more (ref: None)	-0.09(-2.16, 1.99)	1.06	0.933	-13.67(-2181.67, 2154.33)	1106.142	0.990

* Multivariable ordinal logistic regression analysis included scientifically/biological plausible evidenced variables and variable significantly associated at bivarite analysis
**SE = Standard error.

In our study, age of the respondents, parity, abortion history and frequency did not show any statistical significant difference for the increased rate of severity of the CIN. A similar finding has been found in other studies. In a Bangkok study, smoking, hormonal contraceptive or antiretroviral use, condom use, parity and number of lifetime sexual partners were not associated with cytological abnormalities[26] and risk factors for cervical cancer accounted for the presence of HPV infection, being immune compromised, giving birth to three or more children[28].

The odds of SIL did not differ substantially by marital status, educational status, previous exposure to tobacco smoke, previous pill usage, parity, age at first sex, time since HIV diagnosis or CD4 count[29] and in a Tanzania study it was demonstrated that marital status and number of lifetime sex partners were risk factors significantly associated with SIL but not associated with age,

education level, parity or age at sexual debut[29].

In tur study the usage of HAART doesn't show any effect on the increasing severity of CIN. Other studies showed HAART exhibited a protective effect on the recurrence of any CIN and of high-grade CIN [25]. But other studies showed that there was a modest inclination for the effect of HAART on the cervical cancer and reported as ART has not decreased the incidence of cervical cancer, and the reason for this is not well understood[30] and other reviews suggest that HAART has not been shown to affect HPV detection, and data on its effect on the natural history of CIN are mixed[31].

In a Cameroonian study of those on HAART, there was high prevalence of cervical squamous intraepithelial lesions in women. The study revealed that there was a limited role of HAART on the progression of lesions[29] . Duration and type of antiretroviral regimen were not significantly associated with SIL[32] and another study showed that HAART use was associated with increased regression of SIL among HIV-infected women, and among women who used HAART, increased CD4+ T-cell counts were associated with a greater likelihood of regression. However, the majority of cervical lesions among HIV-infected women, even among individuals who used HAART, did not regress to normal[33]. The possible explanation for the contradictory and mixed finding of the use of HAART is that the increasing severity of the cervical lesion depends on the immunological status of the patients and HAART initiated to the patient once the CD4 count is less than 200. It remains the host to boost their immune status to reach the level that can optimize the effect of the regression of the cervical cancer lesion to observe the impact of HAART on human papillomavirus (HPV) infections and HPV-related diseases.

There are some limitations in this study. First there is no comparison group of HIV negative patients to ascertain to what extent is the increasing of the CIN and cervical cancer in the district, secondly, HIV viral load determination and genetic sequencing for the HPV infection is not conducted as it was not available routinely for each patient in low income resource limited countries at the time of the study, thirdly, STI history and other sexual risk factors are not taken in to consideration.

In conclusion, this study found that the current CD4 count is the only independent factor associated with the increased severity of CIN in this study population. The effect of HAART and duration of treatment didn't show any impact on the progression of the CIN. So screening of all HIV infected women, who are under HIV care and treatment, enrolling patients on HAART before their immunological status fall below /CD4 count 200 is recommended to see the net effect of HAART response.

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