Human papilloma virus and cervical neoplasia in HIV positive women: A non systematic review

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Human papilloma-virus (HPV) infection confers 85-90% of the attributable risk for the development of cervical dysplasia. Worldwide and in particular in Nigeria, HPV 16 has been shown as the most prevalent HPV type and it also contributes more to the development of invasive squamous cell carcinoma. Studies have also shown that the prevalence of HPV is higher among HIV-positive women than among HIV-negative women of all age groups. HIV-positive women also have a higher incidence of squamous intra-epithelial lesion (SIL) and invasive cervical cancer. Progression to cervical cancer is also more rapid amongst these patients and often refractory to treatment with high incidence rates. Current screening recommendations for HIV-positive women are accessible and developed in rich countries. The best strategy for screening infected women in poorer nations where human immunodeficiency virus (HIV) is rampant remains uncertain and challenging.

Key words: Human papilloma-virus (HPV), human immunodeficiency virus (HIV), cervical dysplasia, invasive squamous cell carcinoma.

INTRODUCTION

Historical perspective

Historically, Papillomavirus has co-evolved with vertebrates. Virtually all vertebrate species have warts. This has been described for thousands of years. In the beginning of the current century, Cuffo established the viral etiology of human warts (Papillomas) when he used cell-free extracts from wart tissue as an innoculum for man-to-man transmission experiments (Stoler, 2000). In 1933, Shoppe first described Papillomavirus in cotton-nail rabbits (Stoler, 2000).

In 1973, zur Hausen proposed the concept of viral oncogenesis in the development of cervical cancer and in 1977 the same author indicated the possible role of Human Papillomavirus (HPV) in the development of squamous cell carcinoma of the uterine cervix (Ruud et
In the late 1980s, the development of a technology to test for the presence of HPV DNA in cellular specimen in conjunction with multidisciplinary collaborative efforts, made possible the establishment of a definitive etiological role for HPV in cervical cancer (Bosch et al., 2002).

THE HUMAN PAPILLOMAVIRUS

Viruses from Papilomaviridae family have been classified as members of the Papova super-family. Its name was given by taking the first two letters of the major genera: Papilloma, Polyoma and Simian Vacuolating Viruses, respectively. All members of Papilomaviridae family are small, double-stranded DNA viruses that replicate in the nucleus and have icosahedral protein capsules that form non-enveloped virions. They are biologically distinct from the Simian Virus 40 (SV40) and polyoma viruses. They have 55nm capsids.

The HPV genome can be divided into an early region, a late region and a non-coding long control or upstream regulatory region (URR). The early region encodes for proteins that are expressed before the onset of viral DNA replication, while the late region encodes viral capsid proteins. The early and late regions have several open reading frames (ORF) resulting in translation of functional proteins. Through gene splicing ORF encode for all viral gene products. The early region ORF is expressed early in the viral life cycle and they include: E1, E2, E4, E5, E6 and E7. The E1 encodes a protein that maintains the viral genome. E2 is involved in the transcriptional regulation and control of genes E6 and E7. The E4 gene encodes a protein that finally breaks-off the cytoplasmic keratin networks, resulting in koilocytic cells in the upper layers of the epithelium. The E5 gene encodes a protein which boosts the mitogenic responses of the epithelial host cells to stimulate replication of the virus. E6 and E7 encode multifunctional proteins that control proliferation and transformation, and they are the only open reading frames that are conserved and expressed in all HPV-associated pathologies. These pathologies include the full spectrum from low grade lesions with no neoplastic potential to high grade invasive cancers. L2 and L1 encode major and minor capsid protein of the virus, respectively (Stoler, 2000).

HPV-mediated carcinogenesis

Infection with HPV is an early event in the multistep process of cervical carcinogenesis. In benign and low grade lesions, the HPV genome is maintained in an episomal state (free from the nucleus). With the progression of cervical intraepithelial neoplasm (CIN), HPV is often found integrated in the genome of the host cell. This integration process disrupts E2 region and function, leading to over-expression of E6 and E7 (Stoler, 2000). The proteins encoded by E6 and E7 are high-risk oncoproteins. HPV E6 interacts with p53, interfering in this way with its functions. p53 mediates cell cycle arrest during the G1 phase in order to allow for DNA-repair, but also activation of apoptosis to eliminate cells with damaged DNA. Interaction of E6 leads to p53 dysfunction, thus impairing the ability to block the cell cycle when errors develop. Independent of its effects on p53, E6 also activates telomerase, a ribonucleoprotein complex that catalyzes the synthesis of telomere repeat sequences, thereby preventing telomere shortening and leading to cell immortalization (Stoler, 2000).

EPIDEMIOLOGY OF HUMAN PAPILLOMAVIRUS

For decades, the epidemiological profile of women with cervical cancer was recognized as suggestive of a sexually-transmitted process. Several agents were implicated as causative, agents such as syphilis, gonorrhea and type 2 herpes simplex virus (Bosch et al., 2002). However, by the beginning of the current century, sufficient evidence, which included a large and consistent amount of studies, showed beyond all reasonable doubt strong and specific associations, relating HPV infection to cervical cancer (Bosch et al., 2002).

Other studies have also shown that HPV infection preceded the development of cervical cancer by several years (Bosch et al., 2002). Determinants of clinical progression include persistence of infection, involvement of high risk types, high viral load, integration of viral DNA and several other potential risk factors (Cuoltee et al., 2005). Co-factors, which are now viewed as surrogates of HPV exposure, include low socio-economic status, young age at sexual debut, high parity, high numbers of lifetime sexual partners, smoking and use of oral contraceptives, as well as any combinations of the described above (Bosch et al., 2002).

GEOGRAPHIC DIVERSITY IN HPV GENOTYPE DISTRIBUTION

Two and half percent of all cancers in the developed world are associated with HPV, while 7.8% of all cancers in the developing world are associated with HPV (Ruud et al., 2004). HPV genotypes can be divided into mucusotropic types, which are found in the mucous epithelium of the oropharynx and anogenital tracts, and cutaneous types, which predominantly infect the skin (Ruud et al., 2004). More than 35 genotypes have been shown to infect mucosal surfaces, and at least 18 of them have been associated with cervical cancer. HPV genotypes differ widely in their geographic distribution. In sub-Saharan Africa, where two-thirds of the world's HIV infected people live, it has been shown that HPV types vary by

DISTRIBUTION

GEOGRAPHIC DIVERSITY IN HPV GENOTYPE
both country and HIV status, and they differ significantly from types seen in other regions of the world.

To investigate the geographic variations in the distribution of HPV types, Bosch and fellow researchers (1995) obtained more than 1000 specimens from sequential patients with invasive cancer. These specimens were stored frozen at 32 hospitals in 22 countries. Polymerase chain reaction- (PCR)-based assays were used to detect the different HPV types. According the results, HPV DNA was detected in 93% of the tumors. HPV 16 was presented in 50% of the specimens, HPV 18- in 14%, HPV 45- in 8%, and HPV 31- in 5%, respectively. HPV 16 was the most predominant type in all the countries except Indonesia, where HPV 18 was more common. These authors also discovered significant geographic variation in the prevalence of some less common viral types with a clustering of HPV 45 apparent in Western Africa, while HPV 39 and HPV59 were almost confined to Central and South America. They also showed that HPV 16 predominated in squamous cell tumors (51%), while HPV 18 predominated in adenocarcinomas (56%) and in adenosquamous tumors (39%).

In a similar study, carried out by Sanjose et al. (2010) on HPV genotype attribution in invasive cervical cancer, a retrospective cross-sectional worldwide study, paraffin embedded samples of histologically confirmed cases of invasive cervical cancer were collected from 38 countries in Europe, North America, Central and South America, Africa and Oceania. HPV has been detected by PCR with SPF-10 broad spectrum primers, followed by DNA enzyme immunoassay and genotyping with a reverse hybridization line probe assay. According the data obtained, the most common HPV types identified were types 16, 18, 31, 33, 35, 45, 52 and 58. HPV types 16 and 18 were detected in 71% of invasive cervical cancers, while types 16, 18 and 45 were detected in in 94% of cervical adenocarcinomas. Also, related to HPV, types 16, 18 or 45 invasive cervical cancers have been presented in women at a younger mean age than in those, related to other HPV types (Sanjose et al., 2010).

In order to study the relative carcinogenicity of HPV types in Nigeria, as well as to estimate the vaccine preventable portion of invasive cervical cancer (ICC), Okolo et al. (2010) compared HPV type prevalence among 932 women from the general population of Ibadan with that among a series of 75 ICC cases diagnosed in the same city. According to the results obtained, 26.3% of the women were HPV-positive, and among them the prevalence of HPV 35 and 16 has been equally frequent. In ICC patients, however, HPV 16 predominated strongly (67.6%) with the next most common types being 18, 35, 45 and 56 in descending order. It was concluded that in Nigeria, as elsewhere, women infected with HPV 16 and 18 are at a higher risk of developing ICC than those infected with other high risk types and that current HPV 16/18 vaccine have enormous potential to reduce cervical cancer in Nigeria.

Other studies, carried out in other West African countries like Gambia, equally showed HPV 16 to be the most prevalent HPV type, probably strongly associated with squamous intraepithelial lesion (Wall et al., 2005). Similar studies, carried out in Dakar, Senegal, have also indicated HPV 16 (2.4%) and HPV 58 (1.6%) to be the most frequent HPV types in this population, as well as to be the most strongly associated with the risk of high grade squamous intraepithelial lesion and cancer. These data suggest that in addition to HPV type 16, HPV type 58 should be also considered in the strategic planning of vaccination against cervical cancer in this geographic region (Xi et al., 2003).

**HPV and HIV**

It is estimated that 33 million people around the world are living with human immunodeficiency syndrome and acquired immune deficiency syndrome (HIV/AIDS). The burden of this epidemic resides largely in sub-Saharan Africa, which in 2007 accounted for 67% of all people living with HIV and 70% of all AIDS deaths (World Health Organisation HIV burden available at http://www.searo.who.int/Linkfiles). In Nigeria about 4 million people living with HIV/AIDS have been estimated (Anorlu et al., 2007). Cervical intra-epithelial neoplasia is considered an HIV-related condition, while invasive carcinoma of the cervix is an AIDS defining disease (Paintomowitz and Michelow, 2010). Several studies have demonstrated a higher prevalence of HPV in HIV-positive women, when compared with HIV-negative women (Paintomowitz and Michelow, 2010), probably due to the fact that both HIV and HPV are both sexually-transmitted diseases. In HIV-negative women with competent immune systems, most of the infections are cleared spontaneously because of a cell mediated immune response regulated by CD4+ lymphocytes (World Health Organisation HIV burden available at http://www.searo.who.int/Linkfiles). HIV co-infected individuals are at a higher risk of persistent HPV infection largely due to their impaired ability to clear HPV and are thus at an increased risk to develop cervical dysplasia and cancer (Firnhaber et al., 2009).

In 2005, in a study of HPV and cervical cytology in infected and non-infected with HIV Rwandan women, Singh and co-authors carried out an observational prospective cohort study on 710 HIV-positive and 226 HIV-negative Rwandan women. According these authors, the prevalence of HPV was higher in HIV-positive than in HIV-negative women in all age groups. Among HIV infected women, 69% have been positive for greater than one HPV type, 46% - for a carcinogenic HPV type, and 10% - for HPV16, respectively. HPV prevalence peaked at 75% in HIV-positive women aged 25-34 years and declined with age to 37.5% in those greater than 55 years old. Among the study population, certain HPV types (11,
disease progression may not be affected by CD4+ lymphocytes counts (Cardillo et al., 2001).

THE ROLE OF HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART)

The introduction of HAART in the late nineties led to dramatic improvement of clinical outcomes and life expectations for people living with HIV/AIDS. It also gave hope that improved immunological status would lead to better clearance of HPV infection in HIV-positive women, just as occurs in other opportunistic AIDS-associated infections (Bratcher and Sahasrabuddhe, 2010). Increasing number of HIV-infected women are now accessing life prolonging HAART in developing countries. Data regarding the impact of HAART on reducing incidence and progression or facilitating the regression of HPV infection and cervical abnormalities is largely inconsistent (Bratcher and Sahasrabuddhe, 2010). This inconsistency may be due to the study designs, carried out in the past (prospective or retrospective cohorts, or record linkage studies) screening and diagnostic protocols, duration and type of HAART use, recruitment and referral strategies and definition of screening test, as well as disease positivity (Bratcher and Sahasrabuddhe, 2010).

In a study, carried out by Heard et al. (1998) in France, for determination of the outcome of SIL in HIV infected women initiating triple combination antiretroviral therapy, 49 women were examined prior to and after a median of 5 months treatment. It was discovered that the prevalence of SIL decreased from 69 to 53% during follow-up. Among 13 women who initially presented with high grade SIL, conversion to lower grade was observed in 2 women and a full regression to normalcy - in one woman, respectively. Cytology also returned to normalcy in 9 out of 21 women, initially presented with a low grade SIL. These results suggested that HAART may result in reduced prevalence of cervical SIL despite none clearance of HPV infection. Similar studies on the regression of cervical intra-epithelial neoplasia (CIN) in HIV infected women on anti-retroviral therapy (ART) also showed that the risk of regression of CIN was twice as high in women receiving HAART as compared to women not receiving HAART (Heard et al., 2002). It was concluded that the positive impact of HAART on CIN regression may be associated with some restoration of specific immune reactivity. However, studies carried out in South Africa to determine HPV prevalence, viral load and precancerous lesions of the cervix in women initiating HAART therapy, showed that these women have a high prevalence of abnormal Pap smears and high risk HPV, thus emphasizing the need for locally relevant, rigorous screening protocols so that the benefits of HAART are not partially offset by an excess risk in cervical cancer (Moodley et al., 2009).

In Spain, Sierra et al. (2008) carried out a retrospective cohort study to evaluate the effect of HAART on HIV infected women with normal cytology and CD4+ lymphocytes counts (Cardillo et al., 2001).
cytes counts above 350 cells /mm³. The patients were divided into two groups: on HAART and not on HAART. Both groups were similar with respect to demographic characteristics except for HIV viral load and previous HAART inclusion. SIL has been diagnosed in 27 out of 90 (30%) patients in the HAART group and in 7 out of 37 (19%) in the non-HAART group, respectively. The actual probability of remaining free of SIL at 3 years was 70% in HAART group. It was therefore concluded that when patient’s immunological status is above 350 CD4+ lymphocytes/mm³, the HIV infected women, treated with HAART present a similar cervical SIL incidence to HIV infected women not on HAART (Sierra et al., 2008).

According another study, carried out to evaluate the effect of HAART on HPV clearance and cervical cytology, among HIV-positive women with cervical squamous intraepithelial lesions, HAART was associated with an increased likelihood of HPV clearance unlike in HIV-positive women with normal cytology or atypical squamous cells of undetermined significance (Paramsothy et al., 2009). Use of HAART was also not significantly associated with an increased likelihood of cervical cytologic regression or of cervical cytologic progression (Paramsothy et al., 2009).

HIV and squamous intraepithelial lesions (SIL)

HIV-positive women have been characterized with higher rates of squamous intraepithelial lesions as compared to those who are HIV-negative (Anorlu et al., 2007). In the study, performed by Anorlu et al. (2007) for determination the prevalence of abnormal cervical smears in HIV-positive Nigerian women in Lagos, the prevalence of SIL was found to be higher in HIV-positive than in HIV-negative. Also, higher grade SIL among HIV-positive than among HIV-negative subjects has been observed. There was no significant difference in the prevalence of inflammatory smears between the two categories (Anorlu et al., 2007).

It has been proposed that young women are more susceptible to cervical infection due to immaturity of the cervix, which could be explained with the fact that HPV has more access to the basal cells of the differentiating epithelium. Exposure to this virus before the stabilization of the transformation zone and maturation of the cervix could lead to an increased susceptibility to infection (Calore et al., 1998). In a study of cervical smears of 82 adolescent HIV-seropositive women (13-21 years of age), Calore et al. (1998) found that 21 cases (25.6%) possessed characteristic features of HPV infection and SIL. Sixteen cases aged from 17 to 21 years (19.5%) had low grade SIL (LSIL), while five cases (6.1%) had high grade of SIL. There were no significant differences between the mean age of patients with LSIL and HSIL. Two cases have had atypical squamous cells of undetermined significance (ASCUS). It was therefore concluded that HIV-seropositive adolescents have probably a high risk of pre-neoplastic cervix lesions (25.6%), as well as high incidence of more aggressive lesions (6.1% of HSIL), in comparison with the general population of adolescents (Calore et al., 1998). Among HIV-infected women, HPV disease, as manifested by findings of SIL or cervical intraepithelial neoplasia (CIN), is influenced by HIV-induced immuno-suppression. Indeed HIV-positive women with severe immuno-suppression (defined as CD4+ lymphocyte counts below 200 x 10⁶) are at greatest risk of CIN (Ferenzy et al., 2003). While the degree of immuno-suppression may contribute to the development of SIL in HIV-positive women, there appears to be no difference in CD4+ white blood cells counts between women with high and low grade lesions (Cardillo et al., 2001). These data suggest that once there is establishment of SIL, disease progression may not be affected by CD4+ lymphocytes counts alone. The converse may also be true for HIV infected women with high CD4+ cells counts. In a study for determination of the incidence of SILs in HIV-seropositive women with normal cytology data by baseline HPV DNA results, it was discovered that HIV-positive women with CD4+ lymphocytes counts higher than 500 x 10⁶ have had similar incidence of SIL as those who were HIV-seronegative (Lehtovirta et al., 2003). It was therefore suggested that similar cervical cancer screening practices may be applicable to both groups, although the strategy would warrant evaluation in an appropriate clinical trial.

Studies, carried out confirmed the suggestion that HIV infected women with CIN experienced high recurrence rates after treatment (Foulot et al., 2008). Recurrence was also inversely related to CD4+ lymphocytes counts with the highest rates seen in women with values < 200 x10⁶.

INVASIVE CERVICAL CANCER

According to case-control studies, case series and prevalence surveys, performed beyond all reasonable doubt, HPV DNA can be detected in adequate specimens of cervical cancer in 90-100% of cases, as compared to a prevalence of 5-20% in cervical specimen from women identified as suitable epidemiological controls (Bosch et al., 2002). This association has been recognized as causal in nature since the early 1990’s and a claim that it is the first necessary cause of human cancer that has ever been identified has been made. This implies that in the absence of HPV DNA, cervical cancer does not develop (Bosch et al., 2002). HPV-associated malignancies have also been shown to be more common among the patients with HIV/AIDS (Morten et al., 2000). Studies have also shown that cervical cancer is more frequent in HIV infected women than their un-infected counterparts (Morten et al., 2000). Besides that, progression to cervical cancer in these individuals has been found to be more rapid and often more refractory to therapy with high recurrence
rates (Paintomowitz and Michelow, 2010). Cervical cancer has also been considered as an AIDS defining illness since 1993 and studies have also shown that cervical cancer develops several years earlier in people, infected with HIV/AIDS than in uninfected counterparts (Paintomowitz and Michelow, 2010).

In a retrospective review of 60 HIV-sero-positive and 776 HIV-sero-negative new cases of cervical carcinoma in South Africa, it was discovered that HIV–sero-positive patients, presented with invasive cervical cancer almost 10 years earlier than HIV-sero-negative patients. Even though, HIV-sero-positivity on its own did not appear to adversely affect the extent of disease at presentation, patients with CD4+ lymphocytes counts below 200/mm$^3$ are significantly more likely to have advanced –stage disease at initial diagnosis than with HIV-negative patients (Lomalisa et al., 2000).

THE LABORATORY DIAGNOSIS OF GENITAL HPV INFECTION

Specimen collection and transport

Superficial epithelial cells from the ectocervix are usually collected by scraping with a spatula. Cyto-brushes and Dacron swabs are also used to collect cells from the squamo-columnar junction (Coultee et al., 2005). The sensitivity of HPV detection is greater when a cyto-brush is used in the collection of samples than a Daccon swab (Peyton et al., 1998). After specimen collection, exfoliated cells are resuspended into appropriate transport medium used with DNA-based methodology for HPV detection.

Microscopy

Cervical cytology samples are usually viewed with microscope. This may reveal certain lesions such as koilocytes. Those are squamous cell, exhibiting perinuclear halo or clearing with increased density of surrounding cytoplasm. Hallmarks of productive HPV infection include nuclear atypia (enlargement), hyperchromasia, irregular membranes and double nucleation of intermediate and superficial cells (Coultee et al., 2005).

The sensitivity of conventional cytology smears in the detection of cervical lesions ranges from 29-56%. This is due to the fact that at best only 20% of the cells are smeared on a slide with the remaining 80% lost with the collection device (Ferenzy and Franco, 2001). Liquid-based thin layer cytology is a promising alternative that has been shown to improve the sensitivity of conventional cytology for detecting HSIL by 60% and providing an overall sensitivity of 80% (Ferenzy and Franco, 2001). Another advantage of liquid-based cytology medium for the collection of cervical specimen is the fact that multiple tests can be done with a single sample. This is very helpful when considering cases such as atypical squamous cells of undetermined significance (ASCUS), where HPV testing can be performed on the temporarily stored Pap specimen without the need for another follow-up visit (Peyton et al., 1998).

DIAGNOSTIC TESTS FOR HPV DETECTION

Nucleic acid hybridization methods

There are essentially three types of nucleic acid hybridization method formats used to detect HPV. These include hybridization signal amplification, target amplification methods and direct nucleic acid probe method.

Signal amplification DNA-based assays: Hybrid capture system

This test can detect low quantities of DNA by amplifying the detection signal without modifying the initial amount of nucleic acids contained in the samples (Coultee et al., 1997). There are two main types: the first generation hybrid capture tube test and the second generation Hybrid Capture II (HCII), which is the only type approved by the US Food and Drug Administration with an increased analytical sensitivity, but it is also a more efficient kit format (Coultee et al., 2005). Using these tests, exfoliated cervical cells are collected in a conical brush provided by the specimen collection kit and re-suspended in the specimen transport medium that can be kept at room temperature for up to 2 weeks.

Target amplification based assays: Polymerase chain reaction (PCR)

PCR is nowadays the gold standard test of HPV research. Type-specific PCR tests are not practical means of detecting HPV infections in clinical specimens due to the large number of types involved in genital disease. Due to the genetic polymorphisms of HPV, consensus PCR assays are now being employed to amplify in one reaction, the majority of known and novel anogenital HPV genotypes (Coultee et al., 2005). Subsequent typing can be accomplished on filters by hybridization with type-specific oligonucleotide probes, homogenous hybridization reactions with RNA probes, restriction fragment length polymorphisms or by DNA sequencing (Doorn et al., 2002).

Direct probe methods: Southern blotting

This method is the gold standard of HPV genomic analysis. Because formalin-catalysed DNA cross-linking with resulting DNA degradation makes it impossible to per-
form, this assay cannot be carried out on formalin preserved tissues (Hubbard, 2003).

**Cervical cancer screening**

The objective of cervical cancer screening is to prevent the occurrence of cervical cancer and death from it, by detecting promptly and treating precursor lesions of this malignancy. The most widely used screening approach is to detect high grade squamous intra-epithelial lesion (HGSIL) by conventional cytology, followed of the investigation of positive women by colposcopy and directed biopsy (Monsonego et al., 2004). In some parts of the world, such as the United States, the mortality from cervical cancer has been decreased by over 70% owing to the introduction of Papanicolaou (Pap) test. In these regions, pre-invasive lesions of the cervix are detected far more frequently than invasive cervical cancers (Saslow et al., 2002).

There is no single, agreed upon guideline for cervical screening in HIV patients (Paintomowitz and Michelow, 2010). According to the American Cancer Society (ACS), women between the ages of 21 and 30 years, infected with HIV, should be screened annually for cervical cancer, and every 2-3 years for women 30 years and above if three consecutive Pap tests are negative (Saslow et al., 2002). The Center for Disease Control and Prevention (CDC) recommend screening of HIV-positive women at six monthly intervals for the first year after an HIV diagnosis, followed by annual cervical smears if the results are normal (Paintomowitz and Michelow, 2010). The British HIV association recommends that HIV-positive women should do baseline colposcopy soon after diagnosis and cervical smears every year. The age range screened should be the same as for HIV-negative women (Browser et al., 2008). Some authors recommend that surveillance of these women should be based on the individual woman’s risk for cervical intraepithelial neoplasia (CIN). Women who are not immune suppressed (CD4+>500/mm³) and have only slightly increased risk of CIN, may be followed by annual or possibly semiannual Pap smears. Immuno-suppressed women (CD4+<500/mm³), and especially those with CD4+<200/mm³, whose risk for CIN might be the same as in the women from the general population, who have SIL on their Pap smear, should be subsequently subjected on colposcopy (Mark, 1999).

According other investigators, there are significant limitations to cytologic screening for identification of SIL in HIV-positive women, as compared to the general population, which has been proposed to be due to high frequency of occurrence of false negatives in HIV-positive women (Womack et al., 2000). Taking into consideration all that, colposcopy has been suggested to be performed routinely for HIV-positive women (Browser et al., 2008). Baseline colposcopy is also recommended for examination of the entire anogenital region, probably because of the increased vulval, vaginal and anal intraepithelial neoplasia (AIN) in HIV-positive women (Paintomowitz and Michelow, 2010). However, routine colposcopy for all HIV infected women is not supported by everyone. This procedure, however, should need personnel required to be carried out (Paintomowitz and Michelow, 2010), which would be difficult in many resource-poor settings due to the cost. In the presence of both CD4+ lymphocytes counts as alluded above and the results of HPV DNA test, appear to be useful indicators of the risk.

Due to the relative insensitivity of conventional cytology, frequent testing is required for optimal cancer protection, thus compromising cost efficiency. The most cost effective regimen is to use the most sensitive possible test at the longest possible interval, thus relieving the system of the cost of evaluation and treatment of large numbers of abnormal screening tests. In most cases, these tests represent low grade transient abnormalities, whose recognition adds greatly to cost without increasing the cancer protection (Monsonego et al., 2004). Studies have shown that the addition of HPV testing to the two cervical cytology smears obtained in the year after HIV diagnosis, together with subsequent modifying cytology screening intervals, based on the results, appears to be a cost-effective modification to current recommendations for annual cytology screening in HIV infected women (Goldie et al., 2001). However, according to other studies, HPV testing, although characterized by high sensitivity, may not be ideal due to the low specificity that results largely from a very high prevalence in non-diseased women (Womack et al., 2000). Some authors advocate that women who test negative for HPV and who have two negative initial Pap test results, could undergo annual cytology screening. However, those who are positive for high risk of HPV DNA, should have Pap tests every six months. This differs from the recommendations for HIV-negative women, in whom prolongation of screening interval to not less than three years is recommended if both cytology and HPV results are normal (Paintomowitz and Michelow, 2010). Further studies are required to refine appropriate screening protocols, intervals and follow-up algorithms in HIV-positive women (Paintomowitz and Michelow, 2010). The usefulness of HPV test as a screening method for cervical cancer in areas of high HPV prevalence would depend on local health resource availability, disease priorities and policies regarding clinical case management (Womack et al., 2000).

**Treatment**

The British society for colposcopy and cervical cytology recommends only lesions, which are cervical intraepithelial neoplasia (CIN2) and above, should be treated. Women who have lower grade lesions should be monitored by regular cytologic reviews, since these lesions may clear on their own (Browser et al., 2008). Once con-
firmed by tissue biopsy, high grade CIN can be treated by both ablative and excisional methods. Ablative methods include cryo-therapy and laser ablation, while excisional methods include cold knife, laser conization and loop electro surgical excision (LEEP) (Paintomowitz and Michelow, 2010). Studies have also shown that in HIV infected women, CIN may recur despite multiple treatments and that chronic condylomatous changes are common (Frutcher et al., 1996). Intra-vaginal application of 5-Fluorouracil (5-FU) after standard surgery for high grade lesions can reduce recurrence rates of CIN in HIV-positive women (Maimam et al., 1999).

Invasive cervical cancer in HIV-infected patients remains a challenge due to the fact that the management of malignancy may further impact the patient’s immune system (Moodley, 2007). Most HIV-positive patients with cervical cancer present with late stage disease (Moodley, 2007). The standard management of invasive cervical cancer in them is surgery, radiotherapy and chemotheraphy, depending on the cancer stage (Paintomowitz and Michelow, 2010). However, women with early stage cervical cancer are managed by radical hysterectomy and lymph node dissection (Moodley, 2007).

CONCLUSIONS

HPV infection confers 85-90% of the attributable risk for the development of cervical dysplasia (Stoler, 2000). Worldwide and particularly in Nigeria, HPV 16 has been shown to be the most prevalent HPV type and it also contributes more to the development of invasive squamous cell carcinoma (Okolo et al., 2010). Studies have also shown that the prevalence of HPV is higher among HIV-positive women than HIV-negative women of all age groups (Singh et al., 2009). HIV-positive women also have a higher incidence of SIL, and invasive cervical cancer (Anorlu et al., 2007; Morten et al., 2000). Besides that, the progression to cervical cancer is more rapid amongst these patients and it is often refractory to treatment with high incidence rates (Paintomowitz and Michelow, 2010). Current screening recommendations for the HIV-positive women pertain largely to developed countries. However, the best strategy for screening of infected women in poor nations, in which HIV is rampant, remains uncertain and challenging (Paintomowitz and Michelow, 2010). Only lesions that are CIN2 and as was described above, treated and once confirmed on tissue biopsy, high grade lesions could be treated by both ablative and excisional methods. Invasive cervical cancer is currently managed by a combination of surgery, radiotherapy and chemotherapy (Moodley, 2007).

Conflict of interest

The authors declare that they have no conflict of interest.

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