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Cervical Cancer Screening and Prevention for HIV-Infected Women in the Developing World

Jean Anderson, Enriquito Lu, Harshad Sanghvi,
Sharon Kibwana and Anjanique Lu
Jhpiego, Johns Hopkins University
USA

1. Introduction

Cervical cancer ranks as the third most common cancer in women worldwide and is the fourth leading cause of cancer deaths in women, with an estimated 270,000 deaths annually. Over 85% of both cervical cancer cases and deaths occur in developing countries with only 5% of global cancer resources (Lancet 2010). Cervical cancer is the most common cancer in women in most developing countries and most common cause of cancer deaths (Cervical Cancer Action: Report Card 2011). It is the leading cause of years of life lost to cancer in low resource settings (Yang et al. 2004). In sub-Saharan Africa cervical cancer represents 22% of all cancers in women (Parkin et al. 2003).

Currently, an estimated 33.3 million individuals worldwide are living with HIV/AIDS, approximately 68% of whom live in Sub-Saharan Africa; globally over 50% of all those living with HIV are female and in Sub-Saharan Africa, women account for 60% of HIV infections. In 2009 there were an estimated 7000 new infections per day, 51% of these among women (UNAIDS 2010). However, there have been dramatic advances in prevention, care and treatment in the areas that are hardest hit by HIV over the past 10 years, coincident with unprecedented global commitment for funding and other support. These include a global decline of 19% in number of new HIV infections and a >25% decline in HIV prevalence among young people 15–24 years of age in 15 high burden countries, a decrease in global AIDS deaths by 19% from 2004–2009, and an increase in access to antiretroviral therapy (ART) in low and middle-income (LMIC) countries from 400,000 in 2003 to 5.25 million by the end of 2009 (this however, comprises only 35% of those estimated to be in need of therapy) (WHO 2011).

The areas where cervical cancer rates are highest also often have high prevalence of HIV and the presence of HIV increases the risk of cervical precancerous and cancerous changes; furthermore there is general unavailability of effective cervical cancer screening programs in these lower resource settings. This paper will review issues related to cervical cancer screening and prevention for HIV-infected women in low resource settings, with a focus on non-cytology-based techniques.

2. Human papillomavirus infection and cervical cancer

The causal relationship between some microbial pathogens, primarily viral, and human carcinogenesis have been suspected but it has only been in the last 20 years that knowledge

has accumulated to more clearly define the mechanisms and processes that chronic, persistent infections induce cancer development, see Figure 1. Replication of DNA and RNA tumor viruses involve incorporation of the viral genome into the host cell chromosomes inducing several mutations that disrupt the homeostatic balance between proliferation and cell death; in the case of oncogenic HPV, the expression of viral E2, E6, and E7 genes lead to the production of proteins that initiate cell cycle and disable control of growth, allowing the proliferation of genetic damage to accumulate in HPV infected cells. (Georgakilas et al. 2010). Oxidative stress negatively impacting genetic and cellular processes can be brought about by reactive oxygen species (ROS) or free radicals induced by chronic infection (Kryston et al. 2011; Georgakilas et al. 2010). Although additional researches are needed to accurately define the relationship, oxidative stress is linked in several studies with some tumor virus but not HPV (Kryston, et al. 2011)

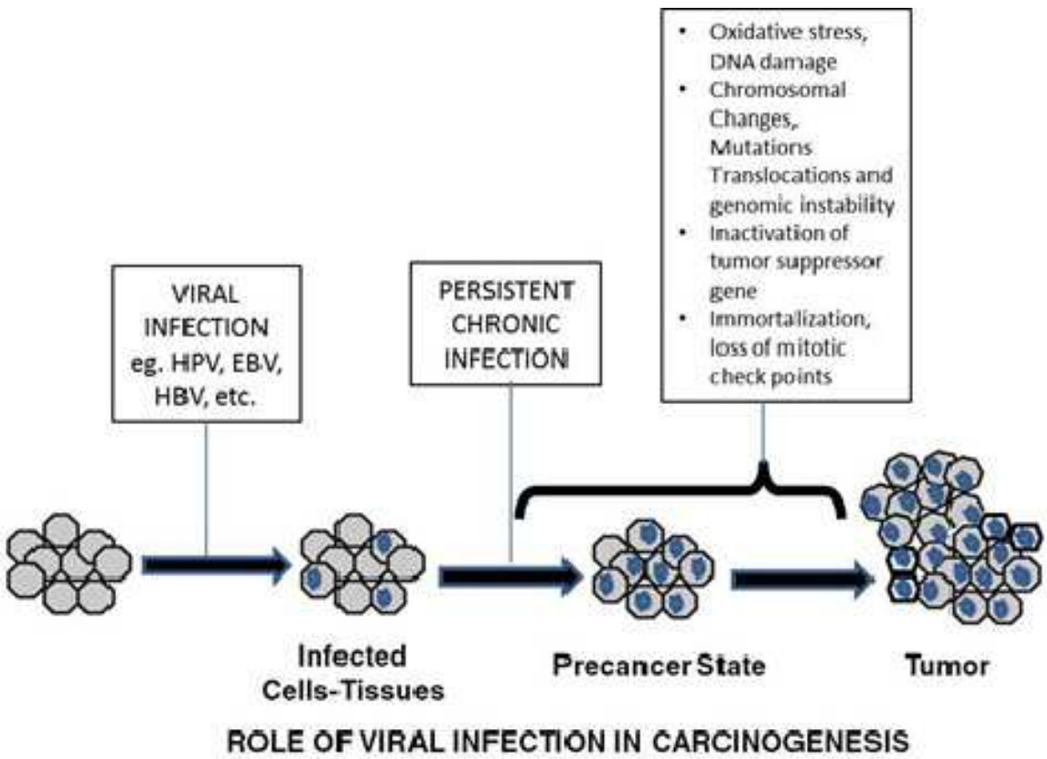

Fig. 1. Role of Viral Infection in Carcinogenesis.

Schematic pathway of viral infection leading to cancer adapted from Figure1 Viral pathogens role(s) in human carcinogenesis based on current status of knowledge and clinical evidence.

Alexandros Georgakilas, William Mosley, Stavroula Georgakila, Dominick Ziech, and Mihalis Panayiotidis. Viral-induced human carcinogenesis: an oxidative stress perspective. Molecular BioSystems Vol 6, pp 1162 – 1172, (2010).

In the 1990s a combination of large-scale epidemiologic studies and the application of new molecular techniques clearly established human papillomavirus (HPV) as the etiologic cause of cervical cancer (Clifford 2003; Walboomers 1999). Using the most sensitive assays, over

99% of invasive cervical cancers have been found to be HPV-positive (Sankaranarayanan 2008). Current evidence suggests that over 50% of sexually active adults have been infected with one or more genital HPV types (Ho 1998; Evander 1995); however, most HPV infections resolve or become latent and undetectable (Ho 1998; Moscicki 1998; Evander 1995). Furthermore, although there are well over a 100 distinct molecular subtypes of HPV, only a small subset have been associated with development of cancer and are considered "high risk" or oncogenic (Cogliano 2005). For cervical cancer to develop, persistent infection with an oncogenic HPV subtype is necessary. The oncogenic or high-risk HPV includes HPV subtypes -16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68 which are strongly associated to cervical precancer (Schiffman 2003).

Cervical cancer is relatively unique in that there is a recognizable preinvasive phase in which progression from initial HPV infection to invasive disease evolves over several years, passing through cytologically and histologically distinct precancerous phases, known as cervical dysplasia (mild, moderate, severe, carcinoma-in-situ) or cervical intraepithelial neoplasia (CIN 1,2,3). The peak prevalence of infection with carcinogenic HPV subtypes is in the teens and twenties, following closely after the initiation of sexual activity; the majority of these infections are transient and are cleared by the body's immune system. When viral persistence and progression do occur, the median time from HPV detection to development of CIN 3 is approximately 7–8 years, with 20% progressing from CIN 1 to CIN 3 within 2 years. Progression from CIN 3 to invasive cancer occurs over an additional 5–7 years. The peak prevalence of invasive cancer occurs in the 40-50 year age range (McIndoe 1984; Kolstad 1976; Melnikow 1998; Josefsson 2000; Schiffman 2005). This prolonged natural history offers numerous opportunities to detect the presence of precancerous lesions and to prevent progression to invasive cancer.

3. HPV, cervical dysplasia and HIV

3.1 Interrelationship of HIV and Human Papillomavirus

Studies have shown that HIV-infected women have higher prevalence of HPV, higher incidence of HPV (Branca 2003; Ahdieh 2001), higher HPV viral load (Jamieson 2002), longer persistence of HPV (Ahdieh 2000; Sun 1997), higher likelihood of multiple HPV subtypes (Jamieson 2002; Firnhaber et al. 2009; Clifford et al. 2007), and greater prevalence of oncogenic subtypes (Minkoff 1998; Uberti-Foppa 1998; Acta Cytol 2009; 53: 10–17) than HIV-uninfected women. HPV viral load is independently associated with HPV persistence (Ahdieh 2001). A recent meta-analysis found that the rate of cervical HPV infection in HIV-infected women with normal cervical cytology varied from more than 55% in South and Central America and Africa to over 30% in Asia, North America, and Europe (Clifford 2006). Furthermore, in HIV-positive women the prevalence and persistence of HPV infection increases with decreasing CD4 count and increasing HIV RNA levels (Palefsky 1999; Denny 2008) and some studies show that oncogenic HPV types may be more common with lower CD4 counts and/or higher viral loads. (Luque 1999; Minkoff 1998; Clifford et al. 2007). A recent cross-sectional study of 109 HIV+ women initiating ART in South Africa (median CD4 count 125/mm3) found a high-risk HPV (HR-HPV) prevalence of 78.9% (Moodley et al. 2009). In another South African cohort of over 123 women with HIV seroconversion HR-HPV infection doubled within 36 months of seroconversion (Wang et al. 2011). Higher HPV viral loads are also associated with lower CD4 counts (Heard 2000).

3.2 HIV and cervical dysplasia

The prevalence and incidence of abnormal Pap smears are increased among HIV-infected women as compared to uninfected women, with up to 10-fold higher rates (Maiman 1998); abnormal cervical cytology is associated with the presence of HPV infection and the degree of immunosuppression. Both frequency and severity of abnormal Pap smears and histologically documented dysplasia increase with declining CD4 counts and have also been associated with higher HIV-RNA levels (Garzetti 1995; Shah 1996; Davis 2001; Ellerbrock 2000; AIDS Care 2007; 19: 1052–1057. Massad 2008; Massad 2001). Two-thirds of 109 HIV+ women initiating ART in South Africa with median CD4 125/mm3 had abnormal Pap smears (Moodley et al. 2009). Increased HPV viral load, seen in women with more advanced HIV, is also associated with increased frequency, severity, and incidence of cervical dysplasia (Heard 2000; Weissenborn 2003; Cohn 2001). HIV is also associated with more extensive/larger volume of cervical involvement, and are also more likely to involve other areas in the lower genital tract (e.g., vulva, vagina, anal regions) (Maiman 1990). Progression and regression of Pap smear abnormalities have also been associated with level of immunosuppression and plasma viremia, as reflected in CD4 count and HIV viral load (Massad 2001; Schuman 200).

The role of effective ART and immune reconstitution in reducing the incidence and progression and promoting the regression of HPV infection and cervical dysplasia remains unclear, but HPV-related lesions do not appear to respond to ART like other opportunistic illnesses. Studies examining this issue have mixed findings, which may be related to differences in study design, virologic and immunologic parameters, duration and type of ART use, length of follow-up or other factors. In one study use of ART was associated with increased likelihood of regression of cervical dysplasia after treatment for 12 months (Heard 2002). In the Women's Interagency HIV Study (WIHS), after adjustment for CD4 count and Pap status, use of ART was associated with increased regression and decreased risk of progression of cervical cytologic abnormalities (Minkoff 2001). The HIV Epidemiology Research Study (HERS), a U.S. observational, multisite cohort study, among women with preexisting abnormal cervical cytology, ART was associated with enhanced HPV clearance but not with regression of abnormal Pap results (Paramsothy et al. 2009). In a study of women initiating HAART there was a high prevalence of cervical HPV DNA at baseline, but this declined over 96 weeks of HAART (Fife et al. 2009). On the other hand, with 15 months of follow-up, persistence of high-risk HPV and progression of SIL were comparable among women without antiretroviral treatment, those treated with nucleoside analogues only, and those treated with ART (Lillo 2001). In a more recent analysis from Women's Interagency HIV Study (WIHS), the prevalence, incident detection, and clearance of HPV infection and/or SIL before versus after ART initiation were compared, using women as their own comparison group. The role of adherence, defined as use of HAART as prescribed > or = 95% of the time, and effective ART, defined as suppression of HIV replication, were also examined. ART initiation among adherent women and among women on effective ART was associated with a significant reduction in prevalence, incident detection of oncogenic HPV infection, and decreased prevalence and more rapid clearance of oncogenic HPV-positive SIL, although strength of these protective effects was only moderate. (Minkoff et al. 2010). Given these conflicting findings, HIV-positive women should continue to be followed closely for evidence of lower genital tract neoplasia, regardless of antiretroviral therapy or viral load.

3.3 Invasive Cervical Cancer (ICC) in HIV disease

In 1993, the Center for Disease Control and Prevention (CDC) expanded the case definition of AIDS to include invasive cervical cancer (ICC). As is the case with HIV- negative women, oncogenic HPV types play a central role in the relationship between HIV and cervical cancer. Recent African data found that without high-risk HPV present, the risk ratio for ICC between HIV-positive and HIV-negative women was approximately 1 (Hawes 2003). HPV types 16 and 18 were the most common HPV subtypes in a study of ICC in Kenyan HIV+ and HIV- women and were detected in 65% of ICCs in the HIV-infected patients. Almost half of the type 16 or 18 associated cancers involved multiple HPV types (De Vuyst et al. 2007).

A study matching data from AIDS registries and cancer registries in 15 US regions found that persons with AIDS (information captured 4–60 months after AIDS diagnosis) had statistically significantly elevated risk of ICC compared to the general population, with standard incidence ratios (SIR) of 68.6, 95% CI = 59.7 to 78.4 (Chaturvedi et al. 2009). During the period 1996—2004 (post-HAART introduction), ICC in women with low CD4 T-cell count was not significantly increased, possibly reflecting active screening but also not showing evidence of decline in incidence with HAART availability. There has been no evidence of increased incidence of ICC with the use of regular screening and appropriate evaluation and treatment of abnormal Paps (Massad et al. 2004; Massad et al. 2009). Case-control or cross-sectional studies in various African countries, including Cote d'Ivoire, Tanzania, South Africa, Kenya and Senegal have found that ICC was associated with HIV infection (Adjorlolo-Johnson et al. 2010; Kahesa et al. 2008; Stein et al. 2008; Hawes et al. 2003; Gichangi et al. 2003). However, studies evaluating the strength of association of HIV with cervical cancer among African women have shown conflicting results, possibly reflecting the competing risk of dying from other HIV-related conditions or other illnesses (Adjorlolo-Johnson et al. 2010; Moodley 2006). A recent mathematical modeling simulation projected that, compared with no ART and no screening, the lifetime cumulative risk of dying from ICC approximately doubled with ART and no screening; however, screening even when done once, had the potential to reduce ICC mortality (Atashili et al. 2011)

When ICC does develop in the setting of HIV, it tends to occur at younger ages and with less immunosuppression as compared with HIV-positive women with other AIDS-indicator conditions. Women with HIV and cervical cancer also tend to be 10—15 years younger than HIV-negative women with cervical cancer (Lomalisa 2000; van Bogaert 2011). HIV-positive women with invasive cervical cancer may present at more advanced stages (especially with CD4 <200/mm^3), may metastasize to unusual locations (e.g., psoas muscle, clitoris, meningeal involvement), have poorer responses to standard therapy, and have higher recurrences and death rates, as well as shorter intervals to recurrence or death, compared with HIV-negative women of similar stage (Klevens 1996; Maiman 1990).

4. Cervical cancer screening in developed countries

In the U.S. there have been marked reductions in cervical cancer incidence and mortality over the past 60 years, largely the result of the development and widespread introduction of the Papanicolau (Pap) test in 1949 (Sawaya 1999; van der Graaf et al. 1986; Eddy 1990), based on cytologic examination of cells obtained from the cervix with a simple scraping using a wooden spatula or brush. It is estimated that 60% of the women who are diagnosed with ICC have never had cervical cytology testing or have not been screened within the 5 years

before diagnosis (NIH 1996). However, conventional Pap smears are not perfect: a single Pap smear is associated with false-negative rates of 10–25%, largely because of errors in sampling or interpretation. False-negative Pap smears are associated with 30% of the new cases of cervical cancer each year (NIH 1996; Shingleton et al. 1995)

Newer Pap smear screening techniques using liquid-based media appear to decrease inadequate smears and also offer the possibility of direct HPV-DNA testing on collected specimens (ACOG 2009). A recent review of over 400 HIV-infected women who underwent both conventional and liquid-based cytologic screening found a significant decrease in the proportion of smears diagnosed as ASCUS/AGUS as well as the ASCUS/SIL ratio, with liquid-based preparations (Swierczynski 2002). HPV testing for cancer-associated HPV subtypes is currently used as a triage test to stratify risk in women with a cytology diagnosis of atypical squamous cells of undetermined significance (ASC-US), in postmenopausal women with a cytology diagnosis of LSIL and is also often used as an adjunct to cytology for primary screening in women older than 30 years (ACOG 2009). The currently used classification system for Pap smear results is known as the Bethesda classification, which includes an indication of adequacy of sample, whether the result is normal and, if abnormal, degree of abnormality (Solomon 2002).

With current US-based guidelines (ACOG 2009), Pap smears are recommended beginning at age 21 and every two years until age 30 if normal. After 30, if the last 3 tests have been normal, screening interval can be increased to 3 years. Providers may consider discontinuation of screening after age 65–70; if there have been no abnormal Pap smears in 10 years and no on-going risk factors. Colposcopy with biopsy of abnormal areas for histologic confirmation is recommended with ASCUS/+HPV or greater abnormality on Pap or with repetitive ASCUS, even if HPV-. The results of both Pap smear and colposcopy/biopsy are used to determine need to treatment, follow-up or further evaluation.

Women with HIV infection are recommended to have more frequent screening with cervical cytology: twice in the first year after diagnosis of HIV and, if normal, annually thereafter (CDC 2009; ACOG 2010) More frequent Pap smears should be considered with previous abnormal Pap smears, with conservative follow-up of cervical dysplasia without treatment (after colposcopic evaluation to rule out HSIL), with other evidence of HPV infection and after treatment for cervical dysplasia (Anderson 2005).

The role of HPV-DNA testing in HIV+ women is unclear. In a WIHS substudy of HIV+ and HIV- women with normal baseline cytology, incidence of squamous intraepithelial lesions (SIL) were examined by baseline HPV DNA results and stratified by CD4 count. Through 3 year follow-up, incidence of any SIL was similar in HIV- and HIV+ with CD4>500 who had negative results for oncogenic HPV or all HPV, suggesting that similar cervical cancer screening practices may be applicable to both groups. On the other hand, after just 2 years follow-up, incidence of any SIL in HIV+ with CD4<500 was increased over HIV-, even among women with negative results for any HPV, suggesting that a closer screening strategy may be needed for women with lower CD4 counts (Harris et al. 1995). In two prospective studies of HIV-infected women with ASC-US, approximately 30% of participants had evidence of oncogenic HPV, a finding that would support the use of HPV testing in this population if HPV testing remained highly sensitive (Massad et al. 2004; Kirby et al. 2004). However, one of these studies reported a sensitivity of HPV testing for the

detection of CIN 2 or higher of 100% (Kirby et al. 2004) and the other study reported a sensitivity of only 50% for detecting high-grade CIN (Massad et al. 2004). Currently CDC and ACOG do not recommend HPV testing for triage of HIV-infected women with abnormal cytology results, for follow-up after treatment for CIN, or to lengthen screening intervals (CDC 2009; ACOG 2010). A study examining HPV DNA testing as a primary screening method for cervical dysplasia in 94 HIV-positive women found that HPV DNA testing identified high-grade cervical dysplasia more accurately than Pap smear (Petry 1999).

Even in locations with high resources, screening for cervical dysplasia in the setting of HIV can be challenging. Women receiving gynecologic and primary HIV care at the same location are more likely to have had Pap smear screening within the previous year (AHRQ 2010). However, despite high rates of HPV and CIN, many women with HIV do not engage in the recommended annual Pap testing (Tello et al. 2008; Oster et al. 2009).

4.1 Cervical cancer screening in low resource countries

Cervical cancer screening is often simply not available in developing world settings. Barriers to cytology-based screening programs include poor health infrastructure, lack of trained cytology technicians and cytopathologists and cost. In addition Pap smears are not point-of-care tests; they require the ability to notify women of abnormal results and to follow-up with further evaluation or treatment. However, in low resource settings, many or most women reside at some distance from health centers, have little access to or cannot afford effective transportation, and there is a lack of effective recall mechanisms for abnormal results (Anorlu 2008). In sub-Saharan Africa there was a 60-80% default rate among those with cytologic abnormalities-(Cronje 2004).

Prevention of cervical cancer by identification and treatment of cervical cancer precursors is key, since treatment resources for invasive disease are scarce. In 2002, the survival rate for invasive cervical cancer was 21% in sub-Saharan Africa vs. 70% in US (Parkin et al. 2005). This is related to the fact that most patients present at late stages, as well as a lack of effective treatment resources, including surgical expertise and radiotherapy (Ashraf 2003). When women present with advanced cervical cancer, palliative care resources are also limited; although morphine is on the WHO list of essential medications (http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf), one study of 47 African countries found that only 11 used morphine for chronic pain (Harding 2005).

Recent work has focused on service delivery models using alternatives to cytology for screening for cervical precancerous lesions in order to improve access to safe and effective treatment, minimize loss to follow-up and prioritize utilization of specialized care. Necessary programmatic components, regardless of the strategy employed, include leadership at national levels making preventing cervical cancer a priority and including development of strategies and guidelines; community awareness building; training of providers and continuing education; data collection systems and outcomes monitoring, including quality assurance measures; administrative management; patient recall and retention plans; and appropriate linkages to assure adequate supplies, timely and high quality laboratory testing, and referrals when needed for higher levels of care. In South Africa, where it is estimated that 1 in 26 women develop cervical cancer in their lifetime, a cervical screening program was initiated in 2001; it called for three free Pap smears, starting

at age 30, at ten year intervals (Cronje 2003; Moodley 2006). By 2005–2006, 100% of primary health care clinics in South Africa had health professionals trained to conduct Pap smears, yet the screening rate was only 1.3% (van Schalkwyk 2008). Several studies have found a lack of awareness of cervical cancer as a disease among women, as well as stigma and cultural beliefs or perceptions related to the reproductive organs and symptoms that may delay care-seeking (Anorlu et al. 2008; Wellensiek et al. 2002; Anorlu et al. 2000); however, studies have also documented that health care workers also often have poor knowledge about cervical cancer (Tarwireyi et al. 2003; Ayinde and Omigbodun et al. 2003).

4.2 Alternatives to cervical cytology

Two primary strategies have been developed as alternatives to cytologic screening. The first technique utilizes visual inspection of the cervix without magnification after application of a dilute solution (3–5%) of acetic acid (VIA) or, less commonly, Lugol's iodine solution (VILI). Most studies report results with VIA. With visual inspection techniques, there are three possible results: negative, positive, or suspicious for cancer requiring referral and further evaluation and management. The accuracy of VIA/VILI depends on the ability to visualize the cervical transformation zone, the area where the original columnar epithelium covering the ectocervix has been replaced by squamous epithelium, and the area where oncogenesis begins. As women approach menopause and afterwards, the transformation zone recedes into the cervical canal and may no longer be visible, reducing accuracy of VIA (Cremer 2011). However, in younger women and women in whom the transformation zone is visible, the high negative predictive value of VIA (see below) suggests that significant lesions can generally reliably be excluded if VIA is negative. A major advantage of these techniques is the ability to offer treatment the same day, known as the single-visit approach (SVA).

The other major alternative to cytology is HPV testing. HPV-DNA testing, with detection of high-risk HPV subtypes, is reproducible and objective. HPV testing has been suggested as primary screening in place of cytology in the US and Europe (Kitchener et al. 2009; Cusick et al. 2006) and a negative HPV test predicts a less than 2% risk of developing cervical dysplasia (Naucler et al. 2009; Lonky et al. 2010; Mesher et al. 2010; Kitchener et al. 2009; Cusick et al. 2006). An advantage of HPV testing is that a pelvic exam is not required, but simply insertion of a swab into the vagina to obtain the sample; furthermore, studies have shown that accurate results can be obtained with self-testing, where the woman inserts the swab into her own vagina (Ogilvie et al. 2005; Balasubramanian et al. 2010), that this compares favorably to collection by clinicians (Bhatla et al. 2009; Petignat et al. 2007) and is acceptable to women (Mitchell et al. 2011; Lack et al. 2005). However, treatment of positive results clearly requires access to and good visualization of the cervix.

Sensitivity and specificity values for these screening strategies vary depending on the comparison technique used as "gold standard", as well as the detection goal, i.e., any cervical intraepithelial neoplasia (CIN) or only high grade CIN (CIN2 or CIN3) which are the immediate precursors to invasive cancer. Low-grade lesions (CIN1) may regress spontaneously up to 60% of the time (Cox et al. 2003) and are not routinely treated. Therefore, it is thought that the most appropriate detection goal is CIN 2 or higher (CIN2+), since these lesions are the ones likely to progress to cancer. Some studies have suggested that use of colposcopically-directed biopsy may overestimate sensitivity of VIA when compared to expanded biopsies, including endocervical curettage (ECC), likely due to

increased detection of nonvisible lesions in the endocervical canal (Pretorius et al. 2007; Cagle et al. 2010).

In a cluster randomized trial in India, 31343 women screened with VIA were compared to 30958 controls, 30–59 years of age. Women who were VIA+ received colposcopy and biopsy with cryotherapy at the same visit for a colposcopic impression of dysplasia. With 7 years of follow-up, VIA was associated with a 24% reduction in cervical cancer incidence, stage 2 or higher, and 35% reduction in cervical cancer mortality (Sankaranarayanan 2007). In a study one year after cryotherapy, 648 women received both VIA by trained nurses and colposcopy and biopsy with VIA+ patients; 42 (6.5%) were referred for colposcopy and three of these had HSIL or cancer. Of those who were VIA-, colposcopically-based diagnosis was HSIL in only two cases (VIA sensitivity 60%, specificity 93.9%, PPV 7.1%, NPV 99.7%, comparable to Pap smear (Chumworathayi et al. 2008). A recent review of published studies of VIA accuracy with histology as the standard and CIN 2 as the outcome measure found sensitivity 79-82%, specificity 91-92% with PPV 9-10% (Sauvaget et al. 2011).

A pooled analysis of approximately 30,000 women from 17 population-based studies in China assessed the diagnostic accuracy of HPV testing for the detection of CIN 3 or greater; all positive tests were referred for colposcopy and biopsy. HPV-DNA testing had higher sensitivity of 97.5% and lower specificity of 85.1% , as compared to cytology (sensitivity 87.9%, specificity 94.7%) and VIA (sensitivity 54.6%, specificity 89.9%) (Zhao et al. 2010). HPV testing was evaluated and compared to both VIA and cytology in a cluster randomized trial in India. The trial had four arms, with >31,000 women aged 30–59 in each arm and 8 years of follow-up. In this study HPV by hybrid capture (detects 13 high risk subtypes) was compared to cytology, VIA and standard of care, which was no screening. With a positive result with any of the three screening tests, colposcopy and biopsy were performed and treatment with cryotherapy or LEEP was offered. When compared to the no screening group, HPV testing was associated with an approximately 50% reduction in detection of advanced cervical cancer and deaths from cervical cancer; neither VIA nor cytology was associated with statistically significant benefit (Sankaranarayanan et al. 2009).

In an analysis of the accuracy of five cervical cancer screening tests assessed in 11 studies in Africa and India, using colposcopically-directed biopsy as the standard and high grade CIN as the outcome, pooled sensitivity for VIA was 79.2%; for VILI 91.2%; for cytology 57% and for HPV testing (using Hybrid-Capture 2 assay) 62%(and pooled specificity for VIA was 84.7% for VILI 84.5% for cytology 93% and for HPV testing 94%). In this study pooled prevalence of CIN2+ was 2.3% and PPV was 11.6% and 12.9%, respectively for VIA and VILI and NPV >99% for both techniques. Accuracy of visual methods and cytology increased over time, while performance of the HPV test was constant (Arbyn et al. 2008).

In the setting of HIV infection, there are more limited data. In one study of 205 women correlating VIA with cytology with biopsy as the standard, VIA was more sensitive than Pap smear (76% vs. 57%, respectively) but less specific (83% vs. 95%, respectively); PPV for VIA was only 34% but was also low for cytology at 55%, but NPV for both techniques was high (97% for VIA, 95% for cytology). The prevalence for CIN in this patient population was 10.2% (Akinwuntan 2008). More recently VIA, HPV testing and cytology were compared to colposcopically-directed biopsy in 498 women in Kenya. Both HPV testing and Pap smear had higher sensitivity than VIA, with HPV showing greatest sensitivity (94%, 89% and 79%, respectively), while VIA was superior to HPV testing in terms of specificity (51% for HPV

testing, 60% for cytology, 63% for VIA). PPV was low for all three methods (18% for HPV testing, 20% for Pap, 17% for VIA) and NPV was high (99% for HPV testing, 98% for PAP, 95% for VIA) (Chung CROI 2011). In a "see and treat" program in Uganda HIV-infected women had higher likelihood of inflammation, resulting in an increase in false-positive results (Mutyaba et al. 2010).A randomized clinical trial of VIA and HPV testing , with cryotherapy treatment for positive results, was performed among over 6500 women in South Africa, of whom 956 were HIV+. Women were followed for up to 36 months after randomization with colposcopy and biopsy to determine the study endpoint of CIN2+. Screen-and-treat using HPV testing significantly reduced CIN2+ in both HIV+ and HIV- women at follow-up (relative risk 0.20 [95% CI 0.06–0.69] and 0.31 [95% CI 0.20–0.50], respectively), compared to controls with sensitivity of 94% and PPV of 29.9% in HIV+ women; VIA also reduced the likelihood of CIN2+ at follow-up, but to a lesser degree and only reached statistical significance in HIV+ women (RR 0.51 [95% CI 0.29–0.89]), where sensitivity was 63.9% and PPV was (Kuhn et al. 2010). Because HIV+ women had higher rates of CIN2+, both screen-and-treat strategies had a stronger impact at the population level in HIV+ women than in HIV- women. It was estimated that for every 100 women screened HPV screen and treat could prevent 11.9 CIN2+ cases in HIV+ women and VIA screen and treat could prevent 7.4 cases of CIN2+ in HIV+ women.

A comparison of VIA and HPV testing is found in Table 1. In computer-based models, both VIA and HPV testing are cost-effective alternatives to conventional cytology-based programs, which usually require three visits, in low resource settings (Goldie et al. 2005). While HPV testing is more objective and reproducible and has higher sensitivity than VIA, it has some significant disadvantages for lower resource countries. A rapid HPV test has now been developed (Care-HPV, Qiagen Inc.) but is not yet commercially available), but costs (estimated at $5–10 US) are still largely prohibitive in areas where annual health expenditures are often under <$5 per person. Furthermore, although results can be available the same day, they are not available instantly, but are run in batches and require up to 3 hours for actual testing. VIA is inherently subjective and less reproducible, as reflected by low inter-rater agreement was seen among both midwives and gynecologists compared to lead reference physicians regarding cryotherapy treatability (Gage et al. 2009), but performance seems to improve with experience. A number of studies have shown the sensitivity of VIA to be similar to or higher than that of cytology. It is inexpensive, with low costs, including cost of supplies and cost to the patient because of the ability to treat abnormalities at the same visit. VIA can be task-shifted to lower level health workers and, most notably, allows single visit screening and treatment. Furthermore, VIA has been shown to be safe, feasible and acceptable in multiple studies (Phongsavan et al. 2011; Sankaranarayanan et al. 2007; Palanuwong 2007; Sanghvi et al. 2008). The positive predictive value of VIA is low and fairly common conditions such as cervicitis may cause false positive VIA results (Davis-Dao 2008). It remains unclear how the greater prevalence of HPV infection in HIV-infected women will affect performance characteristics of HPV testing as a primary screen in this population.

An advantage of HPV testing is that pelvic exam is not required, but simply insertion of a swab into the vagina to obtain the sample; furthermore, studies have shown that accurate results can be obtained with self-testing, where the woman insert the swab into her own vagina (Ogilvie et al. 2005; Balasubramanian et al. 2010), that this compares favorably to

collection by clinicians (Bhatla et al. 2009; Petignat et al. 2007) and is acceptable to women (Mitchell et al. 2011; Lack et al. 2005). However, treatment of positive results clearly requires access to and good visualization of the cervix. On the other hand, VIA is inherently subjective and less reproducible; however a number of studies have shown its sensitivity to be similar to or higher than that of cytology, it is inexpensive, can be task-shifted to lower level health workers and, most notably allow single visit treatment. It remains unclear how the greater prevalence of HPV infection in HIV-infected women will affect performance characteristics of HPV testing as a primary screen in this population.

	Outcome	Sensitivity (%) (min-max-pooled)	Specificity (%) (min-max-pooled)
VIA	CIN 2 +	65-91-79	74-95-85
VILI	CIN 2 +	74-98-91	73-92-85
Cytology	CIN 2 +	33-82-57	87-99-93
HPV Hybrid Capture 2	CIN 2 +	48-68-62	92-95-95

Table 1. Sensitivity and specificity of 4 screening tests for CIN 2+ cervical lesion, minimum, maximum and pooled measures

Minimum, maximum and pooled measure of sensitivity and specificity adapted from Table 3.

Marc Arbyn1, Rengaswamy Sankaranarayanan, Richard Muwonge, Namory Keita, Amadou Dolo, Charles Gombe Mbalawa, Hassan Nouhou, Boblewende Sakande, Ramani Wesley, Thara Somanathan, Anjali Sharma, Surendra Shastri and Parthasarathy Basu. Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. Int. J. Cancer: 123, 153–160 (2008).

As yet, there has been fairly limited programmatic experience with these screening techniques in the setting of HIV. Jhpiego has introduced a VIA/SVA program in Guyana, Cote d'Ivoire and Tanzania, screening over 16,000 women from 2009–2010. Services were provided by trained nurses and midwives at HIV care and treatment sites and general health facilities. In all 3 countries HIV+ women were more likely to be VIA+ than HIV-/unknown women. In all 3 countries HIV+ women who were VIA+ were more likely to have large lesions (occupying >75% cervix) and therefore ineligible for cryotherapy. Eighty-two% of eligible women had same-day treatment with cryotherapy; of those who postponed, 44% did not return for treatment (Anderson 2011). These findings confirm cytology-based studies that HIV+ women are at greater risk for cervical dysplasia and is consistent with other studies suggesting that a larger volume of the cervix involved. It also supports the feasibility of VIA/SVA from a programmatic standpoint and suggests that this approach results in reduction of loss to follow-up as compared to screening requiring a subsequent visit.

As HPV testing becomes more affordable and accessible, and particularly if it can be done as a genuinely rapid point-of-care test, it is possible that a hybrid approach to cervical screening may maximize accuracy and minimize unnecessary treatment. In this scenario, HPV testing could be the primary screening method, with VIA performed on those who are

HPV+ to assess the presence of disease and the feasibility of treatment. Those who are HPV-negative would receive no further screening. Alternatively, VIA could be the initial screen, with those who are VIA+ having HPV testing to improve PPV.

5. Treatment

A cervical cancer screening program cannot be effective unless there is an effective intervention to prevent the development of cervical cancer. Excisional or ablative treatment is indicated for the presence of high grade lesions, which encompasses a diagnosis of moderate-severe cervical dysplasia or carcinoma-in-situ and are the immediate precursors of invasive cervical cancer (ICC). Hysterectomy should not be used as a primary treatment for high-grade cervical dysplasia without first ruling out the presence of invasive cancer with an excisional procedure. The most common procedures used for treatment are loop electrosurgical excisional procedure (LEEP), cryotherapy or cervical conization. Table 2 summarizes the key characteristics of each treatment option.

	Cervical Conization	**LEEP**	**Cryotherapy**
Anesthesia required	General or regional	Local	None
Other resources needed	Operating room supplies, instruments, personnel, anesthetics	Electrical generator, wire loops (different sizes)	Cryoprobes (different sizes), CO_2 tank
Effectiveness *	96%+	96%+	88%
Technical difficulty	Highest	Intermediate	Lowest–nurses, midwives can safely and effectively perform
Complications	Highest: bleeding, stenosis, adverse pregnancy outcomes most common	Intermediate: dependent on amount of tissue removed; excessive bleeding during or after procedure most common	Lowest: <1–2%, generally minor
Pathologic specimen	Yes	Yes	No
Cost	Highest	Intermediate	Lowest

*Effectiveness figures cited based on studies in general populations. In HIV + women, the effectiveness is expected to be lower for all techniques.

Table 2. Comparison of treatment methods for cervical dysplasia.

Cervical conization requires regional or general anesthesia and removes a larger volume of tissue. There are higher complication rates after the procedure, including postoperative bleeding (5–15%), infection (02–6.8%), cervical stenosis (approximately 8%) and increased risk of preterm delivery (Hoffman and Mann 2010; Arbyn et al. 2008). This procedure is typically used when lesions are entirely within the cervical canal (based on pathologic analysis of endocervical curettage), are thought to extend high into the cervical canal or when invasive cancer is suspected, so that accurate pathological examination can be performed and, when preinvasive, the entire lesion can be removed.

LEEP has supplanted cervical conization in many situations, including lesions that are believed to extend more superficially into the canal. LEEP utilizes a thin wire in the shape of

a loop and electrosurgical generators; the loops are available in a variety of sizes and can also be passed through tissue with several passes if needed to remove the entire area of abnormality, therefore tailoring the procedure to the size of the lesion on the extocervix. The depth of excision can be fairly precisely determined and controlled. LEEP can be performed under local anesthesia and removes less tissue than conization. Complications are less common than after conization (postoperative bleeding 0–8%, infection 0–2%, cervical stenosis 4.3–7.7%; preterm delivery-no increased risk) (Hoffman and Mann 2010; Arbyn et al. 2008).

Cryotherapy uses nitrous oxide or carbon dioxide to freeze the cervix and destroy precancerous tissues and can be performed without anesthesia or electricity. Freezing is done in two cycles of three minutes with five minutes of thawing in between (Sellors 2003). Mid-level providers have been trained successfully to perform cryotherapy safely and with a high degree of acceptability (Bradley 2006; Nene et al. 2008). Carbon dioxide (CO2) provides a less expensive alternative to nitrous oxide and produces equally low temperatures (Sirivongrangson 2007). However, some studies report that CO2 may cause cryotherapy blockage up to 50% (Sirivongrangson 2007; Winkler 2010). The quality of cryotherapy devices rather than gas could be responsible for variant temperature (Winkler 2010). The freeze-clear-freeze technique, often employed to reduce gas blockage, may also produce temperatures not sufficiently low enough for treatment to be effective (Winkler 2010). It is important for providers to give adequate treatment by paying attention to visual cues that confirm freezing. Cryotherapy does not provide a tissue specimen. For cryotherapy to be optimally effective, the entire lesion and ideally the entire transformation zone must be visible and the lesion should occupy less than three-fourths of the transformation zone (Sankaranarayanan 2008). Adverse effects after cryotherapy are relatively uncommon and generally minor, reported in 1–2% of women (Cirisano 1999; Sankaranarayanan 2007; Nene 2008). Discomfort usually resolves within a week after treatment (Chamot 2010; Bradley 2006). Significant bleeding after cryotherapy is uncommon. After cryotherapy, watery discharge generally continues for several weeks. Post-treatment infection and pelvic inflammatory disease for LEEP and cryotherapy are both rare (Chamot 2010). The risk of cervical stenosis after cryotherapy is low (<1%) (Loobuyck and Duncan 1993) and the risk of obstetric complications, particularly preterm delivery, is lower after cryotherapy than after excisional procedures. Complications after cryotherapy do not differ among developed and developing countries.

In lower resource areas, the advantages of cryotherapy are significant: the ability to perform the procedure without anesthesia, lack of need for electricity, the lower level of technical expertise required to perform the procedure and lower costs. A significant advantage of LEEP is the ability to examine a tissue sample histologically; however, in areas with few resources, pathological evaluation is usually not available. Studies have generally found LEEP to be associated with somewhat higher cure rates (absence of persistent or recurrent disease) than cryotherapy (Melnikow et al. 2009). A randomized clinical trial of cryotherapy and LEEP for treatment of histologically confirmed high-grade cervical dysplasia found that LEEP had higher overall cure rate of 96.4% as compared to 88.3% for cryotherapy (p=0.026) (Chirenje et al. 2001). Treatment methods are generally consistent among high-income and low-income countries (Luciani 2008). Cryotherapy is less effective in older women, where the transformation zone and any cervical lesions are more likely to recede into the cervical

canal and is less effective with large lesions. This raises potential concerns in the management of HIV+ women, who may have lesions occupying a larger volume of the cervix.

One of the treatment effects with either cryotherapy or LEEP may be stimulation of the immune response, promoting clearance of HPV after treatment, even if the entire lesion or the entire transformation zone is not excised or ablated, although one small study failed to show an effect of cryotherapy on HPV clearance one year after treatment (Taylor 2010; Chumworathayi et al. 2010).

HIV-positive women have an increased incidence of persistence or recurrence after treatment, with some studies documenting >50% recurrence rate (Tebeu et al. 2006). Recurrence rates are increased in the following situations:

- positive surgical margins with LEEP or cervical conization (present in >40% of HIV+ women) (Boardman et al. 1999; Gilles et al. 2005; Lima et al. 2009).
- glandular involvement (Lima et al. 2009).
- greater immunosuppression (Holcomb et al. 1999; Shah et al. 2008)
- lack of suppressive ART (Robinson et al. 2001).

Most recurrences in HIV+ women appear to be low-grade disease, which may be associated with new HPV infections (Massad et al. 2007) but re-excision may be necessary in some cases (Holcomb et al. 1999; Gingelmaier et al. 2007). Follow-up with cervical cytology alone or cytology and colposcopy together at 6-month intervals over the first year after treatment is recommended (CDC 2009; Wright et al. 2007).

There remain limited data on the use of LEEP and cryotherapy in the setting of HIV, especially related to efficacy. A study of HIV-infected and –uninfected women in Zimbabwe, cryotherapy had a 40.5% failure rate among HIV+ women at one year of follow-up, compared to 15.8% failure rate among HIV- women; in the same study, LEEP had 14% and 0% failure rates, respectively, among HIV+ and HIV- women (CHirenje 2003). However, over 50% of failures were low-grade lesions. LEEP was associated with higher complication rates, including excessive bleeding,and discharge, than cryotherapy. A study from Zambia of cryotherapy-ineligible women (many of whom were HIV+), referred for further management, LEEP (performed by physicians) was feasible and safe, with low levels of complications that can be managed locally (Pfaendler et al. 2008).

Abstinence should be emphasized until complete healing has occurred after treatment for cervical dysplasia, since the treatment has been shown to dramatically increase genital tract HIV shedding (Wright 2001) and may increase risk of sexual transmission of HIV. However, a recent study from Kenya found no increase in detectable cervical HIV-1 RNA among HIV-positive women (most on ART) after cryotherapy. (Chung et al. 2011).

6. Research questions and programmatic issues

There remain a number of unanswered questions and challenges regarding the implementation and integration of effective cervical cancer screening programs into HIV care and treatment. Data regarding antiretroviral treatment and CD4 counts correlated with

VIA results are important to further refine screening and treatment protocols and inform guidelines on appropriate screening strategies and intervals. Integration of cervical cancer screening for HIV+ women requires testing of different models for training, implementation and data collection. Given the information currently available of the interaction of HPV and HIV infections and the epidemiology of HIV:

- Will screening earlier in the course of HIV, when there is less immunosuppression, be associated with smaller and more treatable lesions?
- Will ART and associated immune reconstitution make a difference in rates of VIA positivity and lesion size?
- How often should screening occur in HIV+ women?
- Are HIV+ women more likely to accept SVA than HIV- women?
- What is the relative efficacy and safety of LEEP vs cryotherapy in HIV+ women?
- What are appropriate models of care and what is their feasibility?
- How will VIA and HPV testing be best integrated to enhance test performance, feasibility and scale-up?
- How will cervical cancer prevention be taken to scale in low and middle income countries?

7. Primary prevention of HPV/cervical cancer

Given the millions of new HPV infections/ year in 14-44 year olds primary prevention of HPV infections should be a priority. Consistent and correct use of condoms has been associated with reduction in risk for acquisition of genital HPV infection, including genital warts, CIN and cervical cancer (Winer et al. 2006; Vaccarella et al. 2006; Manhart and Koutsky 2002) although data are limited in the HIV setting. Male circumcision (MC) has been shown to reduce by reduce the risk of sexual HIV transmission from female to male by 60% (http://www.who.int/hiv/topics/malecircumcision/en/index.html) in randomized clinical trials. MC was also associated with a lower incidence of multiple high-risk HPV types and increased clearance of HR-HPVs as compared to controls (14.8% vs 22.3%, respectively) in Uganda (Gray et al. 2010); however, MC was not associated with decreased incidence or increased clearance of HR-HPV in the female partners of circumcised men 24 months after the procedure, as compared to partners of men in the control group (Tobian et al. 2011) However, MC has long been associated with reduced risk of cervical cancer in the wives of circumcised men; therefore further study is warranted.

Finally, two HPV preventive vaccines are now available, one quadrivalent, providing protection against HPV types 16, 18, 6, 11, and the second bivalent, protecting against HPV types 16 and 18 only. In the initial trials of these vaccines, there was >95% -100% protection against incident infection with vaccine subtypes in women not previously infected with those subtypes and in CIN2 or greater related to HPV-16 or 18 (FUTURE II Study Group, 2007; Villa et al. 2005; Paavonen et al. 2009, Garland et al. 2007) vaccine effectiveness was maintained through over 7 years of follow-up (FUTURE I/II Study Group 2010). Although there are other high risk HPV types, types 16 and 18 are responsible for approximately 70% of invasive cervical cancers worldwide (de Sanjose et al. 2010). Recent HPV seroprevalence studies in HIV+ African women found that 65% were seropositive for one of the vaccine subtypes (Firnhaber 2011), suggesting that early vaccination may provide significant

protection. However, a recent review found that HIV-infected women in different geographic regions (including Zambia, Brazil, US) appear to be infected with less prevalent HR-HPV types as compared to the general population (McKenzie et al. 2010) . As yet there are limited data on safety, immune response and efficacy of the HPV vaccine in HIV+ women, although studies are on-going. Although data on the safety of the quadrivalent vaccine in HIV-infected children has been demonstrated, efficacy of the currently available HPV vaccines in women or girls with HIV has not yet been established (Levin et al. 2010).

Given the high rates of HPV and cervical cancer in countries with limited health resources, initiatives to introduce HPV vaccination for young people prior to the initiation of sexual activity in these settings are critical. The HPV vaccine is the most expensive vaccine ever developed and costs must be lowered to make this a feasible intervention in the developing world. Fortunately, groups such as GAVI and others are working with governments and other potential donors, as well as with the vaccine makers, to make these vaccines more accessible in areas where they are needed most. Given the high prevalence of both HIV and HPV in many low resource settings and the virologic synergy between these two viruses, with increased rates of HPV-related disease in HIV+ individuals, HIV+ women may be a particular target group for vaccine administration. Furthermore, with improved access to antiretroviral treatment and greater longevity, an increasing number of girls who have been perinatally infected with HIV will be living into adulthood and these girls may particularly benefit from HPV vaccination.

Mathematical models estimate that reduction in incidence and mortality of cervical cancer will be greatest in low/middle income countries with no or limited screening and that HPV vaccination may be cost-effective if cost <$10–25/vaccinated girl (Kim JJ et al. 2008). Currently, the WHO recommends including routine HPV vaccination in national immunization programs, providing prevention of cervical cancer is a public health priority, programmatically feasible, cost-effective, and has sustainable financing (WHO 2009). HIV infection is not considered a contraindication to HPV vaccination (CDC 2007; ACOG 2010; CDC 2009).

8. Conclusion

Cervical cancer is a leading cause of morbidity and mortality in countries with the fewest resources and these resources are often already over-stretched by high levels of HIV infection. Virologic synergy between HIV and HPV infections further exacerbates the problem, and HIV-infected women are at increased risk for HPV and HPV-related diseases, including cervical cancer. Furthermore, unlike other typical opportunistic infections, there is no compelling evidence that the use of effective ART reduces the burden of HPV or HPV-related complications, possibly leading to increased numbers of women at risk for cervical cancer as HIV treatment programs become more accessible and successful. Fortunately, cervical cancer is preceded by an extended precancerous period that can be detected and treated to prevent the development of invasive disease. Cervical cytology, which has revolutionized cervical cancer prevention in the U.S. and other developed countries over the past half-century, is simply not feasible for most countries with few resources. Alternatives such as VIA and HPV testing hold great promise as alternative screening strategies, coupled with the use of cryotherapy or LEEP to treat precancerous lesions. In the new WHO Global health sector strategy on HIV/AIDS an over-arching goal is to achieve universal access to

comprehensive HIV prevention, treatment and care. Two of the four strategic directions noted in this strategy are to leverage broader health outcomes through HIV responses, including strengthening linkages between HIV and other related health programs, notably including cervical cancer screening and care, and to build strong and sustainable heath systems in which HIV and other essential services are available, accessible, affordable and sustainable. This renewed emphasis on comprehensiveness and integration of services is consistent with making further evaluation of the role of these screening techniques, individually or in concert, in the setting of HIV a research priority.

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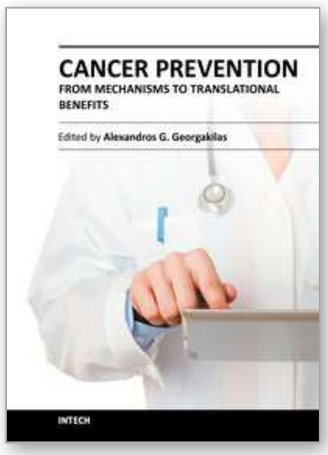

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This unique synthesis of chapters from top experts in their fields targets the unique and significant area of cancer prevention for different types of cancers. Perspective readers are invited to go through novel ideas and current developments in the field of molecular mechanisms for cancer prevention, epidemiological studies, antioxidant therapies and diets, as well as clinical aspects and new advances in prognosis and avoidance of cancer. The primary target audience for the book includes PhD students, researchers, biologists, medical doctors and professionals who are interested in mechanistic studies on cancer prevention and translational benefits for optimized cancer treatment.

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Phone: +86-21-62489820
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