Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya

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Women living with HIV are at increased risk for human papillomavirus (HPV) infection and HPV-related tumours, including cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) and invasive cervical carcinoma (ICC) (Clifford et al, 2006; De Vuyst et al, 2008). The prevalence of HPV and CIN has been reported to increase with the increase of immunosuppression (Denny et al, 2008; Firnhaber et al, 2010). Combination antiretroviral therapies (cART) against HIV have greatly reduced the incidence of opportunistic infections, Kaposis sarcoma, and non-Hodgkin’s lymphoma, but not the incidence of HPV-associated cervical and anal carcinomas (Franceschi et al, 2010). This is perhaps not surprising as HPV-associated carcinomas have a long latent phase. A favourable effect of cART on HPV infection and cervical precancerous lesions has been shown in some (Paramsothy et al, 2009; Minkoff et al, 2010), but not all studies (Bratcher and Sahasrabuddhe, 2010; Shrestha et al, 2010) on the topic.

A favourable effect of cART on cervical cancer and its precursor lesions would be of particular importance in sub-Saharan Africa (SSA), home to three quarters of women living with HIV (WHO, 2011), and 14% of cervical cancer cases worldwide (Ferlay et al, 2010). Access to cART has recently been greatly improved in SSA and by the end of 2010 nearly half of the people who need cART in SSA have had access to it (WHO, 2011). Access to cervical screening is also improving among HIV-positive women in SSA (Brower, 2011), but to a much lesser extent than that to cART.

Human papillomavirus testing has been shown to be superior to cytological screening in terms of sensitivity and duration of negative predictive value against CIN2/3 and cervical cancer in the general female population in high- and low-resource countries (Sankaranarayanan et al, 2009; Ronco et al, 2010; Rijkaart et al, 2012). The use of HPV testing in HIV-positive women and, by and large, in very high HPV prevalence populations have created, however, concerns due to the low test specificity in these settings (Giorgi-Rossi et al, 2012), and hence, the heavy burden of the management of HPV-positive women (Kitchener et al, 2007). Scanty data are available on the detection of high-grade lesions through HPV testing in under-screened populations (Keita et al, 2009; Gage et al, 2012), including in HIV-positive women (Denny et al, 2008; Singh et al, 2009).

The aims of this cross-sectional study from Nairobi, Kenya, were to assess: (1) the distribution of different HPV types at baseline in...
a cohort of HIV-positive women; (2) the association of high-risk (hr) HPV infection and CIN2/3 with various host factors, including age, CD4 count, and cART use; and (3) the positive predictive value (PPV) of HPV testing in HIV-positive women.

MATERIALS AND METHODS

Participants and study procedures

In 2009, 498 HIV-positive women in Nairobi, Kenya were included as part of a study comparing cervical cancer screening methods. Women who attended the Coptic Hope Center for Infectious Diseases for HIV-related conditions were invited to participate in the study and were eligible if they were: between 18 and 55 years of age; not screened in the last year; and never treated for cervical cancer or pre-cancerous lesions. Women received cervical cancer screening with conventional cytology, visual inspection with acetic acid, and HPV testing (Chung et al, 2011a, b). The characteristics of these women at baseline are the object of the present report.

After obtaining a written informed consent, information on clinical and lifestyle characteristics of study women was collected. A venous blood sample was taken to measure CD4 count. Cervical exfoliated cells were collected by a nurse using a Cervex-Brush (Rovers Medical Devices, Oss, The Netherlands) and placed in PreservCyt medium (Hologic, Marlborough, MA, USA) for HPV testing. A medical doctor performed a colposcopic examination and took a biopsy from all women, either from the most abnormal area on the cervix identified by the colposcopic examination, or at 12 o’clock if no lesion was visualised, as this position is the most frequent location for cervical lesions. Biopsy tissues were immediately immersed in 10%-buffered formalin and transported to the pathology laboratory, where they were embedded in paraffin. Cervical disease status in this study was based on biopsy results. Twenty-seven women with inadequate biopsy results had, therefore, to be excluded in the analyses that included histological findings (Tables 1, 4 and 5).

As per Kenyan national guidelines, free cART should have started if: (1) CD4 count was <250 cells µl⁻¹; (2) World Health Organisation (WHO) clinical stage was IV; (3) CD4 count was <350 cells µl⁻¹ and WHO clinical stage was III (Ojoo, 2007). However, full information on history of cART use, CD4 count at beginning of cART, and adherence to treatment was not available in the present study.

The study protocol was approved by the Ethical Review Committees of the Kenyatta National Hospital, Kenya, the University of Washington, USA, and the International Agency for Research on Cancer, France.

Human papillomavirus DNA testing

Human papillomavirus samples were stored at ambient temperature and shipped to the Department of Pathology of the Vrije University Medical Centre, Amsterdam, The Netherlands for HPV DNA testing. Testing was done on exfoliated cells, according to a protocol similar to that used in previous IARC HPV prevalence surveys (Clifford et al, 2005). Beta-globin polymerase chain reaction (PCR) analysis was performed in order to assess the DNA quality. The presence of HPV DNA was first determined using general primer GP5⁺/GP6⁻ -mediated PCR (Jacobs et al, 2000). Polymerase chain reaction products were hybridised using an enzyme immunoassay (EIA) that included two oligoprobes: one for hrHPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 and another for low-risk HPV types 6, 11, 40, 42, 43, 44, 53, 54, 55, 57, 61, 64, 67, 69, 70, 71, 72, 73, 81, 82/mm4, 82/is39, 83, 84, 85, 86, 89, and 90. Subsequent HPV typing was performed by reverse-line blot hybridisation of PCR products, as described previously (van den Brule et al, 2002). Human papillomavirus types of IARC classification group 1 ‘carcinogenic to humans’ (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and group 2A ‘probably carcinogenic to humans’ (HPV68) were considered as hr types (Schiffman et al, 2009). All other HPV types were considered low-risk types. Samples that were positive at hr EIA, but did not reveal positivity in the typing assay were classified as uncharacterised hrHPV types. One sample was negative for beta-globin, but positive for HPV DNA, and hence remained included in the analysis.

Cytology and histology

Cytological slides and biopsies were processed by staff under the supervision of the study pathologist (FR) at the Aga Khan University of Nairobi, who also read all of the cytological and histological slides. Cytology was reported according to the Bethesda 1991 revised classification (Luff, 1992).

Statistical analysis

Prevalence ratios (PRs) and corresponding 95% confidence intervals (CIs) of HPV infection by different characteristics were computed using a binomial regression model with a log link (as opposed to the logistic link used to compute odds ratios) adjusted for age group (< 30; 30–34; 35–39; 40–44; ≥ 45). Prevalence ratios
for HPV infection (any hr types and multiple types) and CIN2/3 were computed by cART use and by CD4 count (overall and stratified by cART use). Prevalence ratios for CIN1 and CIN2/3 among hrHPV-positive women by the age groups were computed with adjustment for CD4 (<250; 250–499; ≥500 cells μl⁻¹), CART use (never, <2 years, ≥2 years), and previous screening. Tests for linear trend of PRs were computed giving an increasing score for each level of the categorised variable and fitting them into the model as continuous variables.

RESULTS

The mean age of 498 study women was 38.1 years (5–95% percentiles: 27–51). Among women with adequate biopsy results, 172 (36.5%) had a normal histology. Cervical intraepithelial neoplasia 1 was detected in 186 women (39.5%); CIN2 in 66 (14.0%); and CIN3 in 47 (10.0%). No ICCs were found.

Table 1 shows the prevalence of HPV types by histological findings and overall. In total, 68.7% of women were HPV-positive, 52.6% were infected with hrHPV types, and 40.2% had multiple infections. High-risk human papillomavirus types were found in 88.0% of multiple infections. Human papillomavirus prevalence was 90.3% in women with CIN2/3. The most frequently found HPV types among women with normal histology were HPV35 (9.9%), HPV32 (7.6%), HPV56 (6.4%), HPV18, and HPV31 (both 5.2%). The prevalence of individual HPV types in women with CIN1 was similar as among women with normal histology, except for an excess of HPV16. HPV16 (26.5%), HPV35 (19.5%), HPV58 (12.4%), and HPV18 and HPV31 (both 10.6%) were the most frequently detected types in women with CIN2/3.

Prevalence ratios for hrHPV-positivity by selected characteristics are shown in Table 2. High-risk human papillomavirus prevalence decreased only slightly with age from 61.3% in women <30 years to 49.5% in women ≥45 years (P_trend PR = 0.136). Women with higher education had a significantly lower HPV prevalence, compared with women with primary education only or no education (PR = 0.74; 95% CI: 0.58–0.95). Positivity for hrHPV was not associated with marital status, number of lifetime or recent partners, use of hormonal contraceptives or number of pregnancies. All findings in Table 2 were similar when positivity for any HPV instead of hrHPV types was assessed.

Figure 1 shows age-specific prevalence of HPV (classified hierarchically into HPV16 and/or 18, hrHPV types but not HPV 16/18, and low-risk types only), and of multiple HPV infections. No significant trends in positivity for HPV 16/18, other hr, low-risk types, and multiple infections were found by age group.

CD4 count at recruitment was 407, 333, and 483 cells μl⁻¹, in women who had never used CART or had used CART for <2 years, or ≥2 years, respectively (data not shown). The presence of hrHPV infection according to CD4 count (overall and stratified by CART use) and CART use is shown in Table 3. High-risk human papillomavirus-positivity was higher in women with CD4 counts <250 cells μl⁻¹ (PR vs CD4 counts ≥500 cells μl⁻¹ = 1.46; 95% CI: 1.22–1.73). The association of CD4 count with hrHPV-positivity was similar in CART users and non-users, although linear trend was significant among CART non-users only. Compared with non-users, CART users for 2 years or longer were less likely to be hrHPV-positive (PR = 0.77, 95% CI: 0.61–0.96). Multiple HPV infections were also more frequent in women with CD4 count <250 cells μl⁻¹ (PR vs CD4 count ≥500 cells μl⁻¹ = 1.89; 95% CI: 1.43–2.50), and less frequent in women with ≥2-year CART use (PR vs non-users = 0.68, 95% CI: 0.53–0.88) (data not shown).

Detection of CIN2/3, according to CD4 count (overall and stratified by CART use) and CART use is shown in Table 4. Cervical intraepithelial neoplasia 2/3 presence increased significantly from 17.2% in women with CD4 count ≥500 cells μl⁻¹ to 36.7% in women with CD4 count <250 cells μl⁻¹ (PR = 1.66; 95% CI: 1.05–2.64). Stratification by CART use showed, however, that the inverse association between CD4 count and CIN2/3 prevalence was restricted to non-CART users (PR = 4.23; 95% CI: 1.27–14.07). Use of CART was not associated with CIN2/3 detection.

Table 5 shows the age-specific detection of CIN1 and CIN2/3 among hrHPV-positive women, which is equivalent to the clinical PPV of hrHPV testing for the corresponding diagnoses. The detection of CIN1 decreased from 40.0% in women <35 years to 22.2% in women ≥45 years (P_trend PR = 0.122). Conversely, the proportion of CIN2/3 in hrHPV-positives increased significantly from 28.9% below age 35 to 53.3% at age 45 or older (PR = 1.71; 95% CI: 1.10–2.66). CIN2/3-to-CIN1 ratio increased, among hrHPV-positive women, therefore, from 0.7 below age 35 to 2.4 at age 45 years or older.
Table 3 PRs for the presence of hrHPV infections and corresponding 95% CIs by CD4 counts and cART use among 497 a HIV-positive women (Kenya, 2009)

| CD4 (cells/μL) | cART non-users (n = 122) | cART < 2 years (n = 171) | cART ≥ 2 years (n = 204) | All (n = 497) |
|----------------|--------------------------|--------------------------|--------------------------|---------------|
|                | n (%)                    | PR b (95% CI)            | n (%)                    | PR b (95% CI) |
| ≥ 500          | 35 (60.0)                | 1                        | 25 (44.0)                | 1             |
| 250–499        | 57 (45.6)                | 0.83 (0.55–1.26)         | 75 (58.7)                | 1             |
| < 250          | 30 (80.0)                | 1.51 (1.02–2.25)         | 71 (66.2)                | 1.48 (0.93–2.38) |
| χ² for trend   | 5.03 (P = 0.025)         | 2.98 (P = 0.084)         |                          |               |
| All            | 122 (58.2)               | 1                        | 171 (59.7)               | 1             |

Table 4 PRs for the presence of CIN2/3 and corresponding 95% CIs by CD4 counts and cART use among 470 b HIV-positive women (Kenya, 2009)

| CD4 (cells/μL) | cART non-users (n = 120) | cART < 2 years (n = 160) | cART ≥ 2 years (n = 190) | All (n = 470) |
|----------------|--------------------------|--------------------------|--------------------------|---------------|
|                | n (%)                    | PR b (95% CI)            | n (%)                    | PR b (95% CI) |
| ≥ 500          | 34 (8.8)                 | 2.99 (0.91–9.80)         | 23 (6.21)                | 0.93 (0.43–2.05) |
| 250–499        | 56 (13.2)                | 4.23 (1.27–14.07)        | 66 (20.3)                | 1.01 (0.46–2.22) |
| < 250          | 30 (36.7)                | 6.23 (P = 0.013)         |                          |               |
| χ² for trend   |                          |                          |                          |               |
| All            | 120 (22.5)               | 1                        | 160 (28.1)               | 1.18 (0.78–1.79) |

DISCUSSION

Human immunodeficiency virus-positive women in our present study had a very high prevalence of HPV infections (68.7%), notably hrHPV type (52.6%), and multiple infections (40.2%). The availability of cervical biopsy in all study participants led to the detection of CIN2/3 in 37.5% of hrHPV-positive women. Cervical intraepithelial neoplasia 2/3 detection and, hence, the PPV of hrHPV-positivity, increased with age. High CD4 count and prolonged cART use were significantly associated with lower prevalence of hrHPV infection. CD4 count was inversely related to CIN2/3 detection only among women who had never used cART and cART use had no clear impact on CIN2/3 presence. Elevated prevalence of HPV (50% or more) and high-grade lesions were consistently reported in HIV-positive women in SSA (Clifford et al, 2006; Singh et al, 2009; Finnhaber et al, 2010; Djigma et al, 2011; Tobian et al, 2011), as well as in high-resource countries (Clifford et al, 2006; Paramsothy et al, 2009). We
Epidemiology of cART on HPV infection (Paramsothy 2010). To date, only few studies have been able to show an impact, 2005; Denny and multiple HPV infections, consistently among cART users and acquisition in HIV-positive women (Strickler lifetime or recent sexual partners may be explained by a stronger high-resource countries. However, an increased risk for hrHPV infection (PR 9.2%, respectively in women with high-grade cervical lesions) comparable in our study and the meta-analysis (e.g., 10.6% and positive women, the PPV of hrHPV-positive results for CIN2/3 in the different age groups. The PPV for CIN2/3 was high across all the age groups but it reached 53% in women aged 45 years or older as CIN2/3 accumulate over time in inadequately screened women (Gage et al, 2012). High PPV demonstrates the effectiveness and potential cost-effectiveness (Vanni et al, 2012) of HPV testing HIV-positive women despite low test specificity (Kuhn et al, 2010; Giorgi-Rossi et al, 2012). A modelling study showed that, at a cost of 13 USD per test, yearly screening using the HPV hybrid-capture2 test followed by cytology was very cost-effective, in respect to the current yearly cytology screening in HIV-positive women in Brazil (Vanni et al, 2012). The advent of a low-cost rapid HPV test in the near future will favour the cost-effectiveness of HPV testing even more.

The greatest strength of our present study is the availability of a biopsy for all women, regardless of cytological findings. An additional strength is the use of a well-validated and widely used HPV test (Clifford et al, 2006; Guan et al, 2012) whose findings were ignored by the local pathologist. Weaknesses include the cross-sectional nature of our present findings that did not allow to investigate the effects of CD4 count and cART on HPV infection and CIN2/3 longitudinally. Unfortunately we were also not able to collect information on either CD4 at the beginning of cART or adherence to treatment, that is, information that would have especially helped interpreting our findings on cART and CIN2/3 prevalence. Finally, although we had a sufficiently large number of HIV-positive women to describe HPV type distribution overall and by CIN presence, some potentially informative subgroups were small (e.g., women with CD4 > 500 cells μl−1).

In conclusion, the burden of hrHPV and CIN2/3 in HIV-positive women in Kenya was high and it was related to immunosuppression level. Combination antiretroviral therapies (>2 year) use had a favourable effect on hrHPV prevalence but antiretroviral treatment in our study population may have been started too late to prevent or reverse CIN2/3. Timely initiation of cART may ultimately decrease cervical cancer in HIV-positive women. Access to HPV vaccination and cervical screening using HPV testing in SSA are needed to reduce cervical cancer among HIV-positive women.

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Conflict of interest
The authors declare no conflict of interest.

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