## Title

Risk factors for cervical precancer detection among previously unscreened HIV-infected women in Western Kenya



## Journal

International Journal of Cancer, 134(3)

## ISSN

0020-7136

## Authors

Huchko, Megan J
Leslie, Hannah
Sneden, Jennifer
et al.

## Publication Date

2014-02-01

## DOI

10.1002/ijc.28401

Peer reviewed

Published in final edited form as:
*Int J Cancer*. 2014 February 1; 134(3): 740–745. doi:10.1002/ijc.28401.

# Risk factors for cervical precancer detection among previously unscreened HIV-infected women in Western Kenya

**Megan J. Huchko, MD, MPH**[1], **Hannah Leslie, MPH**[2], **Jennifer Sneden, MSc**[1], **May Maloba**[3], **Naila Abdulrahim**[3], **Elizabeth A. Bukusi, M.Med, MPH, PhD**[3], and **Craig R. Cohen, MD, MPH**[1]

[1]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, California, USA

[2]Division of Epidemiology, University of California, Berkeley, California, USA

[3]Center for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya

## Abstract

HIV and cervical cancer are intersecting epidemics in many low-resource settings, yet there are few accurate estimates of the scope of this public health challenge. To understand disease prevalence and risk factors for cervical intraepithelial neoplasia 2 or greater (CIN2+), we conducted a cross-sectional study of women undergoing cervical cancer screening as part of routine HIV care in Kisumu, Kenya. Women were offered screening with visual inspection with acetic acid, followed by confirmation with colposcopy and biopsy as needed. Univariable and multivariable analyses were carried out to determine clinical and demographic predictors of prevalent CIN2+. Among 3241 women screened, 287 (9%) had an initial diagnosis of biopsy-confirmed CIN2+. On multivariable analysis, combined oral contraceptives remained significantly associated with detection of CIN2+ among women on HAART (AOR 1.84, CI 1.20-2.82), and not on HAART (AOR 1.72, 95% CI 1.08-2.73), while use of a progesterone implant was associated with increased detection of CIN2+ (AOR 9.43, 95% CI 2.85-31.20) only among women not on HAART. CD4+ nadir over 500 cells/mm$^3$ was associated with reduced detection of CIN2+ (AOR 0.61, CI 0.38, 0.97) in the overall group, but current CD4+ was only associated with reduced detection of CIN2+ among women not on HAART (AOR 0.42, CI 0.22, 0.80). In conclusion, a history of less severe immunosuppression appeared to reduce risk of CIN2+ detection, but current CD4+ count was significant only in non-HAART users. The association of CIN2+ with hormonal contraception should be explored more in prospective studies designed to better control for confounding factors.

## Introduction

HIV and cervical cancer are intersecting epidemics in sub-Saharan Africa, where three quarters of the world's HIV-infected women live and cervical cancer is the second most common cause of cancer-related death in women.[1, 2] HIV-infection increases a woman's

Corresponding Author: Megan J. Huchko, MD, MPH University of California, San Francisco 50 Beale St, Ste 1200 San Francisco, CA 94105 .

**Competing Interests:** The authors have no competing interests to declare.

risk of human papillomavirus (HPV) infection as well as persistence and development of HPV-related precancerous and cancerous lesions.[3, 4] These risks increase as HIV-related immunosuppression worsens.[5] Access to highly active antiretroviral therapy (HAART) in sub-Saharan Africa has dramatically increased over the past decade, improving life expectancy for millions of women living with HIV.[6] However, the impact of HAART on the development of cervical precancer and cancer remains unclear.[7, 8] As a result, there are substantially more women living longer with HIV who remain at higher risk for cervical disease.

Despite the number of HIV-infected women at risk for cervical cancer in sub-Saharan African countries, the magnitude of the problem has not been well described due to a lack of population-based screening programs. Estimates of cervical intraepithelial neoplasia 2 or greater (CIN2+) among HIV-infected women in this region vary widely in published reports, from 7% to 79%. [9-12] Some estimates are based on cytology or visual inspection with acetic acid (VIA) results without colposcopic or biopsy confirmation, [13, 14] while others give aggregate risk for any CIN, rather than CIN2+, the immediate cervical cancer precursor targeted for outpatient treatment. [15] Studies looking at factors associated with CIN2+ prevalence face the additional challenge of defining the longitudinal relationship between various demographic and HIV-related characteristics, especially HAART use and its impact on CD4+ count.

Accurate estimates of CIN2+ prevalence are essential for program planning, including protocol design, staff needs, costs, and prediction of population impact. Identification of factors that may put HIV-infected women at increased risk for the development of CIN2+ are also important, as they may potentially impact clinical care decisions regarding both HIV-treatment and priorities for cervical cancer screening. We sought to measure the prevalence and predictors of newly diagnosed CIN2+ in a previously unscreened cohort of HIV-infected women in Kenya.

## Methods

### Study Design

Cervical cancer screening was offered to women enrolled in care at two HIV clinics supported by the Family AIDS Care and Education Services (FACES) in Kisumu, Kenya starting in October 2007, where previously no organized screening program had been in place.[16] At the main clinical facility, non-pregnant women aged 23 and older were invited for screening with VIA. Those with a positive VIA underwent immediate colposcopy with biopsy for confirmation of any lesions suspicious for CIN2+. Two satellite sites fed into the main clinical facility. At one satellite clinical research site, women underwent cytology screening and were referred for cervical cancer screening with the above protocol if they had results of atypical squamous cells of undetermined significance (ASCUS) or greater. At the second satellite site, women with a positive VIA had an immediate follow-up visual inspection with Lugol's iodine (VILI). Women with a positive result on both VIA and VILI were referred for colposcopy at the main clinical facility. Clinicians biopsied areas suggestive of CIN2+ by standard colposcopic criteria or if the colposcopy was unsatisfactory.[17]

Final diagnoses were based on the colposcopy and histopathology results. Results were categorized as negative (normal squamous epithelium), inflammation, CIN1, CIN2, CIN3, or invasive cancer. For specimens with more than one diagnosis, the participant outcome was defined as the most severe diagnosis. Women with CIN2+ confirmed on biopsy were offered treatment with Loop Electrosurgical Excision Procedure (LEEP) in the clinic. For program planning, lesions were assessed at the time of LEEP to determine whether they would be amenable to treatment with cryotherapy. Clinicians assessed cervical architecture, size of lesion or extension into the endocervical canal. All LEEP specimens were sent for pathological evaluation. Decisions on follow-up or additional treatment were based on the most severe diagnosis at the time of biopsy or LEEP. LEEP was performed on "coag" for optimal hemostasis, so specimen margins were not assessed.

Approval for this analysis of program data was obtained from the Committee for Human Subjects Research at the University of California, San Francisco and the Ethical Review Committee at the Kenya Medical Research Institute.

## Statistical Methods

Information from the cervical cancer screening visit was collected on a paper form and entered into an Access database (Microsoft, Redmond, WA). Demographic variables and clinical information were obtained from enrollment in care until date of screening through the electronic medical record system (OpenMRS). Due to very small numbers and poor performance of visual screening as a diagnostic tool among older women, analyses were limited to women under 50 in order to accurately assess clinical and demographic predictors.[18] To assess sensitivity of the results to further age effects, we repeated analyses within women up to 40. To address missingness in demographic variables (ranging from 0.6% for duration in HIV care to 77.1% for gravida), we performed multiple imputation using chained equations with logistic regression, ordinal regression and predictive mean matching. Observations with missing biopsy results and unknown duration of HIV clinical care were excluded in imputations and subsequent analyses. We imputed 80 datasets and assessed plausibility of the imputed values using diagnostic plots. Imputation was performed for the full data and within strata of HAART for the stratified analyses.

We tested initial predictors of CIN2+ using logistic regression, controlling for age (in years and age squared to account for non-linear relationship) and screening site. To explore the relationship between HIV-related variables and CIN2+ through multivariable models, the predictors were divided into two groups. Trends in odds ratios across categorical predictors were assessed using the generalized least squares test for trend. In order to capture disease severity unmediated by HAART use, we looked at CD4+ count nadir and duration in care prior to HAART initiation or prior to screening for those women not on HAART. With the second group of variables, we sought to describe current health status by looking at CD4+ count at screening and duration HAART for those on HAART. Two sets of multivariable models were constructed to look at these HIV-related predictors separately; both included contraceptive use reported within 90 days of the screening visit and predictors that were significant in the analyses adjusted for age and site. In the model including current health status variables, participants were stratified by HAART use because of the complex

relationship between HAART and the clinical and immunological variables. All statistical analyses were performed in Stata 12 (StataCorp LP, College Station, Texas).

## Results

Between October 3, 2007 and October 22, 2010, 3241 women between 23 and 50 were screened for cervical cancer at three FACES-supported clinics in Kisumu. An additional 224 women over 50 were screened but are excluded from this analysis due to age criteria. Among the 2,208 women (68%) screened with VIA followed by colposcopy at the main clinical facility, 22 (0.8%) had been referred for screening based on abnormal cytology results. The remaining 1,033 (31.8%) were screened using VIA/VILI at a peripheral site, with referral to the main facility for colposcopy. The median age was 32.8 (interquartile range (IQR): 28.5-38.6) years, 53.3% were either married or living with a partner and 34.4% were not using a non-barrier method of contraception. The median CD4+ count at the time of screening was 356 cells/$mm^3$ (IQR: 218-530); median CD4+ count nadir while enrolled in care was 291 cells/$mm^3$ (IQR: 173-444). Forty eight percent of women had WHO 1 or 2 stage disease, and 50.1% were on HAART.

Eight hundred and fourteen colposcopies were performed for either a positive VIA alone, or a positive VIA followed by positive VILI. Only 16 (2.0%) of women had unsatisfactory colposcopy. Among the women undergoing colposcopy, 544 (66.8%) had at least one site biopsied for suspicion of CIN2+ or unsatisfactory colposcopy. The most common abnormal colposcopic findings were aceto-white (724, 88.9%) or iodine-yellow (534, 66%) areas, followed by less common findings of mucosal bleeding (44, 5.4%), punctation (29, 3.6%), mosaicism (13, 1.6%) and atypical vessels (7, 0.9%). Pathology results were available for 488 (89.7%) of the women who had a biopsy performed during colposcopic evaluation. Of these, 287 (58.8%) were diagnosed with CIN2+ reflecting an overall disease prevalence in this population of 8.8%. This group included nine women with a histologic diagnosis of invasive squamous cell carcinoma, reflective of 0.3% prevalence of cervical cancer in this population. Findings of abnormal vasculature on colposcopy (punctation, mosaicism or atypical vessels) did not significantly increase the odds of CIN2+ on biopsy (OR 1.14, 95% CI 0.55-2.37). The remainder of the biopsies showed inflammation (75, 15.4%), CIN1 (58, 11.9%), squamous metaplasia/normal tissues (47, 9.6%) or were unsatisfactory for evaluation (21, 4.3%).

Two hundred and one (67%) women with CIN2+ underwent a LEEP at FACES. At the time of LEEP, 16 (8.0%) had lesions > 2.5cm, 32 (15.9%) had lesions that could not be completely visualized due to extension into the endocervix and 5 (2.5%) had both characteristics. Final LEEP pathology results were available for 145 (72.1%) women. While 133 (92%) had CIN2+ on their LEEP specimen, agreeing with their original pathology, 11 (8%) had less severe lesions, including CIN1, cervicitis and normal squamous epithelium, and one (0.7%) had invasive squamous cell carcinoma.

On analysis controlling for age and screening site, women diagnosed with CIN2+ were significantly younger, had fewer prior pregnancies, were more likely to have used a progesterone implant or combined oral contraceptives and, among those on HAART, had

been on HAART for a shorter period of time (Table 1). Higher CD4+ count at screening was associated with lower odds of CIN2+ diagnosis, with a significant trend across categories (p=0.048). In the multivariable model (Model 1) of variables reflective of disease severity, CD4+ count nadir greater than 500 cells/mm$^3$ was associated with a decreased odds of CIN2+ (AOR 0.61, 95% CI 0.38-0.97) compared to under 200 cells/mm$^3$. In the multivariable model (Model 2) that included HIV-related variables reflective of current health status and stratified by HAART status, among HAART-naïve women, CD4+ count over 500 cells/mm$^3$ at the time of screening was associated with reduced odds of CIN2+ detection (AOR 0.42, 95% CI 0.22-0.80). Recent CD4+ count showed no association with CIN2+ in women on HAART, although duration of HAART had a small protective association (AOR 0.98 0.95-1.00). Combined oral contraceptives remained significantly associated with detection of CIN2+ in both models (AOR 1.72, 95% CI 1.08-2.73 among HAART naïve and AOR 1.84, 95% CI 1.20 - 2.82 in those on HAART), while the association of progesterone implant use with increased odds of detecting CIN2+ appeared to be driven by women not on HAART (AOR 9.43, 95% CI 2.85-31.20). Models limited to women up to age 40 accorded with the results presented (not shown). The models using imputed data, adjusted for age, site, gravidity, partner status and education were not significantly different from the models with missing data (not shown).

## Discussion

In this paper, we present data from a large cohort of HIV-infected women undergoing cervical cancer screening in a real-world clinical setting. In our program, 9% of women who underwent screening were diagnosed with CIN2+, including nine (0.3%) women with invasive cervical cancer. Our rate of disease detection was lower what has been reported among other cohorts of HIV-infected women in Africa, including a recent study out of Nairobi,[9-12] but still represents a significant proportion of the clinic population that would benefit from screening and treatment to prevent invasive cancer.

Studies in various settings have shown CIN2+ to be related to HIV-induced immunosuppression.[4, 19] The role and timing of HAART in mediating this relationship has been difficult to study and remains unclear.[20, 21] Various methods have been employed to characterize the long-term impact of pre-treatment immunosuppression among women on HAART, but experts disagree on the optimal way to measure the relative influence of clinical factors over time on the development of cervical dysplasia. A single CD4+ count at the time of screening is difficult to interpret among HAART users, as it may represent immune-recovery after development of CIN. Past studies have used CD4+ cell count at time of HIV diagnosis, CD4+ cell-count nadir and time since AIDS diagnosis as static proxy measures for disease severity in the era of HAART.[9, 22] None have shown a consistent association with CIN2+ among women on HAART, and in fact have made it difficult to conclusively determine that women on HAART are at lower risk of cervical dysplasia and cancer. [7, 19] Because of the complex interaction between HAART and other markers of immunosuppression, we explored several proxies of HIV disease progression before and after HAART initiation, including duration of time in care prior to HAART initiation, current CD4+ count (at cervical cancer screening) and CD4+ nadir. The results suggest a potential protective effect of higher CD4+ count nadir prior to HAART initiation, of higher

recent CD4+ count among HAART-naïve women, and of longer duration of HAART among those on treatment, although the latter relationship showed only borderline significance. We intend to study this cohort longitudinally to better understand the interaction between HAART, immune status and the development and recurrence of CIN2+.

Another interesting finding from this cohort was the association between recent use of hormonal contraceptives (combined oral and progesterone implants) and detection of CIN2+. Previous studies have shown mixed results when assessing this question, and have not, to our knowledge, been performed in HIV-infected cohorts. [23, 24] Cross-sectional and retrospective studies looking at the relationship between CIN2+ and hormonal contraception, including this one, are limited by measured and unmeasured confounding. In addition, we only asked about contraceptive use within the past 90 days, which likely introduced non-differential misspecification into the results. While we cannot draw any conclusions, there is recent evidence that suggests a plausible biological mechanism to explain the relationship between hormonal contraceptive use and development of cervical dysplasia.[25] Given the widespread use of contraception and relatively high rate of CIN2+ in HIV-infected women, further prospective studies of this relationship are warranted.

This study is important because it is one of the first presentations of program data from cervical cancer screening within an HIV care and treatment program in sub-Saharan Africa. However, this study had several limitations. As these were data collected in a program setting, we were limited on the quality and completeness of some of the variables, reflective of both data management and clinical loss to follow-up. We performed data quality and consistency checks on the demographic and clinical variables, and used multiple imputation to address the missing data. The overall congruence of the imputed and complete case analyses suggest that the missingness was random. In addition, we were limited to outcomes collected for clinical care. Specifically, it would be interesting to see HPV distribution and contribution to disease in this population, however HPV testing was not part of the clinical protocol.

Cervical cancer remains a significant public health threat in many LMICs, especially among women living with HIV. Our experience screening women enrolled in an HIV care and treatment clinic shows that a relatively large number of women have precancerous lesions and are at risk for invasive cervical cancer. Given this high prevalence, HIV care and treatment programs would be efficient sites to screen and treat this population at high risk for cervical disease. Coupling screening modalities with effective treatment of precancerous lesions has the potential to positively impact a significant proportion of HIV-infected women in care.

## Acknowledgments

**Financial Disclosure:** This project was supported by an unrestricted grant from an anonymous donor. Dr. Huchko was supported by the National Center for Research Resources, the National Center for Advancing Translational Sciences, and the Office of the Director, National Institutes of Health, through UCSF-CTSI Grant Number KL2 RR024130. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Abbreviations

| | |
|---|---|
| **CIN** | cervical intraepithelial neoplasia |
| **HAART** | highly active antiretroviral therapy |
| **HIV** | human immunodeficiency virus |
| **HPV** | human papillomavirus |
| **LEEP** | loop electrosurgical excision procedure |
| **VIA** | visual inspection with acetic acid |
| **VILI** | visual inspection with lugol's iodine |

## References


1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer. Journal international du cancer. 2010; 127:2893–917. [PubMed: 21351269]
2. UNAIDS. Global Report: UNAIDS Report on the Global AIDS Epidemic 2010. 2010
3. De Vuyst H, Gichangi P, Estambale B, Njuguna E, Franceschi S, Temmerman M. Human papillomavirus types in women with invasive cervical carcinoma by HIV status in Kenya. International journal of cancer. Journal international du cancer. 2008; 122:244–6. [PubMed: 17764116]
4. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J. Natl. Cancer Inst. 2009; 101:1120–30. [PubMed: 19648510]
5. Denny L, Boa R, Williamson AL, Allan B, Hardie D, Stan R, Myer L. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. Obstet and Gynecol. 2008; 111:1380–7.
6. World Health Organization. Global HIV/AIDS response: Progress report 2011. Key facts on HIV epidemic and progress in regions and countries in 2010. 2011 sub-Saharan Africa.
7. Bratcher LF, Sahasrabuddhe VV. The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research. Infect Agent Cancer. 2010; 5:8. [PubMed: 20462441]
8. Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, Bouchardy C, Dehler S, Jundt G, Ess S, Bordoni A, Konzelmann I, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br. J. Cancer. 2010; 103:416–22. [PubMed: 20588274]
9. De Vuyst H, Mugo NR, Chung MH, McKenzie KP, Nyongesa-Malava E, Tenet V, Njoroge JW, Sakr SR, Meijer CM, Snijders PJ, Rana FS, Franceschi S. Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya. Br. J. Cancer. 2012
10. Parham GP, Sahasrabuddhe VV, Mwanahamuntu MH, Shepherd BE, Hicks ML, Stringer EM, Vermund SH. Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV-infected women in Lusaka, Zambia. Gynecol. Oncol. 2006; 103:1017–22. [PubMed: 16875716]
11. Firnhaber C, Mayisela N, Mao L, Williams S, Swarts A, Faesen M, Levin S, Michelow P, Omar T, Hudgens MG, Williamson AL, Allan B, et al. Validation of Cervical Cancer Screening Methods in HIV Positive Women from Johannesburg South Africa. PLoS One. 2013; 8:e53494. [PubMed: 23326441]
12. Mwanahamuntu MH, Sahasrabuddhe VV, Kapambwe S, Pfaendler KS, Chibwesha C, Mkumba G, Mudenda V, Hicks ML, Vermund SH, Stringer JS, Parham GP. Advancing cervical cancer prevention initiatives in resource-constrained settings: insights from the Cervical Cancer Prevention Program in Zambia. PLoS Med. 2011; 8:e1001032. [PubMed: 21610859]
13. Moon TD, Silva-Matos C, Cordoso A, Baptista AJ, Sidat M, Vermund SH. Implementation of cervical cancer screening using visual inspection with acetic acid in rural Mozambique: successes

and challenges using HIV care and treatment programme investments in Zambezia Province. J Int AIDS Soc. 2012; 15:17406. [PubMed: 22713260]

14. Akinwuntan AL, Adesina OA, Okolo CA, Oluwasola OA, Oladokun A, Ifemeje AA, Adewole IF. Correlation of cervical cytology and visual inspection with acetic acid in HIV-positive women. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2008; 28:638–41. [PubMed: 19003664]
15. Memiah P, Mbuthia W, Kiiru G, Agbor S, Odhiambo F, Ojoo S, Biadgilign S. Prevalence and Risk Factors Associated with Precancerous Cervical Cancer Lesions among HIV-Infected Women in Resource-Limited Settings. AIDS Res Treat. 2012; 2012:953743. [PubMed: 22548156]
16. Lewis Kulzer J, Penner JA, Marima R, Oyaro P, Oyanga AO, Shade SB, Blat CC, Nyabiage L, Mwachari CW, Muttai HC, Bukusi EA, Cohen CR. Family model of HIV care and treatment: a retrospective study in Kenya. J Int AIDS Soc. 2012; 15:8. [PubMed: 22353553]
17. Walker P, Dexeus S, De Palo G, Barrasso R, Campion M, Girardi F, Jakob C, Roy M. International terminology of colposcopy: an updated report from the International Federation for Cervical Pathology and Colposcopy. Obstet. Gynecol. 2003; 101:175–7. [PubMed: 12517664]
18. Cremer M, Conlisk E, Maza M, Bullard K, Peralta E, Siedhoff M, Alonzo T, Felix J. Adequacy of visual inspection with acetic acid in women of advancing age. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2011; 113:68–71. [PubMed: 21272884]
19. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J. Natl. Cancer Inst. 2007; 99:962–72. [PubMed: 17565153]
20. Heard I, Potard V, Costagliola D. Limited impact of immunosuppression and HAART on the incidence of cervical squamous intraepithelial lesions in HIV-positive women. Antivir Ther. 2006; 11:1091–6. [PubMed: 17302379]
21. Adler DH, Kakinami L, Modisenyane T, Tshabangu N, Mohapi L, De Bruyn G, Martinson NA, Omar T. Increased regression and decreased incidence of human papillomavirus-related cervical lesions among HIV-infected women on HAART. AIDS. 2012; 26:1645–52. [PubMed: 22555167]
22. Soncini E, Zoncada A, Condemi V, Antoni AD, Bocchialini E, Soregotti P. Reduction of the risk of cervical intraepithelial neoplasia in HIV-infected women treated with highly active antiretroviral therapy. Acta Biomed. 2007; 78:36–40. [PubMed: 17687815]
23. Longatto-Filho A, Hammes LS, Sarian LO, Roteli-Martins C, Derchain SF, Erzen M, Branca M, Tatti S, Naud P, de Matos JC, Gontijo R, Maeda MY, et al. Hormonal contraceptives and the length of their use are not independent risk factors for high-risk HPV infections or high-grade CIN. Gynecol. Obstet. Invest. 2011; 71:93–103. [PubMed: 21150159]
24. Roset Bahmanyar E, Paavonen J, Naud P, Salmeron J, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Jaisamrarn U, Limson GA, et al. Prevalence and risk factors for cervical HPV infection and abnormalities in young adult women at enrolment in the multinational PATRICIA trial. Gynecol. Oncol. 2012; 127:440–50. [PubMed: 22940493]
25. Samir R, Asplund A, Tot T, Pekar G, Hellberg D. Oral contraceptive and progestin-only use correlates to tissue tumor marker expression in women with cervical intraepithelial neoplasia. Contraception. 2012; 85:288–93. [PubMed: 22067748]

**Novelty**

This paper highlights findings from a large, clinic-based cohort of HIV-infected women undergoing primary cervical cancer screening. We found an association between current CD4+ count and cervical dysplasia only among women not on HAART. Among HAART users, it appears that pre-treatment nadir may be more predictive. Among all women, regardless of HAART use, hormonal contraceptives were associated with increased detection of cervical dysplasia, while progesterone implants increased risk only among HAART non-users.

## Table 1

Demographic characteristics at the time of cervical cancer screening, by CIN2+ status[1]

| | N | No CIN2+ (2898) N (%) or median (IQR) | CIN2+ (287) N (%) or median (IQR) | AOR[2] (95% CI) | p-value[3] |
|---|---|---|---|---|---|
| Age at screening | 3185 | 32.9 (28.5 – 38.9) | 31.2 (28.0 – 36.1) | 0.97 (0.95, 0.99) | |
| Age (tertiles) | | | | | |
| 23-30 | | 1168 (40.3%) | 137 (47.7%) | 1.00 (REF) | p<0.001 |
| 31-40 | | 1148 (43.1%) | 119 (41.5%) | 0.83 (0.64, 1.07) | |
| 41 or older | | 482 (16.6%) | 31 (10.8) | 0.55 (0.37, 0.83) | |
| Screening site | 3185 | | | | |
| Lumumba | | 1958 (67.6%) | 195 (67.9%) | 1.00 (REF) | |
| Kisumu District Hospital | | 930 (32.1%) | 84 (29.3%) | 0.91 (0.70, 1.20) | |
| CIS Referral[4] | | 10 (0.4%) | 8 (2.8%) | 7.95 (3.08, 20.49) | |
| Highest education level | 1446 | | | | |
| None / some primary | | 714 (57.1%) | 108 (55.1%) | 1.00 (REF) | p=0.838 |
| Some secondary | | 417 (33.6%) | 70 (35.7%) | 1.08 (0.78, 1.50) | |
| Some college / technical | | 119 (9.4%) | 18 (9.2%) | 0.97 (0.57, 1.67) | |
| Has current partner[5] | 1419 | 667 (53.5%) | 87 (52.7%) | 0.84 (0.60, 1.18) | |
| **Reproductive History** | | | | | |
| Gravidity | 728 | 3 (2 - 4) | 3 (2 - 4) | 0.95 (0.85, 1.07) | |
| Oral contraceptives | 2719 | 554 (22.6%) | 95 (35.6%) | 1.79 (1.37, 2.36) | |
| Injectable (Depo Provera™) | 2719 | 424 (17.2%) | 59 (21.4%) | 1.32 (0.96, 1.82) | |
| Implant (Jadelle™) | 2719 | 20 (0.8%) | 11 (4.1%) | 4.69 (2.22, 9.94) | |
| Intrauterine Device in Place | 2719 | 20 (0.8%) | 3 (1.1%) | 1.38 (0.40, 4.68) | |
| **HIV-Related Characteristics** | | | | | |
| Duration HIV care at FACES pre-HAART (months)* | 3167 | 1.6 (0 – 12.5) | 1.4 (0 – 9.8) | 0.99 (0.98, 1.00) | |
| Time since first positive HIV test (months) | 1037 | 8.0 (2.9 – 16.8) | 8.0 (2.1 – 16.6) | 0.98 (0.96,1.00) | |
| Most advanced WHO Stage | 3061 | | | | |
| Stage I | | 616 (22.1%) | 66 (23.9%) | 0.98 (0.64, 1.52) | p=0.827 |
| Stage II | | 723 (26.0%) | 70 (25.0%) | 0.92 (0.60, 1.41) | |
| Stage III | | 1083 (38.9%) | 105 (38.0%) | 1.00 (0.67, 1.49) | |
| Stage IV | | 363 (13.0%) | 36 (13.0%) | 1.00 (REF) | |
| CD4+ count at screening | 2025 | | | | |
| <200 | | 391 (21.9%) | 59 (24.8%) | 1.00 (REF) | p=0.048 |
| 201-350 | | 459 (25.6%) | 73 (30.7%) | 1.03 (0.71, 1.50) | |
| 351-500 | | 408 (22.8%) | 49 (20.6%) | 0.80 (0.54, 1.21) | |
| >500 | | 529 (29.6%) | 57 (24.0%) | 0.69 (0.47, 1.02) | |

| | N | No CIN2+ (2898) N (%) or median (IQR) | CIN2+ (287) N (%) or median (IQR) | AOR[2] (95% CI) | p-value[3] |
|---|---|---|---|---|---|
| CD4+ count nadir pre-screening | 2612 | | | | |
| <200 | | 696 (29.7%) | 86 (33.1%) | 1.00 (REF) | p=0.059 |
| 201-350 | | 731 (31.2%) | 87 (33.5%) | 0.93 (0.68, 1.28) | |
| 351-500 | | 472 (20.1%) | 40 (15.4%) | 0.65 (0.43, 0.96) | |
| >500 | | 446 (19.0%) | 47 (18.1%) | 0.77 (0.53, 1.13) | |
| On HAART[6] | 3185 | 1462 (50.5%) | 142 (49.5%) | 1.01 (0.79, 1.30) | |
| Duration HAART (months) | 1604 | 8.2 (2.8 – 13.5) | 6.0 (2.1 – 11.9) | 0.98 (0.95, 1.01) | |

[1] Results in this table represent complete, non-imputed data, which varied by predictor. With the exceptions of injectable family planning and time since HIV test, significant findings in complete data are identical in imputed data.

[2] Age adjusted for site of screening; site adjusted for age. Remaining predictors were adjusted for both age and site

[3] Chi-square for trend across odds ratios

[4] These women were referred for screening after abnormal cytology results

[5] Women who reported living with a partner (married or not) were classified as having a current partner

[6] Defined as use of any three-drug HAART therapy prescribed for clinical indications; excludes use of anti-retroviral therapy for prevention of maternal-to-child-transmission

**Table 2**

Multivariate models of predictors of CIN2+ adjusted for age and site

| Predictors | Model 1 | Model 2 | |
|---|---|---|---|
| | | Not on HAART | On HAART |
| | AOR (95% CI) | AOR (95% CI) | AOR (95% CI) |
| Months in HIV care[1] | 0.98 (0.97, 0.99) | | |
| Months on HAART | | N/A | 0.98 (0.95, 1.01) |
| CD4+ count[2] | | | |
| <200 | 1.00 (REF) | 1.00 (REF) | 1.00 (REF) |
| 201-350 | 0.94 (0.66, 1.34) | 1.00 (0.54, 1.85) | 0.99 (0.60, 1.63) |
| 351-500 | 0.85 (0.55, 1.30) | 0.59 (0.31, 1.15) | 0.85 (0.47, 1.52) |
| >500 | 0.61 (0.38, 0.97) | 0.42 (0.22, 0.80) | 0.95 (0.54, 1.67) |
| Combined Oral Contraceptive [3] | 1.87 (1.35, 2.57) | 1.72 (1.08, 2.73) | 1.84 (1.20, 2.82) |
| Injectable (Depo Provera) [3] | 1.16 (0.78, 1.70) | 1.55 (0.89, 2.70) | 0.95 (0.58, 1.55) |
| Implant (Jadelle) [3] | 4.46 (1.98, 10.05) | 9.43 (2.85, 31.20) | 2.34 (0.62, 8.87) |
| Intrauterine Device in place | 1.93 (0.54, 6.92) | 1.06 (0.12, 9.18) | 2.88 (0.56, 14.83) |

[1]Months in HIV care prior to HAART initiation for women on HAART, overall for women not on HAART

[2]For Model 1 (all women, using predictors reflective of disease severity), CD4+ count was overall nadir or nadir prior to HAART initiation. For Model 2 (stratified by HAART use, using predictors reflective of current HIV status), CD4+ count is from date of screening visit

[3]Contraception use reported within 90 days of screening visit