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Persistence and clearance of high-risk human papillomavirus and cervical dysplasia at one year in women living with human immunodeficiency virus: a prospective cohort study

Rebecca Luckett, MD MPH[1,2], **Helena Painter, MBChB**[2], **Michele R Hacker, ScD**[1,3], **Boikhutso Simon**[2], **Alexander Seiphetlheng, RN BPH**[4], **Adrienne Erlinger, MPH**[1], **Cortney Eakin, MD**[2,5], **Sikhulile Moyo, MSc, PhD**[2,3], **Lynnette Tumwine Kyokunda, MD PhD**[6], **Katharine Esselen, MD MBA**[1,7], **Sarah Feldman, MD MPH**[7,8], **Chelsea Morroni, MD PhD**[2,9], **Doreen Ramogola-Masire, MD, MPH**[10]

[1]Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, USA

[2]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana

[3]Harvard T.H. Chan School of Public Health, Boston, USA

[4]Department of Obstetrics and Gynaecology, Princess Marina Hospital, Gaborone, Botswana

[5]Department of Obstetrics and Gynecology, Creighton University School of Medicine-Phoenix, Phoenix, USA

Corresponding Author: Rebecca Luckett MD MPH, Beth Israel Deaconess Medical Center, Department of Obstetrics and Gynecology, Kirstein, 3rd floor, 330 Brookline Avenue, Boston, MA 02215, Phone: +267 7433 3773, rluckett@aphmfp.org.

Contribution to Authorship

All authors have given final approval to the manuscript submitted. Each author contributed as follows:
RL: Conception, planning, carrying out, analysing and writing up the study.
HP: Carrying out, analysing and writing up the study.
MH: Conception, planning, analysing and writing up the study.
SB: Carrying out and writing up the study.
AS: Carrying out and writing up the study.
AE: Carrying out, analysing and writing up the study.
CE: Carrying out and writing up the study.
SM: Planning, carrying out, analysing and writing up the study.
LT: Carrying out and writing up the study.
KE: Conception, planning, analysing and writing up the study.
SF: Conception, planning, analysing and writing up the study.
CM: Conception, analysing and writing up the study.
DRM: Conception, planning, carrying out, analysing and writing up the study.

Clinical Trial Registration

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Disclosure of Interests

The authors do not have any relevant financial, personal, political, intellectual or religious conflicts of interest to disclose.

Details of Ethics Approvals

The institutional review boards of the following institutions approved this study with accompanying details:
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Authors' Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Proposals should be directed to rluckett@bidmc.harvard.edu. To gain access, data requestors will need to sign a data access agreement.

[6]Department of Pathology, University of Botswana, Gaborone, Botswana

[7]Harvard Medical School, Boston, USA

[8]Brigham and Women's Hospital, Boston, USA

[9]Department of International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK

[10]Department of Obstetrics and Gynaecology, University of Botswana, Gaborone, Botswana

Abstract

Objective: Evaluate one-year outcomes of cervical cancer screening and treatment using primary high-risk human papillomavirus (HPV) testing in women living with human immunodeficiency virus (HIV).

Design: Prospective cohort study

Setting: HIV treatment center in Botswana

Population: Women living with HIV

Methods: Participants underwent cervical cancer screening with high-risk HPV testing and triage evaluation at baseline and one-year follow-up. Excisional treatment was offered as indicated. Histopathology was the gold standard.

Main outcome measures: Persistence, clearance and incidence of high-risk HPV infection; and persistence, progression, regression, cure and incidence of cervical dysplasia.

Results: Among 300 women screened at baseline, 237 attended follow-up (79%). High-risk HPV positivity significantly reduced from 28% at baseline to 20% at one year (p=0.02). High-risk HPV persistence was 46% and clearance 54%; incidence was high at 9%. Prevalence of cervical intraepithelial neoplasia grade (CIN) 2 or higher was most common in participants with incident high-risk HPV (53%). CIN2 or higher was also common in those with persistent high-risk HPV (32%) and even in those who cleared high-risk HPV (30%). 40% of high-risk HPV positive participants at baseline with <CIN2 progressed to CIN2 or higher at follow-up.

Conclusion: The high incidence of high-risk HPV and high-grade cervical dysplasia in women living with HIV after one round of high-risk HPV-based screening and treatment raises concern about the rate of progression of high-risk HPV infection to dysplasia. Persistent disease is common. Caution in spacing cervical cancer screening intervals using high-risk HPV testing in women living with HIV is warranted.

Tweetable Abstract:

High incidence and persistence of HPV and CIN2+ in women living with HIV one year after screening and treatment.

Keywords

Cervical cancer screening; LMICs; HIV; HPV; HPV persistence; dysplasia

Introduction:

Cervical cancer is the leading cause of cancer death in women in sub-Saharan Africa.[1] High-risk human papilloma virus (HPV) testing provides an opportunity for increased access to more sensitive screening for cervical cancer, and has particularly high impact potential in low- and middle-income countries which are disproportionately affected by cervical cancer.[2] While cervical cancer screening guidelines in high-income countries have increasingly incorporated primary high-risk HPV testing, HPV testing has been beyond reach for most low- and middle-income countries.[3,4,5,6,7]

Incorporating high-risk HPV testing into cervical cancer screening guidelines in sub-Saharan Africa is complicated by the co-existing high burden of human immunodeficiency virus (HIV).[8,9] Cervical cancer screening using primary high-risk HPV testing in women living with HIV is not standard in international professional society guidelines.[10,11,12] Women living with HIV have higher prevalence, co-infection, persistence, and reactivation of high-risk HPV.[13,14,15,16] The biology of high-risk HPV clearance, incidence, and associated progression and regression of cervical dysplasia in the setting of HIV remains unclear.[17] Screening intervals for women living with HIV and appropriate triage of positive high-risk HPV results remain areas of uncertainty.[18,19]

Botswana has one of the world's highest population prevalences of HIV.[20] The national HIV programme has been a leader in Africa in achieving "90-90-90" targets, with antiretroviral therapy coverage of nearly 90% of the known HIV-infected population and viral suppression in 88% of those on treatment.[21] Cervical cancer screening has been available in the public sector for three decades, including introduction of see-and-treat services in 2012 and small-scale HPV testing in 2019.[22,23,24] Despite steadily improving access, however, only 52% of women aged 30 to 49 report ever having undergone cervical cancer screening and cervical cancer death rates have remained stagnant.[25,26] HPV vaccination was introduced in 2015 and initially achieved high coverage in 9 to 13 year-old girls; the program has since met access and financing challenges. Increased access to effective screening remains a national and regional priority. Understanding the role of highly effective high-risk HPV-based screening strategies in women living with HIV is essential for progress on cervical cancer elimination.[27]

We evaluated one-year outcomes of cervical cancer screening and treatment using primary high-risk HPV testing in women living with HIV. We hypothesised that one round of primary high-risk HPV screening followed by triage evaluation and targeted treatment would reduce the prevalence of high-risk HPV and high-grade cervical dysplasia.

Methods:

We enrolled a prospective cohort of 300 women living with HIV and receiving care at the infectious disease care clinic at Princess Marina Hospital, the regional tertiary referral hospital in Gaborone, Botswana.

Baseline screening

At enrollment, study participants were screened for eligibility. Women living with HIV over the age of 24 were eligible for the study if they were not pregnant, had an intact uterus, and had no prior diagnosis of cervical cancer. After obtaining informed consent, participants answered a questionnaire with information on demographics, HIV treatment and cervical cancer screening history. We searched the electronic medical record for past cervical cancer screening results.

All participants underwent a speculum examination by a trained study staff, at which time two samples were collected from the cervix, one for HPV testing and the other for cervical cytology using Cervex-brushes®. After collection, the HPV sample was placed in PreservCyt® transport medium and cytology was prepared on-site by spreading cervical cells from from a Cervex-brush® onto a glass slide and applying spray fixative. HPV testing was performed using the Xpert® HPV Assay (Cepheid, Sunnyvale, CA) at the Botswana Harvard AIDS Institute Partnership. This assay tests for 14 high-risk HPV types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 and has demonstrated excellent performance.[28] Xpert® results were reported as HPV 16, HPV 18/45 and other high-risk HPV. Cytology slides were sent to the National Health Laboratory, and read by pathologists, who were blinded to the result of HPV testing, using the revised Bethesda classification.[29]

We referred all participants who tested positive for any high-risk HPV type to visual assessment, colposcopy and biopsy by providers who were blinded to the HPV result. Additionally, because there were no clinical guidelines for management of positive HPV results in Botswana at the time of study implementation, evaluation of cervical cytology was performed in all participants to ensure that the study setting also provided standard-of-care service according to the national cervical cancer screening guidelines. Accordingly, participants with negative HPV results who had a study cytology result of high-grade intraepithelial lesion (HSIL) or persistent atypical squamous cells of undetermined significance (ASC-US) or worse were referred to study colposcopy in accordance with the national screening algorithm.

At the time of the visual assessment and colposcopy visit, participants underwent a speculum examination of the cervix by a nurse trained in visual inspection with acetic acid. 5% acetic acid was applied to the cervix using a cotton swab and visual inspection was performed. The findings of the assessment were recorded by the nurse but no intervention was performed. A gynecologist then performed colposcopy, and all participants had tissue samples collected. If there was a visible lesion, a loop electrosurgical excision procedure (LEEP) was performed according to the see-and-treat national policy. If no lesion was visible, an endocervical curettage or a small endocervical excision was performed. Endocervical excision has developed as an alternative to endocervical curettage due to limited availability of quality endocervical currettes in this clinical setting. Any participant with cervical intraepithelial lesion (CIN) 2 or higher on endocervical curettage was recalled for an excision procedure. Women with histopathology of CIN3 with microinvasion or invasive cervical cancer were referred for further treatment. Outcomes of the baseline screening have been reported.[30]

Follow-up screening:

We offered follow-up to all participants in the cohort who had complete baseline screening results and had consented to future contact between 12 and 18 months, unless they were diagnosed with cervical cancer at baseline or had withdrawn from the study. Participants were screened for ongoing eligibility according to the criteria described for baseline screening. After obtaining informed consent, we administered a modified questionnaire to update demographic and HIV treatment information.

Follow-up participants underwent a speculum examination of the cervix with collection of specimens for HPV testing and cytology as described above, with the exception that HPV specimens were collected using an Abbott Cervi-Collect® specimen kit. HPV testing was performed using the Abbott RealTi*me*® high-risk HPV Assay (Abbott Laboratories, Abbott Park, Illinois) at the Botswana Harvard AIDS Institute Partnership Laboratory following manufacturer's instructions. The Abbott RealTi*me*® HPV assay tests for the same 14 high-risk HPV types as the Xpert® HPV Assay (Cepheid, Sunnyvale, CA) and has excellent performance.[31] Abbott results were reported slightly differently than Xpert®: HPV 16, HPV 18 and other high-risk HPV, where pooled high-risk HPV includes HPV 45.

The same criteria described for baseline screening were used for determination of need for visual assessment and colposcopy. In addition, we recalled participants who tested negative for high-risk HPV to colposcopy if they had a result of CIN 2 or 3 at baseline screening, abnormal pelvic examination or post-menopausal bleeding, in accordance with national guidelines. The same procedure was used for visual assessment and colposcopy as described for baseline screening.

The primary outcomes were persistence, clearance and incidence of high-risk HPV infection and persistence, progression, regression, cure and incidence of cervical dysplasia in women living with HIV at one-year follow-up. We evaluated persistence, clearance, and incidence for any high-risk HPV type, and specifically for HPV 16, HPV 18 and other high-risk HPV. For high-risk HPV, the following definitions applied by high-risk HPV type: persistence was a positive high-risk HPV result at baseline and follow-up (high-risk HPV *positive/positive*); clearance was a positive high-risk HPV result at baseline and a negative high-risk HPV result at follow-up (high-risk HPV *positive/negative*); and incidence was a negative high-risk HPV result at baseline and a positive high-risk HPV result at follow-up (high-risk HPV *negative/positive*). For cervical dysplasia, the following definitions applied: incidence was no or normal histopathologic diagnosis at baseline followed by an abnormal histopathologic diagnosis at follow-up; persistence was an abnormal histopathologic diagnosis at baseline and the same abnormal histopathologic diagnosis at follow-up; progression was an abnormal histopathologic diagnosis at baseline followed by a worse histopathologic diagnosis at follow-up; regression was an abnormal histopathologic diagnosis at baseline followed by a less severe or normal histopathologic diagnosis at follow-up without treatment with LEEP; cure was an abnormal histopathologic diagnosis at baseline followed by a less severe or normal histopathologic diagnosis at follow-up after treatment with LEEP at baseline. The impact of treatment with an excisional procedure at baseline on high-risk HPV clearance and persistence, and high-grade cervical dysplasia persistence and regression at follow-up was evaluated.

Data were entered into a REDCap database[32] by a designated research assistant, and accuracy of data entry was verified by a second study team member and the principal investigator. Descriptive statistics are presented as median [interquartile range] or proportion. We compared categorical variables with the chi-square or Fisher's exact test for unpaired data and McNemar's test for paired data; we compared continuous variables with the Wilcoxon rank-sum test. We considered two-sided p values <0.05 statistically significant and used SAS 9.4 (SAS Institute, Cary, North Carolina) for analyses. The sample size was powered for detecting an improvement in positive predictive value from 24% for high-risk HPV testing alone to 49% for the two-stage screening algorithms, based on the primary outcome for baseline screening.[29]

The institutional review boards of the Botswana Ministry of Health and Wellness, the University of Botswana, and Beth Israel Deaconess Medical Center approved this study. The ethics committee of Princess Marina Hospital also approved this study. No patient or public involvement took place in this study. Funding for this study was provided from the Harvard University Center for AIDS Research (NIH/NIAID 5P30AI060354-14 grant), the Shore Fellowship from the Department of Obstetrics and Gynecology at Beth Israel Deaconess Medical Center, and Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. The funders required external peer review for scientific quality. The funders had no role in the conduct of the study, data analysis or manuscript preparation.

Results:

There were 300 women in the baseline cohort, of whom 88 tested high-risk HPV positive and 212 tested high-risk HPV negative. A total of 237 (79%) participants from the cohort participated in follow-up, including 67 (76%) of the high-risk HPV positive and 170 (80%) of the high-risk HPV negative participants at baseline. Of the 63 participants who did not participate in follow-up, nine were ineligible for follow-up screening, four did not have complete baseline screening data, and 50 were contacted but declined participation. Participant follow-up visits were conducted from May 2019 to November 2019 and the median time to follow-up was 13 months [12 – 15 months] (Figure 1).

Demographic characteristics of follow-up participants

The 237 follow-up participants were classified into four groups based on their high-risk HPV test result at baseline and follow-up (e.g., *positive/positive, positive/negative, negative/positive, negative/negative*). Demographic characteristics were similar across the four groups (Table 1). The median age at follow-up was 45 years [41 – 51 years]. The majority of participants were single, had 1 to 3 children, and 1 to 5 lifetime sexual partners. The cohort had longstanding HIV infection (14 years) and all participants were on antiretroviral therapy both at baseline and follow-up. At baseline 4 (2%) participants had a CD4 count of < 200 cells/microliter, and 11 (5%) participants had a detectable viral load (≥400 copies/milliliter). At one year follow-up, 2 (1%) participants had a CD4 count of < 200 cells/microliter, and 3

(1%) participants had a detectable viral load (≥400 copies/milliliter). Baseline characteristics for the 63 women who did not participate in follow-up were similar to those who attended follow-up (data not shown).

High-risk HPV prevalence, persistence, clearance, and incidence

Of the 237 women living with HIV who returned for follow-up screening, 67 (28%) had a positive high-risk HPV result at baseline, of which 13 (5%) were HPV16, 14 (6%) were HPV18, and 49 (21%) were other high-risk HPV. Of these 67 participants, 45 (67%) underwent treatment with loop electrosurgical excision procedure (LEEP) at baseline.

At follow-up, 47 of 237 participants (20%) were high-risk HPV positive, which was significantly lower than the baseline positivity rate of 28% (p=0.006). Type specific positivity was also lower at follow-up for each of type 16, 18 and other high-risk HPV (3%, 1%, and 17%, respectively). Persistent high-risk HPV infection was found in 31 participants (46%) and clearance in 36 participants (54%). Thirty of the 45 (67%) participants who had LEEP cleared high-risk HPV while only 6 of the 22 (27%) participants not treated with LEEP cleared high-risk HPV (Table 2). Of note, two participants who were positive for one HPV type at baseline acquired an additional type of HPV at follow-up, eight participants who had coinfection at baseline only had one HPV type at follow-up, and one participant had HPV type switch.

Incident high-risk HPV infection during the year between screenings was high. Sixteen of the 170 (9%) participants who were high-risk HPV negative at baseline tested positive for high-risk HPV at follow-up. Incidence by type was 2%, 1%, and 8% for HPV16, HPV18, and other high-risk HPV types, respectively, with one incident co-infection.

Cervical dysplasia prevalence, persistence, regression, cure and incidence

As shown in Figure 1, colposcopy and biopsy were performed in 58 participants at follow-up, including 46 of the 47 participants who were high-risk HPV-positive at follow-up (one participant was ineligible for colposcopy due to pregnancy). Twelve participants who were high-risk HPV negative at follow-up underwent colposcopy per the study protocol detailed in Methods, including eight with CIN2 or higher at baseline, two with persistent low-grade cytology, one with a cervical abnormality on examination, and one with post-menopausal bleeding.

The baseline prevalence of CIN2 or higher in the cohort who attended follow-up was 8% (20 of 237 participants), while the follow-up prevalence of CIN2 or higher was 9% (22 of 237 participants). We compared sequential high-risk HPV results with one-year histopathologic diagnosis (Table 3). While the absolute numbers were small, we saw high rates of CIN2 or higher in all four groups: 8 of 15 *negative/positive* participants, 10 of 31 *positive/positive* participants, 3 of 10 *positive/negative* participants, and 1 of 2 *negative/negative* participants. Of note, a majority of the participants with negative baseline HPV results did not have histopathology results per study protocol.

Overall, the incidence of new high-grade histopathologic disease in participants with no, benign, or low-grade baseline histopathology at one-year follow-up was strikingly high.

Nine of 170 (5%) participants who were high-risk HPV negative at baseline had incident CIN2 or higher at one-year follow-up. Eight of the 20 (40%) participants who were high-risk HPV positive with benign histopathology or CIN1 at baseline progressed to CIN2 or higher at one-year follow-up (Table 4a).

Of the 20 participants with baseline CIN2 or higher, 2 did not have follow-up pathology results and therefore 18 were included in the analysis. Fifteen underwent LEEP at baseline and at follow-up only 2 had persistent CIN3, and 1 had CIN2 following CIN3 at baseline. Among the 3 participants who did not undergo LEEP at baseline, 2 had regression of CIN2 and 1 had regression from CIN3 to CIN2 (Table 4b, Figure 2). None of the 18 participants with CIN2 or CIN3 at baseline had progression of their cervical dysplasia.

Discussion

Main findings

Monitoring the impact of cervical cancer screening using primary high-risk HPV in women living with HIV is essential for establishing an evidence-based screening strategy. The high incidence of CIN2 or higher in women living with HIV one year after high-risk HPV-based screening and treatment is concerning. More than half of women living with HIV with incident high-risk HPV infection had high-grade dysplasia. Over a third of women living with HIV with persistent high-risk HPV had new incident high-grade dysplasia. Just over 5% of women living with HIV who had incident high-risk HPV at one year had co-existent high-grade dysplasia. All of these findings raise concern about the rate of progression of high-risk HPV infection to dysplasia in women living with HIV. Frequent screening at shorter intervals is critical, as widely spaced screening may result in missed opportunities for treatment and prevention of progression to cervical cancer.

Overall prevalence of high-risk HPV among women living with HIV was modestly but significantly reduced at one year, and treatment seemed to correlate with clearance of high-risk HPV. High rates of persistent and incident high-risk HPV infection in women living with HIV have been demonstrated even among those treated with LEEP.[33,34,35] Low rates of clearance (<25%) of high-risk HPV in women living with HIV has similarly been reported.[36] In these studies, various markers of immunocompetence and duration of HIV were associated with clearance, though antiretroviral therapy seemed to have a less clear effect.

Interpretation

Our incidence of CIN2 or higher in women living with HIV of 9% at follow-up is higher than seen in other settings. Incident CIN2 or higher in women living with HIV in sub-Saharan Africa and India who were high-risk HPV negative a year prior was only 2.1–2.3%; persistent high-risk HPV infection conferred greater risk of incident high-grade dysplasia.[37,38,39] It is unclear if the high incidence of high-grade dysplasia detected in our study at a relatively short-term follow-up portends a higher risk of progression to invasive cervical cancer, particularly given our higher rates of cure and regression of high-grade dysplasia in our study than previously reported in the literature on treatment

failure (25–40%) in women living with HIV.[40,41] It is possible that these incident high-grade dysplasia lesions may be transient, productive lesions as opposed to transforming lesions. Furthermore, Botswana's longstanding successful national antiretroviral therapy programme and test-and-treat policy for HIV may in part explain our higher rates of cure and regression.[42]

Eight cases of CIN2 or higher in participants with incident high-risk HPV at one-year follow-up is concerning. First, newly detected high-risk HPV could represent reactivation of dormant infection rather than incident infection, and may behave differently than truly incident high-risk HPV.[43] We did not assess participants' or their partners' sexual risk behaviors; concurrent sexual partnerships are common in Botswana (31%), which may affect risk.[21,44] Second, the biology of high-risk HPV in HIV infection may necessitate frequent high-risk HPV screening—as often as annually—to detect incident high-grade dysplasia early. Third, the baseline high-risk HPV test results in these participants may have been false negatives, suggesting sub-optimal test performance in our setting.

Strengths and limitations

Our study has several limitations. We used different platforms with slightly different results reporting for baseline and follow-up testing. Use of different platforms was pragmatic, as national high-risk HPV screening in Botswana will leverage the infrastruction of the successful HIV viral load testing programme which utilizes decentralized high-throughput polymerase chain reaction platforms. The study was designed assuming a high negative predictive value of high-risk HPV, however, the conclusions regarding incident cervical dysplasia at follow-up was limited by a lack of baseline histopathology data for participants who were high-risk HPV negative at baseline.

Our findings may not be generalizable to other populations of women living with HIV as our cohort is a population engaged in care, a relatively high median age and high rates of prior cervical cancer screening. While we are unable to evaluate the degree of immunosuppression on outcomes in our cohort because of overall high CD4 counts, high rates of viral suppression, and universal coverage with ART, our study may provide insights into screening in other populations of women living with HIV in the modern test and treat era and provide a reference for "best case scenario" of one-year cervical cancer screening endpoints in well-controlled HIV. Longer-term follow-up is necessary to provide meaningful histopathologic outcomes to guide implementation of HPV-based screening programs for women living with HIV. Finally, our cohort is too small to allow significant conclusions, and to appreciate significant effects on cervical dysplasia at one year by high-risk HPV type and LEEP margin status at baseline.

Conclusions

Incident high-risk HPV infection and dysplasia, as well as persistent disease, are common in women living with HIV, necessitating frequent screening. Further study in the sub-Saharan African setting may demonstrate the utility of a high-intensity initial screening period followed by spaced screening as has been shown in other settings.[45] The inclusion of rural populations in future studies both within Botswana and the region are essential, as is the

evaluation of the implementation of widescale self-swab HPV testing. On-going research in screening this at-risk population is essential to move us closer towards the elimination of cervical cancer.

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Reference

1. Arbyn M, Weiderpass E, Bruni L, de Sanjose S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health 2020;8(2):e191–e203. [PubMed: 31812369]
2. Sahasrabuddhe VV, Parham GP, Mwanahamuntu MH, Vermund SH. Cervical cancer prevention in low- and middle-income countries: feasible, affordable, essential. Cancer Prev Res 2012;5(1):11–7.
3. Denny L,Sankaranarayanan R, De Vuyst H, Kim J, Adefuye P, Alemany L, et al. Recommendations for Cervical Cancer Prevention in Sub-Saharan Africa. Vaccine 2013;31:F73–F74. [PubMed: 24331750]
4. U.S. Preventive services task force. Final recommendation statement cervical cancer screening. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/cervical-cancer-screening. Retrieved September 29, 2020.
5. Ronco G, Dillner J, Elfstrom KM, Tunesi S, Snijders P, Arbyn M, et al. , for the International HPV screening working group. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014;383:524–32. [PubMed: 24192252]
6. Sankaranarayanan R, Nene B, Shastri S, Jayant K, Muwonge R, Budukh A, et al. HPV Screening for cervical cancer in rural India. N Eng J Med 2009;360(14):1385–94.
7. Mayrand M, Duarte-Franco E, Rodrigues I, Walter S, Hanley J, Ferenczy A, et al. Human Papillomavirus DNA versus Papnicolaou screening tests for cervical cancer. N Eng J Med 2007;357(16):1579–1588.
8. Chibwesha C, Stringer J. Cervical cancer as a global concern. JAMA, 2019;322(16):1558–1560. [PubMed: 31638658]
9. Looker K, Ronn M, Brock P, Brisson M, Drolet M, Mayaud P, et al. Evidence of synergistic relationships between HIV and Human Papillomavirus (HPV): systematic reviews and met-analyses of longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status. J Int AIDS Soc 2018;21(6):e25110. [PubMed: 29873885]
10. American College of Obstetrians and Gynecologists. Practice Bulletin No. 167: Gynecologic care for women and adolescents with human immunodeficiency virus. Obstet Gynecol 2016;128(4):e89–e110. [PubMed: 27661659]
11. Waters L, Lord E, Mackie N, Melvin L, Ashby J, Babu C, et al. BHIVA/BASHH/FSRH guidelines for the sexual and reproductive health of people living with HIV. Available at: https://www.bhiva.org/file/zryuNVwnXcxMC/SRH-guidelines-for-consultation-2017.pdf. Retrieved March 14, 2020.
12. European AIDS Clinical Society. Cancer screening, Cancer screening methods, Cervical cancer. Available at: https://eacs.sanfordguide.com/prevention-non-infectious-co-morbidities/cancer-screening-methods. Retrieved 14 March 2020.
13. Castle PE, Varallo JE, Bertram MM, Ratshaa B, Kitheka M, Rammipi K. High-risk human papillovirus prevalence in self-collected cervicovaginal specimens from human immunodeficiency

virus (HIV)-negative women and women living with HIV living in Botswana. PLoS One 2020;15(2):e0229086. [PubMed: 32053659]

14. Sun XW, Kuhn L, Ellerbrock TV, Chiasson MA, Bush TJ, Wright TC. Human papillomavirus infection in women infected with the human immunodeficiency virus. N Engl J Med 1997;337:1343–910 [PubMed: 9358128]
15. Heard I, Cubie HA, Mesher D, Sasieni P, for the MACH-1 Study Group. Characteristics of HPV infection over time in European women who are HIV-1 positive. BJOG 2013;120(1):41–9. [PubMed: 23121095]
16. Denny LA, Franceschi S, de Sanjose S, Heard I, Moscicki AB, Palefsky J. Human Papillomavirus, Human Immunodeficiency Virus and Immunosuppression. Vaccine 2012;30:F168–F174. [PubMed: 23199960]
17. Santesso N, Mustafa R, Schunemann H, Arbyn M, Blumenthal P, Cain J, et al. World Health Organization guidelines for treatment of cervical intraepithelial neoplasia 2–3 and screen-and-treat strategies to prevent cervical cancer. Int J Obs Gyn 2016;132:252–258.
18. Harris TG, Burk RD, Palefsky JM, Massad LS, Bang JY, Anastos K, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. JAMA 2005;293(12):1471–6. [PubMed: 15784870]
19. Cohn JA, Gagnon S, Spence MR, Harrison DD, Kluzak TR, Langenberg P, et al. , for the Cervical Disease Study Group of the American Foundation for AIDS Research Community Based Clinical Trials Network. The role of human papillomavirus deoxyribonucleic acid assay and repeated cervical cytologic examination in the detection of cervical intraepithelial neoplasia among human immunodeficiency virus-infected women.. Am J Obstet Gynecol 2001;184(3):322–30. [PubMed: 11228481]
20. Our world in data. HIV/AIDS. Available at: https://ourworldindata.org/hiv-aids#almost-1-million-people-die-from-hiv-aids-each-year-in-some-countries-it-s-the-leading-cause-of-death, accessed 12 February 2021.
21. Makhema J, Wiirth KE, Holme MP, Gaolathe T, Mmalane M, Kadima E, et al. Universal testing, expanded treatment, and incidence of HIV infection in Botswana. NEJM 2019;381(3):230–42. [PubMed: 31314967]
22. Grover S, Raesima M, Bvochora-Nsingo M, Chiyapo S, Balang D, Tapela N, et al. Cervical cancer in Botswana: current state and future steps for screening and treatment programs. Front Oncol 2015;5:239. [PubMed: 26579491]
23. Ramogola-Masire D, de Klerk R, Monare B, Ratshaa B, Friedman HM, Zetola NM. Cervical cancer prevention in HIV-infected women using the “See and Treat” approach in Botswana. J Acquir Immune Defic Syndr (2012) 59(3):308–13. doi:10.1097/QAI.0b013e3182426227. [PubMed: 22134146]
24. Kitheka M. Feasibility and acceptability of HPV self-collection and testing using Xpert® HPV in Botswana. J Virus Erad 2019;5(Suppl 1): 8–9. [PubMed: 30997146]
25. Lemp J, De Neve J, Bussman H, Chn S, Manne-Goehler J, Theilmann M, et al. Lifetime prevalence of cervical cancer screening in 55 low- and middle-incom countries. JAMA 2020; 324(15):1532–42. [PubMed: 33079153]
26. Our world in data. How many people in the world die from cancer? Available at: https://ourworldindata.org/how-many-people-in-the-world-die-from-cancer, accessed 12 February 2021.
27. World Health Organization. Global Strategy Towards the Elimination of Cervical Cancer as a Public Health Problem. Available at: who.int/activities/a-global-strategy-for-elimination-of-cervical-cancer. Retrieved August 18, 2020.
28. Mbulawa Z, Wilkin T, Goeieman B, Swarts A, Williams S, Levin S, et al. Xpert human papillomavirus test is a promising cervical cancer screening test for HIV-seropositive women. Papillomavirus Res 2016;2:56–60. [PubMed: 29074186]
29. Nayar R & Wilbur DC The Bethesda system for reporting cervical cytology: definitions, criteria, and explanatory notes. Springer, 2015.
30. Luckett R, Mogowa N, Li HJ, Erlinger AL, Hacker M, Esselen K, et al. Performance of two-stage cervical cancer screening strategies utilizing primary hrHPV testing for women living with HIV. Obstet Gynecol 2019;134(4):840–849. [PubMed: 31503167]

31. Xu L, Ostrbeenk A, Poljak M, Arbyn M. Assessment of the Roche Linear Array HPV genotyping test within the VALGENT framework. J Clin Virol 2018;98:37–42. [PubMed: 29241150]
32. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81. [PubMed: 18929686]
33. Liu G, Sharma M, Tan N, Barnabas RV. HIV-positive women have a higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. AIDS 2018;32(6):795–808. [PubMed: 29369827]
34. Konopnicki D, Manigart Y, Gilles C, Barlow P, deMarchin J, Feoli F, et al. Sustained viral suppression and higher CD4+ T-cell count reduces the risk of persistent cervical high-risk human papillomavirus infection in HIV-positive women. J Infect Dis 2013;207:1723–9. [PubMed: 23463709]
35. Smith JS, Sanusi B, Swarts A, Faesen M, Levin S, Goeieman B, et al. A randomized clinical trial comparing cervical dysplasia treatment with cryotherapy vs loop electrosurgical excision procedure in HIV-seropositive women from Johannesburg, South Africa. Am J Obstet Gynecol 2017;217(2):183.e1–183.e11. [PubMed: 28366730]
36. Branca M, Garbuglia AR, Benedetto A, Cappiello T, Leoncini L, Migliore G, et al. Factors predicting the persistence of genital human papillomavirus infections and PAP smear abnormality in HIV-positive and HIV-negative women during prospective follow-up. Int J STD AIDS 2003;14:417–25. [PubMed: 12816671]
37. Finhaber C, Goeieman B, Faesen M, Levin S, Williams S, Rameotshela S, et al. Prospective one year follow up of HIV infected women screened for cervical cancer using visual inspection with acetic acid, cytology and human papillomavirus testing in Johannesburg South Africa. PLOS One 2016:11(1):e0144905. [PubMed: 26730710]
38. Joshi S, Muwonge R, Kulkarni V, Deodhar K, Mandolkar M, Lucas E, et al. Incidence of cervical intraepithelial neoplasia in women infected with human immunodeficiency virus (HIV) with no evidence of disease at baseline: Results of a prospective cohort study with up to 6.4 years of follow-up from India. Int J Cancer 2019;144:1082–1091. [PubMed: 30132840]
39. Kelly H, Ngou J, Chikandiwa A, Sawadogo B, Gilham C. Omar T, et al. Associations of human papillomavirus (HPV) genotypes with high-grade cervical neoplasia (CIN2+) in a cohort of women living with HIV in Burkina Faso and South Africa. PLOS One 2017;12(3): e0174117. [PubMed: 28333966]
40. Russomano F, Reis A, Camargo MJ, Grinsztejn B, Tristao MA. Recurrence of cervical intraepithelial neoplasia grades 2 or 3 in HIV-infected women treated by large loop excision of the transformation zone (LLETZ). São Paulo Med J 2008;126:17–22. 12. [PubMed: 18425282]
41. Reimers LL, Sotardi S, Daniel D, Chiu L, Arsdale A, Wieland D, et al. Outcomes after an excisional procedure for cervical intraepithelial neoplasia in HIV-infected women. Gynecol Oncol 2010;119(1):92–97. [PubMed: 20605046]
42. Kelly H, Weiss HA, Benavente Y, de Sanjose, Mayaud P, for the ART and HPV Review Group. Association of antiretroviral therapy with high-risk human papillomavirus, cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis. Lancet HIV 2018;5:e45–58. [PubMed: 29107561]
43. Paul P, Hammere A, Rositch A, Burke A, Viscidi R, Silver M, et al. Rates of new human papillomavirus detection and loss of detection in middle-aged women by recent and past sexual behavior. J Infect Dis 2020; jiaa557.doi:10.1093/infdis/jiaa557. Epub ahead of print.
44. Ho-Foster A, Laetsang D, Masisi M, Anderson M, Tlhoiwe D, Cockcroft A, et al. Gender-specific patterns of multiple concurrent sexual partnerships: a national cross sectional survey in Botswana. AIDS Care 2020;22(8):1006–1011.
45. Massad L, Xie X, D'Souza G, Darragh T, Minkoff H, Wright R, et al. Incidence of cervical precancers among HIV seropositive women. Am J Obstet Gynecol, 2015;212(2):606. [PubMed: 25499260]

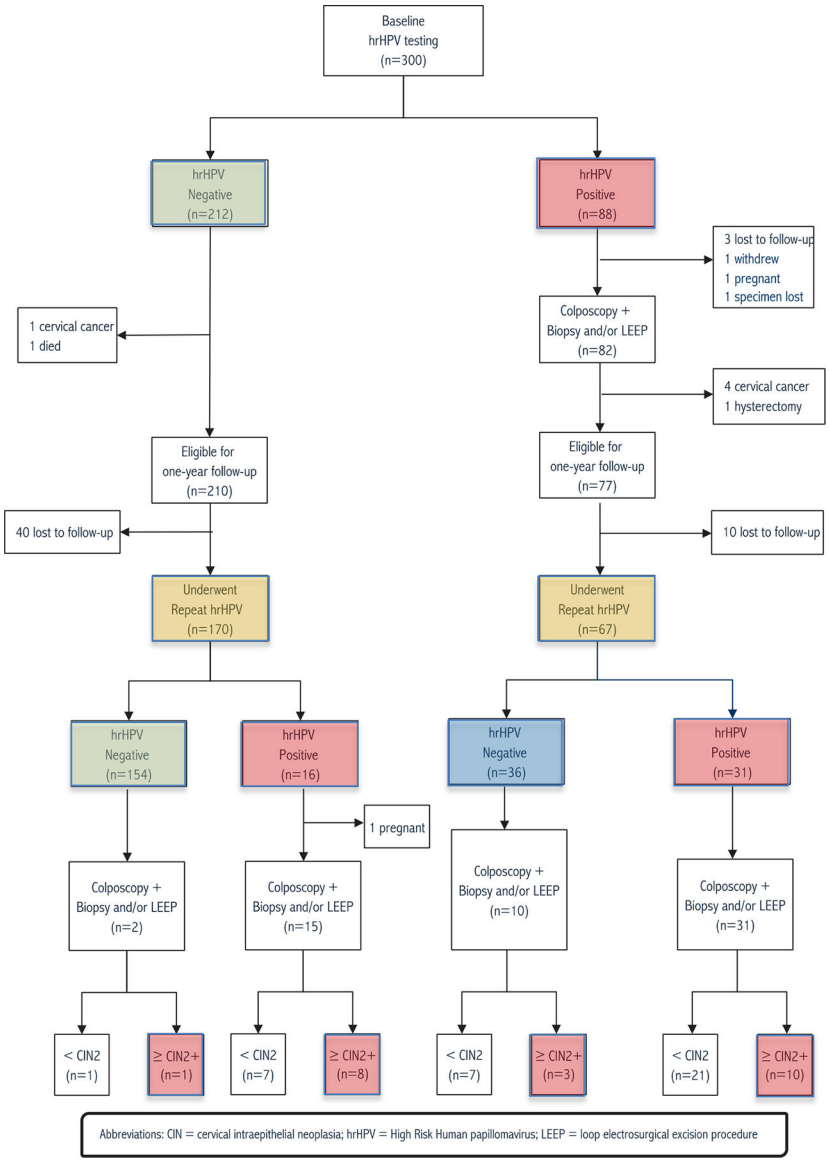

Figure 1.
Baseline and follow-up study flowchart

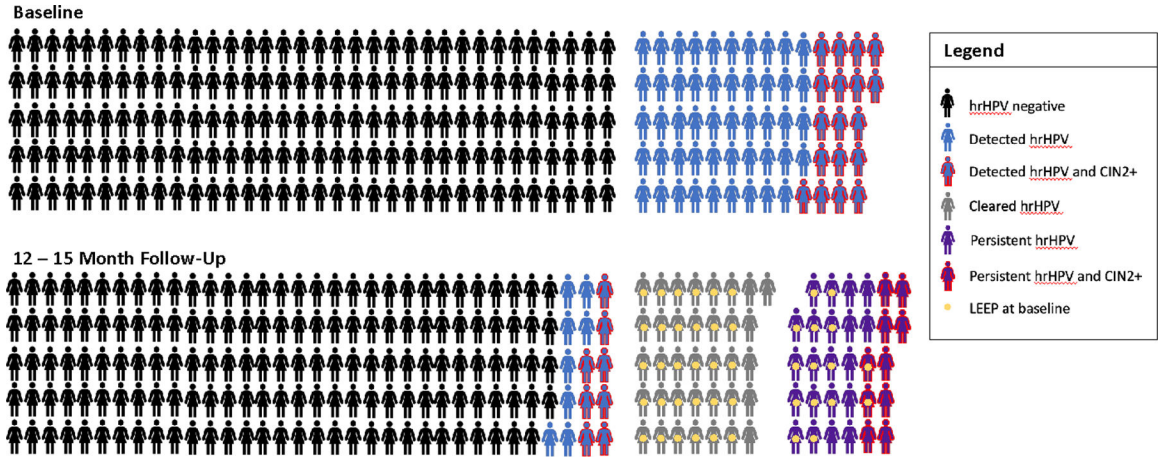

Figure 2.

Pictorial image of high-risk HPV infection and high-grade dysplasia in 237 WLHIV who underwent screening and treatment and baseline and one-year follow-up

Table 1:

Demographic characteristics of WLHIV who were screened at baseline and follow-up with high-risk human papillomavirus (HPV) testing *

Characteristic	All participants n = 237	All participants (by baseline high-risk HPV status)			
		High-risk HPV (+)		High-risk HPV (−)	
		By follow-up high-risk HPV status			
		High-risk HPV (+)	High-risk HPV (−)	High-risk HPV (+)	High-risk HPV (−)
		n = 31	n = 36	n = 16	n = 154
Age, years	45 [41–51]	44 [39–50]	42 [38–49]	48 [42–52]	46 [42–52]
Education					
≤Primary	79 (33)	10 (32)	8 (22)	8 (50)	53 (34)
≥Secondary	158 (67)	21 (68)	28 (78)	8 (50)	101 (66)
Employed	155 (65)	24 (77)	26 (72)	9 (56)	96 (62)
Marital status					
Single	169 (71)	23 (74)	25 (69)	12 (75)	109 (71)
Married	43 (18)	5 (16)	8 (22)	3 (19)	27 (18)
Divorced/separated	10 (4)	1 (3)	1 (3)	1 (6)	7 (5)
Widowed	15 (6)	2 (6)	2 (6)	0 (0)	11 (7)
Parity					
0	10 (4)	1 (3)	3 (8)	0 (0)	6 (4)
1–3	163 (69)	21 (68)	27 (75)	10 (63)	105 (68)
≥4	52 (22)	8 (26)	6 (17)	5 (31)	33 (21)
Missing	12 (5)	1 (3)	0 (0)	1 (6)	10 (6)
Age of sexual debut					
<16 years	17 (7)	2 (6)	2 (6)	2 (13)	11 (7)
≥16 years	219 (92)	29 (94)	34 (94)	14 (88)	142 (92)
Missing	1 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Sexual partners					
1–5	145 (61)	16 (52)	23 (64)	13 (81)	93 (60)
≥6	84 (35)	15 (48)	10 (28)	3 (19)	56 (36)
Missing	8 (3)	0 (0)	3 (8)	0 (0)	5 (3)
Post-menopausal	92 (39)	11 (35)	10 (28)	6 (38)	65 (42)
HIV duration	14 [12–15]	13 [10–16]	14 [11–15]	14 [11–14]	14 [13–15]
CD4 count at baseline (per microliter)					
< 200	4 (2)	1 (3)	1 (3)	0 (0)	2 (1)
200–349	17 (7)	2 (6)	3 (8)	3 (19)	9 (6)
350–500	43 (18)	6 (19)	8 (22)	3 (19)	26 (17)
> 500	173 (73)	22 (71)	24 (67)	10 (63)	117 (76)

Characteristic	All participants n = 237	All participants (by baseline high-risk HPV status)			
		High-risk HPV (+)		High-risk HPV (−)	
		By follow-up high-risk HPV status			
		High-risk HPV (+)	High-risk HPV (−)	High-risk HPV (+)	High-risk HPV (−)
		n = 31	n = 36	n = 16	n = 154
CD4 count at follow-up (per microliter)					
< 200	2 (1)	1 (3)	0 (0)	0 (0)	1 (1)
200–349	9 (4)	1 (3)	1 (3)	0 (0)	7 (5)
350–500	35 (15)	0 (0)	5 (14)	6 (38)	24 (16)
> 500	181 (77)	29 (94)	28 (78)	10 (63)	114 (74)
Missing	10 (4)	0 (0)	2 (6)	0 (0)	8 (5)
Detectable viral load at baseline (≥400 copies/milliliter)	11 (5)	2 (6)	4 (11)	1 (6)	4 (3)
Detectable viral load at follow-up (≥400 copies/milliliter)	3 (1)	0 (0)	1 (3)	0 (0)	2 (1)
On antiretroviral therapy at baseline and follow-up	237 (100)	31 (100)	36 (100)	16 (100)	154 (100)
Years on antiretroviral therapy at baseline	13 [10–14]	13 [7–15]	12 [8–14]	12 [10–14]	13 [11–15]

*All values are number of participants (%) or median [interquartile range] unless otherwise indicated

Table 2:

Distribution of persistence and clearance of high-risk human papillomavirus (HPV) infections in 67 women living with HIV who were high-risk HPV positive at baseline attended one-year follow-up

	Any high-risk HPV diagnosis at baseline n=67	HPV 16 infection* at baseline n=13	HPV 18 infection* at baseline n=14	Other high-risk HPV type infection* at baseline n=49
Persistence† of high-risk HPV infection				
Treated with LEEP at baseline, n (%)	15 (22)	0 (0)	0 (0)	14 (29)
Not treated with LEEP at baseline, n (%)	16 (24)	3[a] (23)	2 (14)	12 (24)
Clearance‡ of high-risk HPV infection				
Treated with LEEP at baseline, n (%)	30 (45)	6 (46)	8[b] (57)	20 (41)
Not treated with LEEP at baseline, n (%)	6 (9)	4 (31)	4[c] (29)	3 (6)

Abbreviations: LEEP: loop electrosurgical excision procedure

*At baseline, 6 women were co-infected with HPV 16 and other hrHPV, 3 women were co-infected with HPV 18 and other hrHPV.

†Persistence is defined as positivity of the same hrHPV type at baseline and at one-year follow-up.

‡Clearance is defined as having a negative result for the same hrHPV type at one-year after a positive baseline hrHPV result.

[a]One participant was positive for both HPV16 and other high-risk HPV at baseline had persistent HPV 16 only

[b]Includes 1 participant with type switch from HPV18 at baseline to other high-risk HPV at follow-up

[c]Includes 1 participant with type switch from HPV18 at baseline to other high-risk HPV at follow-up

Table 3.

Histopathology result at one-year follow-up correlated with sequential high-risk HPV screening results among 236 women living with HIV

Histopathology result at one-year follow-up	High-risk HPV + / high-risk HPV + n = 31[a]	High-risk HPV + / high-risk HPV − n = 36[b]	High-risk HPV − / high-risk HPV + n = 15[c]	High-risk HPV − / high-risk HPV − n = 154[d]
Benign	12 (39)	6 (17)	6 (40)	0 (0)
CIN1	9 (29)	1 (3)	1 (7)	1 (1)
CIN2	3 (10)	2 (6)	2 (13)	1 (1)
CIN3	7 (23)	1 (3)	6 (40)	0 (0)

Note: Excludes the 1 participant who was not eligible for colposcopy at one year due to pregnancy

[a]Of the cases of CIN2 and CIN3 in this category, four had persistent HPV16 or 18, four had persistent other high-risk HPV, and two had cleared HPV16 but acquired other high-risk HPV at follow-up.

[b]Only participants with indications underwent colposcopy according to the study protocol or clinical guidelines. These participants included: 8 who had CIN2 or higher at baseline, 1 with persistent low-grade cytology, and 1 with postmenopausal bleeding. The three cases of CIN2 or higher all had other high-risk HPV at baseline.

[c]Of the cases of CIN2 and CIN3 in this category, seven were associated with other high-risk HPV and one with co-infection with HPV16 and HPV18.

[d]Only women with indications underwent colposcopy. These participants included: one who had persistent low-grade cytology and one who had an abnormal cervical examination.

Table 4a.

Incidence of histopathologic disease among the 40 women who had no, benign or low-grade histopathologic results at baseline, stratified by high-risk HPV type at baseline

	No histopathologic diagnosis at baseline		Benign histopathologic diagnosis at baseline				CIN1 histopathologic diagnosis at baseline			
	High-risk HPV negative n=17	Any High-risk HPV type n=3	Any high-risk HPV type n=15	HPV 16* n=3	HPV 18* n=4	Other high-risk HPV type* n=12	Any high-risk HPV type n=5	HPV 16* n=1	HPV 18* n=1	Other high-risk HPV type* n=4
Benign	6	1	6	2	3	5	3	0	0	3
CIN1	2	1	2	0	0	2	1	0	1	0
CIN2	3	0	3	0	1	2	0	0	0	0
CIN3	6	1	4	1	0	3	1	1	0	1

* Infection with these types is not mutually exclusive

Table 4b.

Persistence, progression, regression of histopathologic disease among women treated with loop electrosurgical excision procedure (LEEP) at baseline compared to women who were not treated with LEEP

	Baseline results*			
	Treated with LEEP		**Not treated with LEEP**	
	CIN2 n=7	**CIN3 n=8**	**CIN2 n=2**	**CIN3 n=1**
Persistence† n (%)	0 (0)	2 (25)	0 (0)	0 (0)
Progression‡ n (%)	0 (0)	--	0 (0)	--
Cure/Regression§ n (%)	7 (100)	6 (75)	2 (100)	1 (100)

*2 of the 20 participants with CIN2 or higher at baseline did not have follow-up pathology results

†Persistence: the same abnormal histopathologic diagnosis at baseline and follow-up

‡Progression: abnormal histopathologic diagnosis at baseline and a worse histopathologic diagnosis at follow-up

§Regression: abnormal histopathologic diagnosis at baseline and a less severe or normal histopathologic diagnosis at follow-up