original report

# Cervical Abnormalities in South African Women Living With HIV With High Screening and Referral Rates

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abstract

**Purpose** **To determine the prevalence of screening, cervical dysplasia, and malignancy on the basis of histologic diagnoses from colposcopy and large loop excision of the transformation zone among women living with HIV (WLWH) who attended an urban antiretroviral treatment (ART) clinic in KwaZulu-Natal, South Africa.**

**Materials and Methods** **We performed a retrospective cohort study to examine a random sample of 462 WLWH during a 5-year period from 2004 to 2009. Women on ART for < 3 months were excluded. Data were abstracted from electronic records and paper charts to assess rates of cervical abnormalities detected on Pap smears as well as time to colposcopy.**

**Results** **During the study period, 432 women (93.5%) had at least one evaluable Papanicolau test. At baseline, 237 women (54.9%) had an abnormal Papanicolau test, and of these patients, 181 (76.3%) had a Papanicolau test that qualified for further colposcopic evaluation. In addition, 115 women (63.5%) received colposcopy within a median of 39 days from referral. This yielded 74 evaluable histologic samples (64.3%), of which 21.6%, 27.0%, 27.0%, and 1.4% had cervical intraepithelial neoplasia (CIN) 1, CIN2, CIN3, and invasive cervical cancer, respectively.**

**Conclusion** **In a large sample of WLWH who received ART in KwaZulu-Natal, South Africa, where Papanicolau test coverage and rates of referral for colposcopy and large loop excision of the transformation zone were high, > 75% of women with evaluable histologic samples had evidence of cervical dysplasia or malignancy. These findings underscore the importance of routine cervical screening upon entry into HIV care to optimize survival.**



## INTRODUCTION

Cervical cancer is the fourth most common cancer among women worldwide and accounts for > 500,000 cases diagnosed annually.[1] The burden of cervical cancer is borne primarily by low- and middle-income countries, in particular, in sub-Saharan Africa, where the age-standardized annual incidence is 35 per 100,000 women compared with seven per 100,000 women in North America.[2] Cervical cancer is the leading cause of cancer-related death in sub-Saharan Africa.[3] The high prevalence and mortality from cervical cancer among African women is multifactorial, as a result of, in part, lack of funding, infrastructure, and access to clinicians. Even in countries with national screening policies, rates of cervical cancer range from 2% to 20% in urban areas and 0.4% to 14% in rural areas.[4,5]

Women in South Africa are uniquely at risk. This is because of the synergistic effects of a nation that is heavily burdened with HIV[6,7] and poor access to adequate diagnostic screening for precancerous lesions.[8-10] Women living with HIV (WLWH) have been shown to be at increased susceptibility for the development of precancerous lesions,[11-13] including both high-grade squamous intraepithelial lesions (HSILs) and cervical intraepithelial neoplasia (CIN),[14-16] and cervical cancer.[13,17-20] Unfortunately, most do not receive adequate screening,[21-24] despite recommendations made in 2014 that promote annual screening among WLWH.[25]

Access to antiretroviral therapy (ART) has improved significantly in South Africa since 2005,[26] which has resulted in increased life expectancy[27] and reduced morbidity.[28,29] Yet, linkage studies of HIV and cancer registries have indicated a two- to 22-fold increase in cervical cancer in WLWH compared with HIV-negative women.[30-36] These data show that the high

mortality associated with delayed diagnoses of advanced cervical cancer may undermine the benefits of ART in this region. As the government expands care for WLWH, it will be critical to understand the public health burden of cervical dysplasia in this population as well as the feasibility of effective and timely cervical screening for this high-risk population. We undertook this study during a 5-year period to assess the prevalence of screening, cervical dysplasia, and histologic diagnoses from colposcopy and large loop excision of the transformation zone (LLETZ) in a region of South Africa with a high prevalence of HIV.

## MATERIALS AND METHODS

### Study Design

We performed a retrospective cohort study to determine the prevalence of cervical dysplasia and malignancy among WLWH who attended an urban ART clinic in KwaZulu-Natal, South Africa, during a 5-year period from 2004 to 2009. A random sample of eligible women enrolled in HIV-care was generated from each study year and was stratified by year of ART initiation.

### Setting

The Sinikithemba HIV clinic was located at McCord Hospital in Durban, South Africa, and received funding from the President's Emergency Plan for AIDS Relief from 2004 until it closed in 2012 as a result of shifts in funding.[37-39] The Sinikithemba cervical screening policy was based on international guidelines. Specifically, the hospital policy was to offer a Papanicolau test (Pap) within the first 3 months of initiating ART, a second smear within the first year, and annual smears thereafter. In addition to receiving annual Pap smears, women were referred for colposcopy and/or LLETZ if they were found to have a single Pap test with HSIL or two consecutive Pap tests with abnormal cytology, which could have either been two low-grade squamous intraepithelial lesions (LSILs) or one LSIL and one lesion that showed atypical squamous cells of undetermined significance (ASCUS).

### Participants

Eligibility criteria included WLWH age > 18 years and who attended the clinic for > 3 months. Women with a hysterectomy before enrollment were excluded. Of 2,891 eligible women, 462 were randomly sampled for inclusion and were stratified by year of ART enrollment at the clinic (n = 77 per annum).

### Data Collection and Analysis

Data were abstracted from electronic records to a paper form and included date of birth, $CD4^+$ counts, viral load (VL), and results from initial Papanicolau test, colposcopy, and LLETZ. We also tracked time to colposcopy among women with abnormal Pap smears. Women who presented for colposcopy were presumed to have been referred even if this was not documented in the medical record. Laboratory results that were not recorded in the chart or were noted to be lost or damaged were considered not evaluable for this study.

As a measure of quality control and to determine the reliability of the abstraction instrument, 5% of charts were randomly selected and checked for data accuracy by a second data abstractor (J.G.). Data were entered into an EpiInfo database.

### Statistical Analysis

Descriptive statistics (medians and proportions) were used to characterize the variables. The prevalence of abnormality with the initial Pap test was calculated along with the cumulative prevalence of abnormality over the course of the observation period. The incidence of Papanicolau test abnormality was estimated in women with normal initial Pap tests and available subsequent cytology results. For both analyses, Pap smears with ASCUS, LSIL, and HSIL were considered abnormal, and descriptive statistics were also generated for colposcopy outcomes. Cytology and histology results were dichotomized at clinically relevant cutoffs: for cytology—ASCUS, LSIL, or HSIL; and for histology—CIN 1, -2, and -3. Differences in median age, $CD4^+$ count, and VL between women who had

**Table 1** – Papanicolau Test Results and Referrals for Colposcopy and Large Loop Excision of the Transformation Zone

| Characteristic | All Women (N = 462) | Women With ≥ 1 Pap (n = 432) | Never Pap (n = 30) | *P* |
|---|---|---|---|---|
| Age, years | 33.0 (27.9-38.8) | 33.0 (28.0-38.6) | 32.2 (27.3-40.5) | .84 |
| CD4, cells/μL | 115 (58-174) | 117.5 (55-177) | 100.5 (72-131) | .11 |
| Viral load, copies/mL | 49 (24-66) | 49 (24-61) | 49 (24-670) | .28 |

NOTE. Data are given as median (interquartile range).
Abbreviation: Pap, Papanicolau test.

at least one Pap versus those who never had a Pap were determined by using an exact Wilcoxon method. Analyses were performed in SAS (SAS/STAT User's Guide, Version 9.3; SAS Institute, Cary NC).

Ethical approval for this study was obtained from the University of Toronto Ethics Research Committee and from the McCord Hospital Research Ethics Committee.

## RESULTS

In our cohort of 462 women who were enrolled in ART care, the median age was 33.0 years (interquartile range [IQR], 27.9 to 38.8). Women had a median baseline CD4$^+$ count of 115 cells/$\mu$L (IQR, 58 to 174 cells/$\mu$L) and median baseline VL of 49 (IQR, 24 to 66; Table 1). During the study period, 432 women (93.5%) had at least one evaluable Papanicolau test, and, of those, 330 (76.4%) had two or more Pap smears (median, 3; IQR, 2 to 4). There were no significant differences between women who received at least one Pap test and those who never had a Pap with respect to age (33.0 years *v* 32.2 years; $P = .84$), baseline CD4$^+$ (118 *v* 100 cells/$\mu$L; $P = .11$), or VL (49 *v* 49; $P = .28$).

In this study, 237 women (54.9%) had an abnormal Pap test at baseline, when they initiated ART. Of 237 women with abnormal Pap smears, 62 (26.2%) had ASCUS and these women were followed with sequential Pap smears. Of 175 remaining women, 125 (28.9%) had LSIL and 50 (11.6%) had HSIL, which warranted immediate referral for colposcopy. Figure 1 shows the progression of women, both those who qualified and those who did not, with Pap smears through colposcopy and subsequent histologic results. Of 181 women who qualified for colposcopy during the study period, 72.4% (n = 131) were referred. Of these, 115 (87.8%) had documentation of completed colposcopy within a median of 39 days (IQR, 20 to 95 days).

Referrals yielded 74 (64.3%) of 115 evaluable histologic samples, and of these, 75.6% were found to have CIN. Specifically, 21.6%, 27.0%, and 27.0% had CIN1 CIN2, and CIN3, respectively. In addition, 1.4% were found to have invasive cervical cancer (Fig 1).

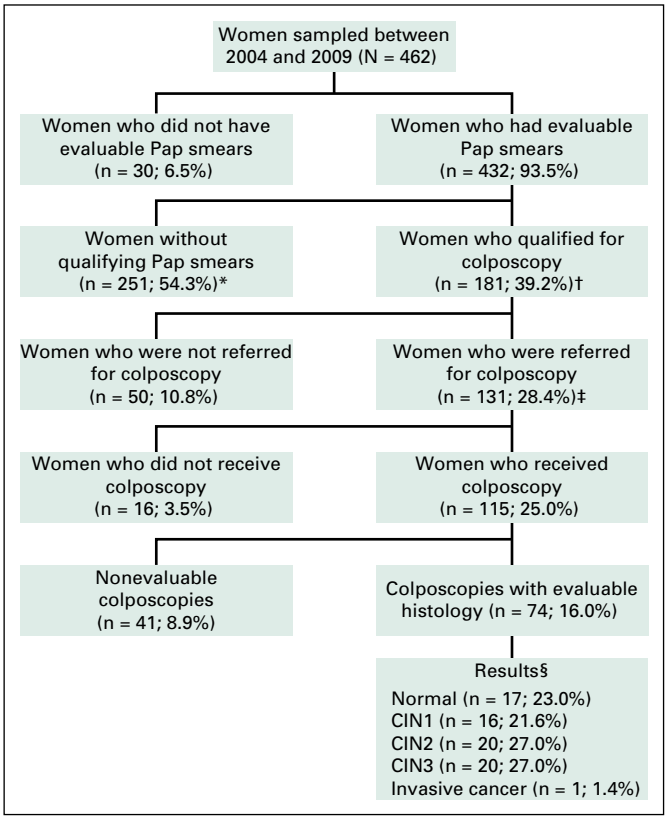


**Fig 1 –**
Losses in the diagnostic referral change. *Of these women, three had no referral in the chart but underwent colposcopy; five received colposcopy, of which four had evaluable results: cervical intraepithelial neoplasia (CIN) 1, 2 (50.0%); CIN2, 1 (25.0%); and CIN3, 1 (25.0%). †Two hundred thirty-seven women had abnormal Papanicolau test (Pap) at baseline, of which 50 qualified at the first visit on the basis of high-grade squamous intraepithelial lesions, and 131 women went on to qualify on the basis of presence of atypical squamous cells of undetermined significance (ASCUS), followed by low-grade squamous intraepithelial lesion (LSIL), LSIL then ASCUS, or sequential LSIL lesions. ‡Ten women had no referral in the chart but underwent colposcopy. §Cervical dysplasia results are prevalent among those with evaluable colposcopy.

## DISCUSSION

In a cohort of WLWH who accessed care at an urban clinic in KwaZulu-Natal, South Africa, where Pap test coverage and rates for referral for colposcopy and LLETZ were high, we observed that > 75% of women with evaluable histologic samples had evidence of cervical dysplasia or malignancy. In addition, we found the crude incidence of invasive cervical cancer to be > 200-fold higher than incidence rates of cervical cancer in the United States (seven per 100,000).[40]

Prior studies in South Africa have shown similarly high rates of premalignant lesions on cytology from Pap smears, with prevalence of HSIL = 33% in WLWH.[21] These findings demonstrate the significant public health burden of cervical dysplasia in this population. Given that invasive cervical cancer is preceded by gradual progression of premalignant CIN,[41-44] our findings highlight the importance of cervical screening upon entry into care to optimize the potential for early interventions and cure. This is essential among WLWH, given the higher prevalence of CIN[11,13] and the worse treatment outcomes among this population compared with HIV-negative women.[45-47]

WLWH in South Africa now have improved access to ART, and, provided they start treatment before their CD4$^+$ count drops < 200 cells/$\mu$L, they are expected to have a near normal life expectancy.[48] Yet the benefits of ART may be undermined by the risk of cervical cancer acquisition.[49] Prior research has shown that ART is associated with increased regression of squamous intraepithelial lesions among WLWH.[50]

Despite this, the majority of cervical cancers among WLWH, even among individuals who are on treatment, do not regress to normal.[51]

As South Africa continues to expand care for those living with HIV,[38] national outreach programs should be revised to reflect the higher risk of cervical cancer among WLWH. It is also critical to reach women who may not be accessing care.[52] Improved screening services will require more resources and infrastructure throughout sub-Saharan Africa, coupled with integrated, community-based health education to emphasize the need for regular screening. This will ultimately enable clinicians to provide timely diagnoses and referrals for cervical abnormalities.

This study is limited by the fact that these data were collected retrospectively from a single site and, therefore, may be limited in generalizability. Furthermore, all participants in this study were already receiving ART, thereby precluding our ability to determine the effect of treatment on screening. Despite these limitations, these data provide histologic evidence of the burden of cervical disease in this high-risk population that is rarely seen in the literature, given the paucity of centers providing colposcopy and LLETZ in sub-Saharan Africa.

South African policymakers must ensure coordination and resourcing of sexual and reproductive health programs as well as their integration with HIV treatment programs. The Department of Health needs to develop a national cancer control program, with an investment in capacity building to ensure accurate evaluation of the burden of disease,[33] including both cancer detection and treatment, to support women with HIV so that they may live long and healthy lives.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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