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Research article

Highly active antiretroviral therapy and cervical dysplasia in HIV-positive women in South Africa

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Abstract

Background: The risk of squamous intra-epithelial lesions (SIL) is higher in HIV-positive women. As these women begin to live longer due to highly active antiretroviral therapy (HAART), their risk of cervical cancer may increase. Few data exist regarding the effect of HAART on the incidence and progression of SIL in HIV-positive African women. The aim of this study was to evaluate the effect of HAART on the incidence and progression of SIL in HIV-positive women in South Africa.

Methods: A prospective observational study of HIV-seropositive women was conducted over 5 years in an HIV treatment clinic in Johannesburg, South Africa. The participants consisted of 601 women on and off HAART who had repeat Pap smears greater than 6 months apart. The effect of HAART use on incidence and progression rates of SIL was determined using multivariate Poisson regression to obtain incidence rate ratios (IRRs), adjusted for age, CD4 count and other potential confounders.

Results: Median follow-up time was 445 days (inter-quartile range 383, 671). The crude rate of incidence of any SIL was 15.9 episodes (95% confidence limit (CL) 12.7, 19.9) per 100 person-years; the crude rate of all progression of cervical dysplasia among women was 13.5 episodes (95% CL 11.3, 16.1) per 100 person-years. HAART use was associated with a robust reduction in the rate of incidence and progression of cervical lesions, adjusted IRR = 0.55 (95% CL 0.37, 0.80). Sensitivity analyses confirmed this main association held for incidence and progression when they were considered separately, and that the result was not dependent on the length of HAART exposure.

Conclusion: HAART use was associated with a reduction in the rate of both incidence and progression of cervical lesions among HIV-positive women.

Keywords: HAART effect; cervical dysplasia; HIV-positive women; South Africa.

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Background

HIV-positive women in sub-Saharan Africa have a higher prevalence of cervical squamous intra-epithelial lesions (SIL) and invasive cervical cancer than HIV-positive women in other regions of the world [1–3]. Women with lower CD4 counts consistently have higher rates of high-grade squamous intra-epithelial lesions (HSIL) [1,2]. The prevalence of high-risk human papillomavirus (HPV) infection, the etiologic agent of cervical cancer, is high in sub-Saharan Africa [4,5]. HPV infections persist longer in HIV-positive women [6,7]. Limited access to cervical cancer screening programmes in this region of the world places women at an increased risk for the development of cervical cancer.

With increasing access to highly active antiretroviral therapy (HAART) through governmental and donor organizations, HIV-positive women in resource limited countries are living longer as deaths from opportunistic infections decline [8]. HAART use has been shown to reduce the risk of opportunistic malignancies such as Kaposi sarcoma and some lymphomas [9,10]. However, the relationship between the use of HAART and the development of cervical lesions remains unclear, with some studies showing benefit with HAART [11,12] and others showing no benefit [13,14].

At present, there are few data examining the impact of HAART on the natural history of cervical lesions from the region of sub-Saharan Africa with the highest prevalence of both cervical cancer and HIV. We present results here on the relationship of HAART use and cervical lesions from an observational study of HIV-positive women from a public sector HIV treatment clinic in Johannesburg, South Africa.

Methods

Study population and enrolment

An observational longitudinal study of HIV-positive women was conducted within the South Africa Cervical Cancer Cohort (SACCC) [1]. The cohort included HIV-positive women aged from 18 to 65 who were recruited from an adult HIV outpatient clinic in a teaching hospital affiliated with the University of Witwatersrand in Johannesburg. Women were eligible to participate in this study unless they (1) were

pregnant; (2) had undergone a hysterectomy or cone biopsy; (3) were severely ill per investigator's opinion; or (4) had signs/symptoms suggestive of a sexually transmitted infection (STI). Women were study-eligible following the treatment of any symptomatic STI, and 6 weeks after the end of pregnancy. Women were also eligible to participate in this study if they had two Pap smears 6 months apart. After an educational session was presented on cervical cancer screening in English or in an appropriate African language, women were invited for a conventional Pap smear and to participate in this observational study. Health workers screened for exclusion criteria, explained study aims, and obtained written informed consent. A medical history was obtained through a participant interview including information on demographics characteristics, antiretroviral therapy status, and lifestyle factors, including smoking/snuff (traditional chewing tobacco), reproductive/menstrual characteristics, previous Pap smear results if applicable, sexual history/behaviour, history of STIs and contraceptive use. All protocols were reviewed and cleared by the Human Ethics Committee (Medical) of the University of the Witwatersrand and, for secondary data analyses, by the University of North Carolina.

Laboratory analysis

During a pelvic examination, cervical exfoliated cells were collected using an endo-cervical brush for a conventional Pap smear diagnosis. Conventional cervical smears were performed as standard of care for HIV-positive women in South Africa. Liquid-based cytology is currently not available in the government sector of care in South Africa. Cytology slides were read and analyzed according to Bethesda 2001 guidelines [15]. Women with HSIL and atypical squamous cells-high (ASC-H) were referred to immediate colposcopy [16]. Women with atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intra-epithelial lesions (LSIL) were followed with a repeat Pap smear after 1 year per standard of care in South Africa if their CD4 count was above 200 cells/mm^3 or after 6 months if their CD4 count was 200 cells/mm^3 or below. Women were also referred for colposcopic biopsy if they presented with three consecutive LSIL results over 18 months or greater. For quality control, 10% of the conventional cytology slides were sent to the University of North Carolina for blinded double readings on two occasions, with an observed concordance rate of 81% and 85% [1]. HIV-positive women were treated according to the South African guidelines on Comprehensive HIV and AIDS Care, Management and Treatment [17], by which at the time of the study HAART was initiated at WHO Stage 4 or CD4 counts of <200 cells/mm^3.

Statistical methods

Women with two Pap smears at least 6 month apart were included in data analyses. In the main analysis, ASC-US results were classified as LSIL results, while ASC-H results were classified as HSIL results; alternatives were explored in sensitivity analysis. Outcome was defined as the time to the first incidence or first progression of cervical dysplasia from baseline status, that is, from negative Pap smear to LSIL, HSIL, or cancer; or from LSIL to HSIL or cancer. A HSIL diagnosis resulted in treatment (specifically, a loop electrosurgical excision procedure (LEEP)). Because individuals with HSIL at baseline were not at risk of cervical lesion progression in the same way as those with negative or LSIL diagnoses due to treatment, HSIL cases were excluded from analyses of progression.

The main analyses examined the effect of HAART at the time of first Pap smear (baseline) on the rate of incidence or progression of cervical lesions. The main analyses were intent-to-treat, in that changes in exposure after baseline were not considered. These analyses used multivariate Poisson regression to compare the rate of incidence and progression of any SIL using HAART at baseline to no HAART at baseline. All analyses considered confounding by age, CD4 count, age at first intercourse, lifetime number of sexual partners, history of STI, use of hormonal contraception, condom use at last sex, employment status, current smoking, snuff use (traditional chewing tobacco) and education level. CD4 counts and age were both modelled as four-knot restricted cubic splines; other covariates were modelled categorically. Last, we evaluated the modification of the effect of HAART by CD4 counts by including an interaction term with dichotomized CD4 count (≥ 350 cells/mm^3, <350 cells/mm^3) in the multivariate model.

Results

Cohort characteristics

There were 601 women eligible for analyses. Median follow-up time among these women was 455 days (interquartile range (IQR) 385, 704) between baseline visit and end of follow-up (at either time of event or last follow-up visit without an event). Of the 601 women, 122 (17%) of women experienced an incident cervical lesion or a progression event; the median time to incidence or progression in these women was 407 days (IQR 361, 622). Among women with an incident lesion or lesion progression receiving HAART ($n=75$), the median time to incident lesion/progression was 420 days (IQR 362, 682); among women not receiving HAART ($n=47$), the time to incidence/progression was 390 days (IQR 357, 494) (Wilcoxon rank-sum test $p=0.18$).

Of the 601 participating women, 54% ($n=326$) had a negative Pap at baseline, and 46% ($n=275$) had baseline LSIL; these baseline proportions of cervical lesions did not vary by baseline HAART status (chi-square test for non-zero correlation, $p=0.37$). Women included in the study had a median age of 35 years (IQR 31, 41), and approximately a third (37%) of these women had a CD4 count under 200 cells/mm^3 at baseline. Over two-thirds of women were receiving HAART at their first visit ($n=424$, 71%). Median time on HAART was 0.92 years (IQR 0.36, 1.74). Table 1 presents additional baseline demographics of these 601 women stratified by baseline HAART status.

Crude risks of incidence and progression

Among individuals who had a negative Pap baseline status, the crude rate of incidence of LSIL, HSIL, or invasive cancer was 15.9 (95% confidence limit (CL) 12.7, 19.9) episodes per 100 person-years. Among those with LSIL at baseline, the

Table 1. Characteristics of 601 HIV-positive women by baseline exposure to HAART at study entry

	HAART ($n=424$)		No HAART ($n=177$)		
	No.	%	No.	%	p Value[a]
Age[b]	35 (31, 41)		34 (30, 41)		0.094
Parity[b]	2 (1, 3)		2 (1, 2)		0.131
CD4 count (cells/mm^3)[b]	248 (152, 382)		299 (174, 448)		0.009
CD4 count (cells/mm^3)					
<200	166	39.2	52	29.4	0.036
200–349	124	29.3	52	29.4	
≥ 350	134	31.6	73	41.2	
Baseline negative Pap	225	53.1	101	57.1	0.371
Reported history of STIs	292	68.9	113	63.8	0.231
Condom used at last sex	317	74.8	126	71.2	0.364
Current hormonal contraception	60	14.2	16	9.0	0.086
Lifetime # sex partners ≥ 5	179	42.2	61	34.5	0.077
Age at first sex <15 years	34	8.0	12	6.8	0.603
Unemployed	235	55.4	86	48.6	0.126
High school graduate	174	41.0	64	36.2	0.265

STIs, sexually transmitted infections.
[a]Categoric variables are compared by chi-square test for general association; continuous variables by Wilcoxon rank-sum test; [b]median (interquartile range).

crude rate of progression to higher stages of cervical lesions was 10.8 (95% CL 8.1, 14.4) per 100 person-years. The crude combined rate for first incidence or progression was 13.5 (95% CL 11.3, 16.1) per 100 person-years; these and other crude incidence and progression rates are summarized in Table 2. Crude incidence and progression rates differed by the CD4 count, as shown in Table 3. The CD4 count significantly affected the rates of progression of cervical dysplasia. Progression rates were quite marked in women with CD4 counts of <50 cells/mm^3 and were lower when CD4 counts were >350 cells/mm^3 (Table 3) in women with both negative and LSIL baseline Pap smears. The test for linear trend of progression rate by CD4 category was $p=0.08$.

Effect of HAART on incidence and progression

In the main analysis of the effect of HAART use at first visit on the rate of first incidence or progression of cervical dysplasia, the crude Poisson model resulted in an estimated incidence rate ratio (IRR) of 0.63 (95% CL 0.43, 0.90); that is, women receiving HAART at the time of first visit had 0.63 times the combined rate of cervical dysplasia incidence and progression when compared with women not receiving HAART at first visit. Results from a multivariate analysis were stronger than the crude analyses, yielding an adjusted rate ratio of 0.55 (95% CL 0.37, 0.80). Sensitivity analyses confirmed main results; results were essentially identical when restricting to analysis of incidence or progression only, when excluding those with ASCUS results, and when using a Cox proportional hazards model. These results are summarized in Table 4. In addition, we conducted a sensitivity analysis and adjusted results for the time on HAART, and progression results were similar, rate ratio = 0.54 (95% CL 0.37, 0.80).

The effect of baseline HAART exposure was strongly modified by baseline CD4 count (Table 4). Among those with CD4 counts of <350 cells/mm^3, the rate ratio was 0.47 (95% CL 0.30, 0.73). Among those with baseline CD4

Table 2. Crude cervical dysplasia progression counts and rates by baseline and follow-up Pap result among 601 HIV-positive women in Johannesburg, South Africa

From	To	No. of progressions	Progression rate[a]	95% CL
Negative or LSIL	Any higher	122	13.5	11.3, 16.1
Negative	LSIL, HSIL+[b]	76	15.9	12.7, 19.9
Negative	LSIL	68	14.6	11.5, 18.5
Negative	HSIL+	8	2.1	1.0, 4.2
LSIL	HSIL+	46	10.8	8.1, 14.4

CL, confidence limit; HSIL, high-grade squamous intra-epithelial lesion; LSIL, low-grade squamous intra-epithelial lesion.
[a]Progression rates given per 100 person-years; [b]HSIL+: HSIL and invasive cervical cancer.

Table 3. Crude rates of cervical dysplasia incidence and progression by baseline CD4 count among 601 HIV-positive women in Johannesburg, South Africa

	Incidence or progression		Incidence only		Progression only	
CD4 count[a]	Rate[b]	95% CL	Rate[b]	95% CL	Rate[b]	95% CL
<50	18.0	10.0, 32.6	25.8	12.9, 51.5	10.0	3.2, 31.0
50–199	15.4	11.4, 20.8	18.8	12.0, 29.5	13.4	8.9, 20.2
200–349	13.5	9.7, 18.7	18.1	12.2, 26.7	8.6	4.7, 15.5
$\geq 350+$	10.8	7.7, 15.2	11.6	7.8, 17.3	9.3	4.8, 17.8

CL, confidence limit.
[a]Unit: cells/mm^3; [b]rates per 100 person-years.

counts of ≥ 350 cells/mm^3, the rate ratio was 0.84 (95% CL 0.42, 1.72).

Discussion

Our study presents some of the first information on the effect of HAART on the incidence and progression of cervical lesions among HIV-positive women in sub-Saharan Africa. HAART is associated with a sizable reduction in the combined rate of incident lesions and the progression of any SIL in HIV-positive women in this population, as well as with incidence and progression of any SIL considered separately.

Observed rates of overall first incidence or progression of cervical lesions are higher (at 13.5 per 100 women-years) than in studies of HIV-positive women from other countries. One pre-HAART study in the United States found lower rates of incidence of histologic-proven SIL, 8.3 per 100 person-years (95% CL 6.5 to 10.6) [14]. Another study of the US women with histologic-proven cervical intra-epithelial neoplasia 1 (CIN-1) found a very low rate of progression to HSIL or greater, 1.2 per 100 person-years (95% CL 0.5, 2.4) [18]. Higher rates observed in this cohort may be explained in part by lower CD4 cell counts in our cohort (median 267 cells/mm^3), in contrast to the US and European cohorts (medians typically above 350 cells/mm^3) [14, 18–20]. Moreover, 70% of this cohort was on HAART, implying lower CD4 counts in the past for most women [21]. Another possible contributor to higher rates is the deficiency in folate and B12 tocopherols among South African women [22], which is thought to increase the risk of cervical dysplasia [23–25].

Table 4. Estimates of the effect of HAART on rate of incidence and progression of cervical dysplasia among 601 HIV-positive women in Johannesburg, South Africa

	Rate ratio	95% CL
Crude	0.63	0.43, 0.90
Adjusted[a]	0.55	0.37, 0.80
Modification by CD4 count[a]		
CD4 $<$ 350 cells/mm^3	0.47	0.30, 0.73
CD4 $\geq$ 350 cells/mm^3	0.85	0.42, 1.72
Sensitivity analyses[a]		
Incidence only	0.55	0.34, 0.90
Progression only	0.52	0.27, 1.01
Excluding ASC-US	0.59	0.38, 0.90
Cox PH model[b]	0.45	0.30, 0.67

CL, confidence limit.
[a]Adjusted for age, CD4 count, age at first intercourse, lifetime number of sexual partners, history of sexual transmitted diseases, use of hormonal contraception, condom use at last sex, employment status, current smoking, snuff use (traditional chewing tobacco) and education level; [b]the Cox proportional hazards model yields an adjusted hazard ratio, not an adjusted rate ratio.

Data on the relationship between HAART and progression of cervical disease have been inconsistent [26–32]; a study of HIV-positive Italian women found no beneficial effect of HAART therapy on the risk of incident or progression rates of SIL [26], while a US-based study found that women on HAART had an increased clearance of HPV infection, though not with cervical cytologic regression or progression [27].

In contrast, our results are largely consistent with the Women's Interagency HIV study cohort, which found that the use of adherent HAART was associated with lower detection of incident oncogenic HPV (hazard ratio (HR) $= 0.49$; 95% CL 0.30, 0.82) and an improved clearance rate of oncogenic HPV and SIL (HR $= 2.4$; 95% CL 1.1, 5.2) [28]. A second Italian cohort also showed that HAART significantly reduced the risk of developing CIN (HR $= 0.3$; CL 0.13, 0.68) [29]. A recently published South African study also found that women on HAART had a reduced risk of progression of cervical neoplasia, albeit with a smaller magnitude of effect than observed in our study (HR $= 0.72$; 95% CL 0.52, 0.99) [30]. Differences in the magnitude of the effect of HAART on the incidence/progression of SIL in different cohorts may be due to the differences in adherence to HAART [28]. Adherence to HAART in our clinic, as measured by HIV virologic suppression, was 90% at 6 months and 85% at 1 year follow-up [21].

Another potential reason for the different magnitudes of the HAART effect on SIL incidence/progression might be related to the average baseline CD4 counts of the participants in these studies. This is consistent with the observation that immunosuppression is a risk factor for acquiring cervical dysplasia [1,2]. Our study shows that rates of incidence or progression of cervical lesions were higher with lower CD4 counts and that HAART had a stronger effect on reducing the rate of progression at lower CD4 counts. Two additional analyses from a cohort in Spain are consistent with our

results. A retrospective study from Spain showed that women on HAART with controlled HIV disease (defined as an undetectable HIV viral load and a CD4 count of >200 cells/mm^3) had a reduction in SIL. The significant effect of HAART was seen in women with CD4 counts of <350 cells/mm^3 as there was no difference seen in the effect of HAART on any SIL with women with CD4 counts of >350 cells/mm^3 [31,32]. The stronger relationship of HAART's effect in lower CD4 ranges may be due to the significant immunosuppression in patients with CD4 counts of <350 cells/mm^3. This is an important finding as the median CD4 count of patients coming to our clinic is 76 cells/mm^3 (IQR 28, 136) [33], thus potentially explaining why HAART treatment reduced the progression of dysplasia in our population in South Africa. Immune reconstitution of HAART, however, is often incomplete, especially in populations that initiate HAART at a CD4 count below 200 cells/mm^3 [34,35] as per the South Africa guidelines during this study [17]. Even in patients with successful immune reconstitution measured by CD4 counts, the risk for opportunistic infections such as tuberculosis is still higher than that among the HIV-seronegative population [36,37]. Future research should consider CD4-stratified effect estimates to help clarify these issues and to evaluate if women with complete immune reconstitution are still at higher risk of SIL progression than HIV-negative women. In addition, in resource-limited countries especially where access to cervical cancer screening programmes are limited, initiating women on to HAART should be strongly considered especially among women with CD4 counts of <350 cells/mm^3.

The strengths of this study include that it was conducted in a government HIV treatment clinic, allowing results to be extrapolated more closely to the actual clinical environment in which our women are seen, relatively large sample size and long follow-up.

This work has several limitations. First, histologic verifications of Pap smears are lacking. Colposcopic biopsies in women with negative or a single LSIL Pap is not standard of care in South Africa; however, Pap smears from this cohort were independently reviewed as noted previously. We also did not control for other factors such HIV viral load, real-time STI and HPV infection status. Baseline HIV viral load information is not routinely collected in South Africa at HAART initiation [17]. HPV testing was not done in this study as it is not available in South African government hospitals or clinics. The history of recent STI was per patient recall on our questionnaire making the timing and accuracy of diagnosis of STI difficult to ascertain. Laboratory testing for STI in the government system in South Africa is not performed, and treatment is based on clinical symptoms.

One additional limitation is the relative poor sensitivity of cytology, potentially leading to an under-diagnosis of LSIL at baseline. This misclassification would cause us to overestimate the incidence of LSIL. However, such misclassification is likely to be independent of current HAART status and is, therefore, likely to be non-differential misclassification. If so, then our reported incidence rate ratio is likely (though not guaranteed) to underestimate the true effect of HAART on incidence or progression of cervical dysplasia. Of course, if such misclassification depends on HAART status, the effects are more difficult to predict.

Conclusions

This study demonstrates high baseline rates of incidence and progression of cervical lesions among HIV-positive women in South Africa, as well as the effect of HAART at reducing risks of both incidence and progression. Given that the median time to an incidence or progression event was 407 days, yearly cervical cancer screening should be considered for HIV-positive women. WHO HIV 2010 revised treatment guidelines recommend resource-limited countries initiate HAART in HIV-positive patients with CD4 counts of <350 cells/mm^3 in WHO Stage 1 and 2 [38]. Our data suggest a potential benefit of initiating HAART use in these women at CD4 counts of <350 cells/mm^3. Integrating cervical cancer screening programmes into HIV treatment programmes is a public health imperative in South Africa.

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Competing interests

The authors have no conflict of interest to declare related to this work.

Authors' contributions

All authors participated in the study and the writing and reviewing the data and the manuscript. Cynthia Firnhaber was the PI of the cohort, project manager and the primary writer of the manuscript. Daniel Westreich performed the statistically analysis. Doreen Schulze was the data manager of the project. Sophie Williams and Maureen Siminya were responsible for the daily care of the patients. Pam Michelow was the cytologist, and Simon Levin and Mark Faesen were gynaecologist consultants on this project. Jennifer S Smith participated in the epidemiology and statistical analysis of this project and paper.

Abbreviations

ASC-H, atypical squamous cells-high; ASCUS, atypical squamous cells of undetermined significance; CL, confidence limit; HAART, highly active antiretroviral therapy; HPV, human papillomavirus; HR, hazard ratio; HSIL, high-grade squamous intra-epithelial lesions; IQR, inter-quartile range; IRR, incidence rate ratio; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intra-epithelial lesions; SACCC, South Africa Cervical Cancer Cohort; SIL, squamous intra-epithelial lesions; STI, sexually transmitted infection.

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