Injectable and oral contraception and the incidence and progression of cervical disease in HIV-infected women in South Africa

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Abstract

Background—Few data exist regarding the effect of hormonal contraception (HC) on incidence and progression of cervical disease (e.g., cervical dysplasia, squamous intraepithelial lesions, cervical intraepithelial neoplasia) in HIV-infected African women.

Study Design—We conducted an observational study of HIV-seropositive women in Johannesburg, South Africa. The effect of individual HC types on the incidence and progression of cervical disease was determined using Poisson regression to obtain adjusted incidence rate ratios (IRR).

Results—We evaluated 594 HIV-infected women, with median follow-up time of 445 days; 75 of these women were receiving some form of hormonal contraception (largely DMPA, NET-EN, or COCs) at baseline. Risks of incidence and progression of cervical disease were similar comparing women not receiving HCs to women receiving DMPA, NET-EN, or COCs both individually by HC-type and considering all HC together.

Conclusions—There was no statistically significant effect of particular HC methods or of HC use in general on rates of incidence or progression of cervical disease in this study. These results should reassure us that use of HC is unlikely to substantially increase risks of cervical disease among HIV-positive women.

1. INTRODUCTION

Cervical cancer is currently the third most common cancer in women globally [1] and the most common in sub-Saharan Africa [2]. Up to 85% of the disease burden is in the less-developed world, and large parts of the African continent including southern Africa are considered to be high-risk regions. In South Africa, the age-standardized incidence rate is 26.6 per 100,000 women per year, making it the second most common female cancer [1]. Within South Africa the prevalence of HPV infection is approximately 21% in the general female population; the majority of diagnosed invasive cervical cancer cases are attributed to high-risk human papillomavirus (HPV) types, particularly 16 and 18 [3].

South Africa is also home to the highest number of people living with HIV/AIDS, approximately 5.7 million people, the majority of whom are women [4]. High-risk HPV is seen in 60–90% in HIV positive women with HPV-16 being the most common cause of invasive cervical cancer [5–7]. Studies from across the globe suggest the progression of cervical neoplasia to cervical cancer to be higher in HIV positive women [8–11], although progression rates might be reduced [12–14] and regression improved[15] by use of highly active antiretroviral therapy.

Among young HIV-positive South African women, unintended pregnancy is common [16–19] and use of modern contraceptive methods including hormonal contraception is high [20]. HIV-positive women have an increased incidence of HPV-associated cervical disease (e.g., cervical dysplasia, squamous intraepithelial lesions (SIL), cervical intraepithelial neoplasia) [8–11]. But unfortunately, hormonal contraceptives - critical in this setting not only to prevent unintended pregnancy and attendant maternal morbidity and mortality, and also to prevent mother-to-child transmission of HIV - may increase the risk of high-risk cervical disease including invasive cervical cancer, possibly due to effects of estrogens and progestins on key HPV proteins (e.g., HPV-16 E2 and E7) [21–23]. This may be a particular concern with oral contraceptives. Women who use oral contraceptives over a longer duration [24] may be at higher risk, and risk may be reduced after discontinuation of HC for several years [24]. For example, a collaborative reanalysis of 24 previous studies found a near-doubling of risk of invasive cervical cancer after five years use [2]. In contrast, a South African case-control study found no association between recent users of oral contraceptives (compared to never users) and cervical cancer[25]. Other studies have found associations of oral contraceptives with increased prevalence [26,27] and persistence [28] of HPV.

Injectable hormonal contraceptive methods (particularly depot-medroxyprogesterone acetate, or DMPA), are more popular than oral contraceptives among prevalent and new users of contraception throughout much of Africa including South Africa [16,19,29–31] (norethisterone oenanthate, also called Nur-sterate, Noristerat or NET-EN is also popular in South Africa). There have been few studies addressing if progesterone-based injectables change risk of the development of cervical disease. A small Latin American case control study [32] found evidence of increased risks of invasive cervical cancer in longer-term users of injectable contraceptives. Two studies in Jamaica found associations between use of hormonal contraceptives (including DMPA in particular) and cervical disease [33,34], while two South African studies found contrasting results: one found no such association [35], while another found that women using DMPA or NET-EN were more likely to be HPV-DNA positive at study enrollment [36]. A Bangladeshi case-control study found a raised risk

of cervical cancer with use of oral contraceptives but not injectable methods [37]. A final study which did not distinguish among types of hormonal contraception (including oral contraceptives, injection methods, rings, patches, and progesterone intrauterine devices) found no association between hormonal contraception and high-risk HPV or high-grade cervical disease [38].

None of these studies were conducted primarily among HIV-positive women; some (e.g., [2]) excluded HIV-positive women specifically. Given the significant burden of both HIV and HPV in South Africa, and recommendations of increased integration of hormonal contraception with HIV care [17,19,39], we investigated whether use of hormonal contraception was associated with increased incidence or progression of cervical disease in a cohort of HIV-positive women in Johannesburg, South Africa.

2. MATERIALS AND METHODS

2.1. Study population

We conducted this analysis inside the South Africa Cervical Cancer Cohort, an observational, longitudinal study of HIV-infected women [6]. The cohort included HIV-infected 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, South Africa (SA). Women were eligible to participate in this study unless they (i) were pregnant; (ii) had undergone a hysterectomy or cone biopsy; (iii) were severely ill per investigator's opinion; or (iv) had signs and/or 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 approached for inclusion were given an educational session on cervical cancer screening in English or in an appropriate African language, and then invited for a conventional Pap smear. A medical history was obtained through a participant interview including antiretroviral therapy status, reproductive/ menstrual characteristics, sexual history/behaviour, history of STIs, and contraceptive use. Women were treated according to the HIV South African Guidelines on Comprehensive HIV and AIDS Care, Management and Treatment[40], including HAART initiation at WHO stage 4 or CD4 count < 200 cells/mm^3. Women were excluded from the present analysis if they had high grade squamous intra-epithelial lesions (HSIL) at baseline.

2.2. Laboratory analysis

Cervical exfoliated cells were collected during a pelvic examination using an endocervical brush for a conventional Pap smear diagnosis. Such conventional cervical smears were performed as standard of care for HIV-positive women in South Africa; liquid-based cytology is currently not available in this setting. Cytology slides were read and analyzed according to Bethesda 2001 guidelines[41]. Women with atypical squamous cells-high (ASC-H) or HSIL were referred for immediate colposcopy, while women with atypical squamous cells of undetermined significance (ASCUS) or low-grade intra-epithelial lesions (LSIL) were followed with a repeat Pap smear after 1 year 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 who presented with 2–3 consecutive LSIL results over 18 months were also referred for colposcopic biopsy.

The cytology program at the National Health Laboratory Services and University of Witwatersrand pathology has a rigorous internal QA which all positive results ASC-US are reread by two different readers and all negative Pap smears are rapidly reviewed again. Any discrepancy between cervical cytology and histology results are re-examined. The cytologists participate in the Australian Royal College Pathology Association Quality assurance program. In addition, 10% of the conventional cytology slides were sent to the

University of North Carolina at Chapel Hill for blinded double-readings on two occasions, with an observed concordance rate of 81% and 85% [6]. Discrepant results where one of the two diagnoses was HSIL were resolved by colposcopic biopsy.

2.3. Exposure and outcome definitions

Exposure was type of hormonal contraception exposure at baseline (including DMPA; NET-EN; combination oral contraceptives; and other methods e.g. Norplant). In secondary analysis, we also considered an exposure of "any HC" compared with none at baseline. Outcome was defined as the time to the first incidence or first progression of cervical SILs from baseline status, that is, from negative Pap smear to LSIL, HSIL, or cancer; or, from LSIL to HSIL or cancer. HSIL Pap smear results triggered a referral for confirmative colposcopic biopsy and then treatment (specifically, a Loop Electrosurgical Excision Procedure (LEEP)); as such, individuals with HSIL at baseline were not at risk of cervical lesion progression in the same way as those with negative or LSIL diagnoses, and so HSIL cases were excluded from analyses of progression. In the analysis, ASC-US results were classified as LSIL results, while ASC-H results were classified as HSIL results. AGUS results were excluded as per the Bethesda classification system [41]. Note that because only two visits were included, women could experience incidence or progression of SIL, but not both.

2.4. Statistical methods

Women with two Pap smears at least 6 months apart were included in data analyses. In main analysis the exposure was the use of HC by type at first visit in the cohort; changes in exposure after baseline (including initiation or discontinuation of HC) were not considered. These analyses used multivariable Poisson regression to compare the rate of incidence or (separately) progression of SIL using HC at baseline to no HC at baseline; Poisson regression was used to account for differing lengths of follow-up. All analyses considered confounding by use of HAART (which reduces rate of SIL progression [13,14]) age, CD4 count, history of sexually transmitted infections, parity, lifetime number of sexual partners, age at first intercourse, condom use at last sex, employment status, current smoking, snuff use (traditional chewing tobacco), and education; these variables were selected from baseline substantive knowledge about factors which might be associated with HC use and were risk factors for the outcome. CD4 counts and age were both modelled as restricted four-knot cubic splines; other covariates were modelled categorically.

2.5. Ethics

Written informed consent was obtained from all participants. 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 and Duke University.

3. RESULTS

There were 594 women eligible for this analysis, of whom 75 (13%) were using hormonal contraception of any kind at their first visit; another 110 women had HSIL at baseline and were excluded from analysis. Of these 594 women, most (n=50) were using an injectable method, with 24 using DMPA and 26 using NET-EN; only 18 were using oral contraceptives and an additional 7 were using another method. Compared to women not using any form of hormonal contraception, women using hormonal contraception were younger (p<0.01) and somewhat more likely to use HAART (p=0.06; see Table 1).

At baseline, 326 women had normal Pap values, while 268 women had LSIL. These 594 women were followed up for a mean of 551 days (median 446 days; IQR 383, 671). Of 326 women with normal baseline Pap, 76 (23%) experienced an incident LSIL or HSIL during follow-up, a rate of 15.9 (95% confidence limits [CL] 12.7, 19.9) per 100 person-years; of 268 women with baseline LSIL, 45 (17%) experienced a progression to HSIL during follow-up, a rate of 10.8 (95% CL 8.0, 14.4) per 100 person-years [14].

We analyzed the impact of DMPA, NET-EN, and combined oral contraceptives (COCs) separately among those with and without LSIL at baseline (progression and incidence, respectively) in a separate Poisson models adjusted for confounding (see list above). We found that injectables (and particularly NET-EN) were associated with a slight but highly imprecise increased rate of incident SIL, but not SIL progression (Table 2), and that COCs were generally associated with lower rates of both incidence and progression. No findings were statistically significant.

We explored simpler models by assessing Akaike's Information Criterion (AIC): first when combining DMPA and NET-EN into a single exposure; then combining all HC into a single exposure; then eliminating distinctions between incidence and progression of SIL. In all cases, AIC favored the simpler model, and thus we proceeded with sensitivity analyses using all HC as a single category, assessing incidence and progression together. After simplifying the model, we reincorporated "other" hormonal contraceptive users in analysis, for a total sample size of 594.

The effect of any exposure to any hormonal contraception on incidence or progression of SIL was 1.11 (95% CL 0.62, 1.97), which is compatible with all three of the by-HC-type confidence intervals (Table 2). To maximize power in the presence of small event counts, we performed several sensitivity analyses using this simplified analysis. As shown in Table 3, we found slightly higher point estimates when excluding ASC-US from the LSIL category, when using a Cox proportional hazards model rather than a Poisson model, among women not on HAART, and among women with higher CD4 counts (who, it should be noted, are less likely to be on HAART, odds ratio 1.6 for association). However, all point estimates were based on few events and consequently had very wide confidence intervals compatible with the hypothesis that any variation is due to chance alone.

4. DISCUSSION

Our study presents some of the first information on the effect of hormonal contraception on the incidence and progression of cervical disease among HIV-infected women in sub-Saharan Africa. Overall we saw no statistically significant effect of individual HC methods including DMPA and COCs on incidence or progression of SIL in this cohort, as well as no effect of HC overall. These findings are contrary to expectations on effects of oral contraceptive pills [21–23], but consistent with most of the data regarding cervical cancer risk in HIV-negative women using progesterone-based injectable [2,24,37]. In addition, here we saw no effect of HC on SIL progression within individuals with lower CD4 counts; since SIL progression rates are often higher with lower CD4 counts, these results are reassuring. However, all these results are based on few users and events (Table 2, Table 3), and must not be over-interpreted. Future work should investigate these same relationships by type of contraceptive, with substantially greater sample sizes.

These results are reassuring, as progesterone-based injectable contraceptive methods are used in the majority of the women in South Africa (13, 20–22). Preventing unplanned pregnancies is an important and crucial method of preventing mother-to-child transmission of HIV, maternal health, empowerment, and child spacing. The convenience of progesterone-based injectables makes these an important tool in preventing pregnancy.

Beyond relatively small numbers of women using hormonal contraception in this study, especially of oral contraception, this work has several other limitations which bear mention. First, histological verifications of the Pap smears are lacking. Confirmatory colposcopic biopsy 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 above. We could not control for baseline HIV viral loads because this information is not collected in South Africa at HAART initiation [40]. Further, loss to follow up due to migration, transfer to other clinics, and death was a challenge in our clinic generally. In this study, we limited analysis to individuals with at least one follow-up visit; loss to follow-up may impact the generalizability of these results, although we do not believe that a biological impact of HC use on incidence and progression of SIL, if it exists, is likely to be biased by patterns of loss to follow-up. Also, follow-up rates among participating HIV-seropositive women were not optimal due to socio-cultural factors and limited funding for the follow-up, with the follow up resources focused on women with HSIL or greater Pap smear diagnoses. Finally, limitations in the data required us to treat use of hormonal contraception as fixed from baseline visit, although some women both stopped and started use of hormonal contraception during follow-up. An informal sensitivity analysis which assigned half an exposure unit to women who started or stopped hormonal contraception during follow-up yielded results very similar to main results for all forms of HC combined.

Despite these limitations, the study has significant strengths, including 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 patients are seen; a relatively large sample size; and long follow-up.

While more study of this issue with greater sample size is needed, the present work shows no association of hormonal contraception generally, or injectable hormonal contraception in particular, with incidence and progression of cervical disease among HIV-positive women in South Africa, including those taking HAART.

Acknowledgments

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Table 1

Characteristics of 594 HIV-positive women in Johannesburg, South Africa by exposure to specific types of hormonal contraception (HC) at study entry.

| Baseline characteristic[‡] | No HC (N=519) | Hormonal contraception | | |
| | | Injectable (N=50) | Oral (N=18) | Other (N=7) |
	N (%)	N (%)	N (%)	N (%)
Age in years[‡]	35 (31, 41)	31 (28, 35)	33 (32, 38)	36 (35, 47)
Parity[‡]	2 (1, 3)	2 (1, 2)	2 (1, 2)	3 (1, 3)
CD4 count (cells/mm3)[‡]	266 (158, 413)	275 (195,378)	307 (160,441)	343 (138,435)
CD4 count (cells/mm3)				
<200	197 (38)	13 (26)	7 (39)	2 (29)
200–350	144 (28)	21 (42)	4 (22)	2 (29)
>350	178 (34)	16 (32)	7 (39)	3 (43)
Current HAART use	361 (70)	43 (86)	11 (61)	6 (86)
Baseline negative Pap	290 (56)	25 (50)	7 (39)	4 (57)
Reported history of STIs	354 (68)	32 (64)	12 (67)	3 (43)
Condom used at last sex	378 (73)	38 (76)	16 (89)	4 (57)
Lifetime # sex partners 5	205 (40)	20 (40)	8 (44)	2 (29)
Age at first sex <15 years	42 (8)	3 (6)	0 (0)	1 (14)
Unemployed	278 (54)	24 (48)	11 (61)	4 (57)
High school graduate	206 (40)	22 (44)	6 (33)	2 (29)
Current smoker	17 (3)	2 (4)	0 (0)	0 (0)

N, number; STIs, sexually transmitted infections; HC, hormonal contraception

[‡]Categorical variables are compared by chi-square test for general association; continuous variables by two-sided Wilcoxon rank-sum test.

Table 2

Estimates of the effect of hormonal contraception by type on rate of incidence of cervical disease (low or high grade SIL among women with baseline normal Pap) and separately progression of cervical disease (high grade SIL among women with baseline low grade SIL) among HIV-positive women in Johannesburg, South Africa.

Incidence (n=322)	Events/Person-years		Rate ratio	95% CL
	Exposed	Unexposed[‡]		
NET-EN	4/13		1.79	0.58, 5.46
DMPA	4/23	66/427	1.28	0.44, 3.70
Combined oral contraceptives	1/10		0.55	0.07, 4.61

Progression (n=265)	Events/Person-years		Rate ratio	95% CL
	Exposed	Unexposed[‡]		
NET-EN	3/21		1.51	0.41, 5.55
DMPA	1/14	40/360	0.91	0.12, 6.95
Combined oral contraceptives	1/17		0.43	0.05, 3.38

CL, confidence limits. DMPA, depot-medroxyprogesterone acetate. NET-EN, norethisterone oenanthate, or Nur-sterate or Noristerat. SIL, squamous intra-epithelial lesions. HAART, highly active antiretroviral therapy.

Estimates derived from separate models for incidence and progression, each of which was adjusted for: use of HAART, age, CD4 count, history of sexually transmitted infections, parity, lifetime number of sexual partners, age at first intercourse, condom use at last sex, employment status, current smoking, snuff use (traditional chewing tobacco) and education. Analyses in this table excluded 7 individuals who used other forms of hormonal contraception and who experienced 1 event.

[‡] Unexposed to any hormonal contraception, same value for all table rows.

Table 3

Estimates of the effect of any hormonal contraception (combined exposure) on rate of incidence of cervical disease (low or high grade SIL among women with baseline normal Pap) and progression of cervical disease (high grade SIL among women with baseline low grade SIL) among 594 HIV-positive women in Johannesburg, South Africa.

	Events/Person-years		Rate ratio	95% CL
	Exposed	**Unexposed**		
Crude	15/109	106/787	1.02	0.59, 1.75
Adjusted[‡]			1.11	0.62, 1.97
ASCUS-excluded[‡]	13/67	90/597	1.24	0.67, 2.31
Cox proportional hazards model[†]	15/109	106/787	1.24	0.69, 2.24
Modification by HAART[‡]				
On HAART	9/87	65/560	0.97	0.48, 1.99
Not on HAART	6/22	41/227	1.42	0.56, 3.58
Modification by CD4[‡]				
CD4 350 cells/mm^3	10/69	79/527	0.87	0.44, 1.73
CD4>350 cells/mm^3	5/40	27/261	1.82	0.68, 4.93

CL, confidence limits. HAART, highly active antiretroviral therapy. SIL, squamous intra-epithelial lesions.

[a]Adjusted for: age, CD4 count, age at first intercourse, lifetime number of sexual partners, history of sexually transmitted diseases, use of hormonal contraception, condom use at last sex, employment status, current smoking, snuff use (traditional chewing tobacco) and education level.

[†]The Cox proportional hazards model yields an adjusted hazard ratio, not an adjusted rate ratio.