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Hormonal contraception and vaginal infections among HIV serodiscordant couples in Lusaka, Zambia

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Abstract

Objective: To examine the relationship between hormonal contraception (HC) and vaginal infections with bacterial vaginosis (BV), vaginal candidiasis, or trichomoniasis.

Methods: HIV serodiscordant couples in Zambia were enrolled in a longitudinal cohort. From 1994 to 2002, both partners were seen quarterly and received physical exams including genital examinations. Separate rates for three outcome infections of interest (BV, vaginal candidiasis, and trichomoniasis) were calculated. Bivariate associations between baseline and time-varying covariates and outcome infections of interest were evaluated via unadjusted Anderson-Gill survival models. Adjusted hazard ratios (aHRs) were generated using multivariable Anderson-Gill survival models including demographic and clinical factors found to be associated with both hormonal contraceptive use and each infection of interest.

Results: There were 1558 cases of BV, 1529 cases of vaginal candidiasis, and 574 cases of trichomoniasis over 2143.42 person-years of observation. DMPA users had significantly lower rates of trichomoniasis and BV. In adjusted models, DMPA was protective for BV (aHR=0.72; 95% confidence interval (CI) 0.54-0.95), candidiasis (aHR 0.75, 95%CI 0.57-1.00)

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and trichomoniasis (aHR=0.43, 95%CI 0.25-0.74). Oral contraceptive pills (OCPs) were protective for candidiasis (aHR=0.79, 95%CI 0.65-0.97).

Conclusions: We confirm that DMPA use was associated with reduced rates of the three most common causes of vaginitis and OCP use was associated with reduced rates of candidiasis among women in HIV-discordant couples. Further research is necessary to understand the factors that may alter the vaginal environment leading to increased HIV risk.

Precis:

Depot medroxyprogesterone acetate was associated with reduced rates of bacterial vaginosis, vaginal candidiasis and trichomoniasis and oral contraception was associated with reduced rates of vaginal candidiasis.

Introduction:

Globally, over 17 million women are living with HIV. With an estimated 900,000 new cases occurring annually among women, prevention efforts are critical to curb the global HIV epidemic[1]. Providing safe contraceptive care for women at-risk or living with HIV is essential to adequately address their family planning needs and is primary strategy recognized by the WHO to reduce perinatal transmission of HIV via prevention of unintended pregnancy[2]. For reproductive aged women, hormonal contraception is a central component for preventing unintended pregnancy. Challenging HIV prevention efforts, there are concerns that hormonal contraceptives, specifically depot medroxyprogesterone acetate (DMPA), may contribute to the spread of HIV by increasing a woman's susceptibility to infection[3-7]. While several high quality studies have not demonstrated an increased risk of HIV with hormonal contraceptive use, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have recognized this important knowledge gap and encourage research to explore mechanisms associated with hormonal contraceptives that may underlie an increase in HIV transmission risk, if such an association exists [8-10].

There are several postulated mechanisms[11,12] that could lead to increased HIV susceptibility. One of the potential mechanisms is through the disruption of the vaginal microenvironment[13-22] that may occur in association with vaginal infections. When the vaginal flora is dominated by *Lactobacillus* species, particularly with *Lactobacillus crispatus*, studies have shown a decreased incidence of HIV[23] compared to women with bacterial vaginosis (BV)[24]. Current data, however, suggest that hormonal contraception would not increase HIV susceptibility through this mechanism. While evidence suggests that use of hormonal contraception either does not alter or may even decrease BV incidence, many studies are limited due to small sample sizes, analytically grouping different hormonal contraceptive methods, cross-sectional study designs, and incomplete control of confounders such as unprotected sex and sexual frequency[16,18,25,26]. Further, as different populations may have different prevalence of vaginal infections or altered vaginal microenvironments, it is important to evaluate this potential association in high risk couples in an area of high HIV prevalence and among women with HIV, as several of these infections may increase the risk of HIV transmission or acquisition to uninfected partners[35,36].

Trichomonas vaginalis, or trichomoniasis, is one of the most prevalent sexually transmitted infections (STIs) worldwide, with an estimated 5% of reproductive aged women infected globally[37]. Trichomoniasis has a bidirectional relationship with HIV, meaning that trichomoniasis increases risk of HIV acquisition and HIV infection increases risk of trichomoniasis acquisition[38-40]. Trichomoniasis is also often correlated with BV[41-43]. The relationship between trichomoniasis and hormonal contraceptive use has been relatively understudied with study findings limited by similar methodological concerns as BV studies.

Vaginal *Candida* infection, or candidiasis, is the second most common cause of vaginitis and affects up to 20% of women worldwide annually[47]. The association between candidiasis and HIV acquisition is unclear. Similarly, the relationship between candidiasis and hormonal contraceptive use is inconsistently demonstrated. In some studies, use of hormonal intrauterine devices (IUDs) or OCPs have been associated with increased risk of candidiasis, while others have shown no association [17,22,31,48-52].

We sought to explore the association between different hormonal contraceptives and BV, trichomoniasis, and candidiasis within a longitudinal cohort of HIV serodiscordant couples in Zambia. Our goal was to confirm prior findings of no association or a protective association of between hormonal contraceptives and these vaginal infections within a longitudinal study, add additional information on implants where there is limited information in the literature, and contribute a high-quality evaluation controlling for important confounders.

Materials and Methods:

Study Design, Participants and Ethics:

This study is a secondary analysis of a longitudinal cohort of HIV serodiscordant couples (in which the man is HIV-positive and the woman HIV-negative or the man is HIV-negative and the woman HIV-positive in Lusaka, Zambia. Married or cohabiting couples attending couples' voluntary HIV counseling and testing (CVCT) were invited to enroll in an open cohort of between 1994 and 2012 [53]. The primary study objectives were to evaluate correlates of HIV acquisition and transmission. The study recruitment [54,55], intervention design, uptake of contraception immediately after an educational intervention [56], impact of informed consent on knowledge and concerns about contraceptive methods [57], demographics of the cohort, rates of unintended pregnancy and impact of contraceptive method on unintended pregnancy [58], impact of the intervention on incident pregnancy [59], patterns of contraceptive use and discontinuation [60], impact of hormonal contraception on HIV acquisition risk[61] and HIV transmission to partners [62], and impact of hormonal contraception on HIV disease progression [63] have been previously reported. This study was approved by the Institutional Review Boards at Emory University and the University of Zambia. Written informed consent was obtained from all participating couples.

Exposure of interest

Contraceptive method used since last study visit (none, condoms only, OCPs, DMPA (150mg IM dosage), copper IUD, contraceptive implant (Levonorgestrel implant: Norplant,

Jadelle), or permanent methods (hysterectomy, tubal ligation, vasectomy)) was recorded at baseline and three-monthly follow-up visits. The exposure was time varying to account for method switching, starting a new method or stopping a method. The majority of OCPs were combined pills containing both an estrogen and progestin, with progesterone-only pills being primarily prescribed to breastfeeding women until children were 6 months old or women with contraindications to estrogens. Contraceptive methods were categorized as implant, injectable, or OCP versus non-hormonal (non-HC) methods that included none, condoms only or permanent methods. Given relatively infrequent IUD use, intervals with IUD use were excluded from our primary analysis with person-time during IUD use removed from the analysis. All methods were provided at the research site.

Outcomes of interest

The three repeated outcomes of interest were BV, vaginal candidiasis, and trichomoniasis. These time-varying outcomes were diagnosed by a vaginal swab wet-prep at baseline and at scheduled visits at intervals of three-months or client-initiated interim follow-up visits. BV was determined by a modified Amsel's criteria with vaginal discharge, >20% clue cells per high-power field, or positive whiff test with potassium hydroxide. Vaginal pH, which is part of Amsel's criteria, was not consistently available and thus not included in our determination of BV. Candidiasis was diagnosed based on the presence of hyphae or budding yeast. Trichomoniasis determined by the presence of trichomonads. Certified biomedical laboratory technicians with additional training by the site senior technologist performed wet-prep evaluations following standardized study procedures. This laboratory team was responsible for interpretation of results, quality control and release of those results to the clinic and had no access to the participant clinical data.

Baseline covariates

At enrollment, baseline demographic data was collected including age, monthly income, and literacy in Nyanja. Clinical and behavioral characteristics included number of previous pregnancies, current pregnancy, couple HIV status (Male Positive, Female negative or Male Negative, Female Positive), viral load (VL, log10 copies/mL) of the positive partner, HIV stage of positive partner, and herpes simplex virus (HSV-2) serology for both partners (categorized as positive, negative or discrepant).

Time-varying covariates

At scheduled quarterly (or client-initiated interim) follow-up visits, time-varying variables of interest collected included pregnancy, number of unprotected sexual acts since last visit, any self-reported unprotected sex act since last visit, sperm present on vaginal swab wet-prep, active genital or perianal ulcers for woman or male partner (by self-report or examination finding), positive Rapid plasma regain (RPR) serology for syphilis [64], male genital inflammation, male foreskin smegma, and circumcision status of male partner. As we had three distinct time-varying outcomes of interest, BV, vaginal candidiasis, and trichomoniasis were each evaluated as a potential covariate in models where they were not the primary outcome of interest.

Longitudinal data collection

Data collection varied by type and frequency of data collected over 17 years of follow-up (1994-2012). This analysis is restricted to visits taking place between 1994 and 2002, a period in which both partners were seen quarterly and received physical examinations, including genital examinations and wet-prep at each visit irrespective of patient symptoms. After 2002, physical examinations and wet-prep diagnoses were performed at baseline and thereafter only if signs and symptoms of infections were present. Plasma banking for VL testing was available beginning in 1999.

Data analysis

Analyses were conducted with SAS v9.4 (Cary, NC). Rates with corresponding Taylor series 95% confidence intervals (CIs) for each outcome of interest were calculated as the number of incident infections per couple-year of follow-up, stratified by contraceptive method type. Couple years of follow-up were calculated from enrollment until the couple was censored. Couples were censored when either partner died, the couples separated, the positive partner started antiretroviral treatment (ART), or if either partner was lost to follow-up.

Descriptive analyses of baseline and time-varying measures were stratified by intervals where outcome infections were detected. Counts and percentages (calculated over all study intervals for baseline and time-varying variables) described categorical variables while means and standard deviations described continuous variables (again, calculated over all study intervals).

Bivariate associations between baseline and time-varying covariates and repeated outcome infections of interest were evaluated via unadjusted Anderson-Gill survival models to generate crude hazard ratios (HRs) and 95% confidence intervals (CIs). Anderson-Gill survival models estimated the total effect of time-varying contraceptive method type on time to repeated outcome infection. Covariates significantly ($p<0.05$) associated with both the exposure (hormonal contraceptive use) and outcome of interest (BV, Candidiasis, or Trichomoniasis) were considered as potential confounders. Variable multi-collinearity was assessed and was not determined to be present, using condition indices of 30 and variance decomposition proportions of 0.05 as cutoff criteria. Adjusted HRs (aHRs) and 95% CIs are presented for covariates in the final multivariate models. All analyses were initially stratified by couple HIV status, but couple HIV status was not found to be an effect measure modifier. Couple HIV status was forced into the final multivariable models.

Sensitivity analyses: Though HSV-2 infection was believed to be a potential confounder of the relationship between hormonal contraceptives and outcome infections of interest, it was excluded from adjusted models in primary analyses due to high levels missingness (half of observations). Sensitivity analyses including male and female HSV-2 status in multivariate models were conducted. Second, we conducted a sensitivity analysis including copper IUD users in our non-HC using reference group. Additionally, as unprotected intercourse is known to be associated with both vaginitis and HIV acquisition based on the literature, we repeated all models forcing self-reported unprotected sex and sperm on wet-prep into

the models, even if they did not meet our criteria for inclusion based on our confounding assessment.

Results:

Rates of infection by contraceptive method (Table 1):

Among the 1082 couples enrolled and in follow-up between 1994 and 2002, there were 1558 cases of BV, 1529 cases of candidiasis, and 574 cases of trichomoniasis over 2143.42 person-years of observation. Among the 7,908 number visits included in primary analyses (data not shown), implants were used at 47 visits (0.59%), injectable methods at 679 visits (8.59%), OCPs at 1049 visits (13.27%), tubal ligation or vasectomy at 77 visits (0.97%), and no method or only condoms at 6056 visits (76.58%). The copper IUD, which was excluded from primary analyses, was used at 43 visits (0.54%). DMPA users had significantly ($p<0.05$) lower rates of trichomoniasis and BV compared to non-hormonal contraceptive users. There were no other significant differences in outcome rates by contraceptive method.

Unadjusted and multivariable evaluation of BV (Table 2 and supplemental Table 1):

In the bivariable analysis, woman's younger age, being HIV positive, having active genital ulcers, and trichomoniasis all increased risk of BV, while DMPA use, breastfeeding was protective for BV. Reporting unprotected sex and having sperm noted on wet-prep increased risk of BV. Significant ($p<0.05$) confounders with contraceptives included in the multivariable model included woman's age, couple HIV status, breastfeeding, active genital ulcer and trichomoniasis. In the final model (Table 2), DMPA was protective for BV (aHR 0.72, 95% CI 0.54, 0.95)), while there was no significant difference in BV incidence with implant or OCP use.

Unadjusted and multivariable evaluation of vaginal candidiasis (Table 3 and supplemental Table 1):

In the bivariable analysis, woman's younger age, and being pregnant was associated with increased risk of candidiasis, while having more prior pregnancies and being HSV-2 positive was associated with reduced risk. No male partner factors were associated with candidiasis risk. In the bivariable analyses, DMPA and OCPs were significantly associated with decreased candidiasis risk. Significant ($p<0.05$) confounders with contraceptives that were included in the multivariable model included couple HIV status, woman's age, number of previous pregnancies and breastfeeding. In the final model, DMPA and OCPs decreased the risk of candidiasis (aHR 0.75, 95% CI 0.57, 1.00 and aHR 0.79, 95% CI 0.65, 0.97, respectively).

Unadjusted and multivariable evaluation of vaginal trichomoniasis (Table 4 and supplemental Table 1):

In bivariable analysis, DMPA use was protective against trichomoniasis. Younger age, having fewer prior pregnancies, being HIV positive, vaginal discharge, active genital ulcers, BV, and male partner foreskin smegma were associated with increased risk of trichomoniasis, while breastfeeding was protective. Significant ($p<0.05$) confounders of contraceptive use included in the multivariable model were couple HIV status, pregnancy

status, breastfeeding, active genital ulcers, BV, and candidiasis. In the final model, DMPA reduced risk of trichomoniasis (aHR 0.43, 95% CI 0.25, 0.74).

Sensitivity analyses:

When copper IUDs were included within the non-hormonal contraceptive referent group and when HSV-2 was included in the analysis, the magnitude of adjusted HRs and their significance did not differ substantially from primary models. For all models, inclusion of self-reported unprotected sex and sperm on wet-prep did not substantially change our study findings (data not shown).

Discussion:

In this longitudinal cohort of HIV serodiscordant couples in Lusaka, Zambia, use of DMPA decreased rates of BV, candidiasis and trichomoniasis, and use of OCPs decreased the rate of candidiasis. No method of hormonal contraception was associated with significant increased rate of any of the outcome vaginal infections. This study augments existing knowledge through rigorous epidemiologic evaluation of quality data collected from serodiscordant couples accounting for a broad range of potential confounding factors. These findings concur with previous findings that contraceptive use does not increase risk of vaginal infections[16,18,22,45-48]. In a recent meta-analysis, all studies reviewed showed either statistically significant decrease in BV in hormonal contraceptive users or no significant difference when compared to non-hormonal contraceptive users [22,27-31]. Further, the three highest quality studies report a 10-20% reduction in BV in combined oral contraceptive pill (OCP) users and 18-30% reduction in DMPA users [32-34]. Another meta-analysis including 55 studies reported an approximate 25% reduction in both incident and prevalent BV in hormonal contraceptive users compared with non-users, irrespective of whether the method of hormonal contraception was progestin-only or a combined estrogen-progestin method[26]. DMPA use has been shown to be protective or have no association with trichomoniasis risk, while contraceptive implants and OCPs have shown a negative association[33,42,44-46]. We have previously reported that BV may modify the association between hormonal contraception and HIV acquisition [65]. While our current study findings do not indicare an increase in vaginal infections with hormonal contraceptive use, our prior study findings highlight the need for ongoing consideration of these vaginal infections as potential modifiers of the association between hormonal contraception and HIV.

This cohort reflects the reality of women's lives in which pregnancy, breastfeeding and contraception alternate, with each stage associated with alterations in the hormonal environment. The observed protective association between DMPA and BV may be related to alterations to the menstrual cycle. Menses is an important factor in altering vaginal microbiota, and the variations in cycle length or frequency resulting from hormonal contraception may have an impact on these shifts [66,67]. The mechanism by which DMPA use protects against *T. vaginalis* infection is unclear, but it has been suggested that exogenous hormones interfere with binding to androgen and estrogen receptors present on the parasite [68].

Though we did not find evidence of increased incidence of vaginal infections associated with hormonal contraceptive use, these results may not be applicable to other methods of birth control such as the intravaginal hormonal contraceptive methods like the vaginal ring and hormonal IUDs. Both hormonal IUDs and intravaginal rings have been shown to aid in the formation of *Candida* biofilm, particularly among women with BV infection [72,73]. Recent studies have found no evidence of impact on the vaginal microbiome caused by hormonal IUDs or sustained vaginal ring usage [74-76], however these studies were limited in size and future research is needed to confirm the results.

Our study benefits from a longitudinal design and our ability to account for and control for changes in contraceptive use and the impact of time-varying clinical and behavioral characteristics. Although vaginitis is associated with unprotected sex, inclusion of unprotected sex and semen on wet-prep in our models did not alter our study findings. As couples were no longer included in this cohort when the HIV-positive partner initiated antiretroviral therapy, our findings specific to HIV may lack generalizability to women in discordant couples with sicker index partners or those with greater access to treatment. While our study is limited by self-report of many indices, we have several objective measures to reduce self-reported bias, such as utilizing semen presence in addition to self-reported unprotected sex. HSV-2 status was only available for a subset of our cohort, thus our ability to evaluate the influence of HSV-2 status on study findings is reduced. Further, as many individuals who are HSV-2 positive may not have ulcers, combining repeated serologic assessment with examination findings would provide a more rigorous evaluation. While our outcome infections have been confirmed by laboratory diagnosis, the sensitivity and specificity of techniques used in diagnosing infections limit our ability to make firm conclusions. Future evaluation with more sensitive techniques, such as 16srRNA analyses, may identify changes in vaginal microbiota and its diversity associated with hormonal contraceptive use. Similar to other studies from sub-Saharan Africa, BV in our cohort is highly prevalent and often asymptomatic. It remains unclear what factors influence the regional differences in vaginal microenvironment or what underlies the development of clinical symptomatology associated with BV, however it is possible there may be regional differences in how contraception impacts the vaginal microenvironment.

Conclusions

Our study reports that vaginal infections are not increased in the presence of hormonal contraceptives; rather there may be some protective benefits of hormonal contraceptive use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Rates of infection by contraceptive method

	Number of events	Couple-years of follow-up time	Rate per 100 couple-years (95% CI)
Bacterial Vaginosis	1558	2143.42	73 (69-76)
Non-hormonal[≠]	1265	1695.43	75 (71-79)
DMPA	89	168.39	53 (42-65)
Implant	13	11.96	109 (58-186)
OCPs	191	267.65	71 (62-82)
Vaginal Candidiasis	1529	2143.42	71 (68-75)
Non-hormonal[≠]	1255	1695.43	74 (70-78)
DMPA	101	168.39	60 (49-73)
Implant	9	11.96	75 (34-143)
OCPs	164	267.65	61 (52-71)
Trichomoniasis	574	2143.42	27 (25-29)
Non-hormonal[≠]	489	1695.43	29 (26-32)
DMPA	18	168.39	11 (6-17)
Implant	2	11.96	17 (2-60)
OCPs	65	267.65	24 (19-31)

[≠]no method, condoms, permanent (excludes IUDs; CI: confidence interval; OCP: oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate

Table 2.

Unadjusted and Adjusted Association between method of contraception and bacterial vaginosis

Contraceptive method (time-varying)	**Non-BV intervals (%)**	**BV intervals (%)**	**cHR (95% CI)**	**aHR[#] (95% CI)**
Non-hormonal[ǂ]	4851 (67%)	1265 (81%)	*Ref*	*Ref*
DMPA	588 (8%)	89 (6%)	0.67[*] (0.50-0.91)	0.72[*] (0.54-0.95)
Implant	34 (0%)	13 (1%)	1.69 (0.74-3.86)	----
OCPs	1808 (25%)	191 (12%)	1.00 (0.81-1.23)	1.00 (0.81-1.21)

BV: bacterial vaginosis; Ref: reference; OCP: oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate; cHR: crude hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval

[#]Adjusted for women's HIV status, age, breastfeeding, active genital ulcer, and trichomoniasis

[ǂ]no method, condoms, permanent (excludes copper intrauterine devices)

[*]p-value<0.05.

Number of events in Implant group too few to allow for adjusted estimates.

Table 3.

Unadjusted and Adjusted Association between method of contraception and vaginal candidiasis

Contraceptive method (time-varying)	**Non-Candidiasis intervals (%)**	**Candidiasis intervals (%)**	**cHR (95% CI)**	**aHR[#] (95% CI)**
Non-hormonal[ǂ]	4794 (76%)	1255 (82%)	*Ref*	*Ref*
DMPA	574 (9%)	101 (7%)	0.72 [*](0.54-0.96)	0.75 [*](0.57-1.00)
Implant	38 (1&)	9 (1%)	0.96 (0.54-1.71)	---
OCPs	880 (14%)	164 (11%)	0.77 [*](0.63-0.94)	0.79 [*](0.65-0.97)

Ref: reference; OCP: oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate; cHR: crude hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval

[#]Adjusting for couple women's status, age, number of previous pregnancies, and breast feeding

[ǂ]no method, condoms, permanent (excludes copper intrauterine devices)

[*]p-value<0.05

Number of events in Implant group too few to allow for adjusted estimates.

Table 4.

Unadjusted and Adjusted Association between method of contraception and trichomoniasis

Contraceptive method (time-varying)	Non-Trichomoniasis intervals (%)	Trichomoniasis intervals (%)	cHR (95% CI)	aHR[#] (95% CI)
Non-hormonal[≠]	5626 (77%)	489 (85%)	*Ref*	*Ref*
DMPA	659 (9%)	18 (3%)	0.38[***] (0.22-0.65)	0.43[**] (0.25-0.74)
Implant	45 (1%)	2 (0%)	0.62 (0.10-3.73)	----
OCPs	981 (13%	65 (11%)	0.87 (0.63-1.20)	0.95 (0.7-1.31)

OCP: oral contraceptive pill; IUD: copper intrauterine device; DMPA: Depot Medroxyprogesterone Acetate; cHR: crude hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval

[#]Controlling for women's HIV status, pregnancy status, breastfeeding, active genital ulcer, bacterial vaginosis, and vaginal candidiasis

[≠]no method, condoms, permanent (excludes copper intrauterine devices)

[*] p-value<0.05

[**] p-value<0.01

[***] p-value<0.001.

Number of events in Implant group too few to allow for adjusted estimates