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# Concordance of self-reported hormonal contraceptive use and presence of exogenous hormones in serum among African women

Maria Pyra [a,b], Jairam R. Lingappa [b,c,d], Renee Heffron [a,b], David W. Erikson [e], Steven W. Blue [e], Rena C. Patel [c], Kavita Nanda [f], Helen Rees [g], Nelly R. Mugo [b,h,i], Nicole L. Davis [j], Athena P. Kourtis [j], Jared M. Baeten [a,b,c,*], for the Partners in Prevention HSV/HIV Transmission Study and Partners PrEP Study Teams

[a] Department of Epidemiology, University of Washington, Seattle, WA, USA
[b] Department of Global Health, University of Washington, Seattle, WA, USA
[c] Department of Medicine, University of Washington, Seattle, WA, USA
[d] Department of Pediatrics, University of Washington, Seattle, WA, USA
[e] Endocrine Technologies Support Core, Oregon National Primate Research Center, Beaverton, OR
[f] FHI 360, Integrated Health Sciences, Research Triangle Park, NC, USA
[g] Wits Reproductive Health and HIV Institute (WRHI), University of the Witswatersrand, Johannesburg, South Africa
[h] Department of Obstetrics & Gynaecology, University of Nairobi
[i] Sexual, Reproductive, Adolescent and Child Health Research Program, Kenya Medical Research Institute, Nairobi, Kenya
[j] Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

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ABSTRACT

*Objectives:* Studies that rely on self-report to investigate the relationship between hormonal contraceptive use and HIV acquisition and transmission, as well as other health outcomes, could have compromised results due to misreporting. We determined the frequency of misreported hormonal contraceptive use among African women with and at risk for HIV.

*Study design:* We tested 1102 archived serum samples from 664 African women who had participated in prospective HIV prevention studies. Using a novel high-performance liquid chromatography–mass spectrometry assay, we quantified exogenous hormones for injectables (medroxyprogesterone acetate or norethisterone), oral contraceptives (OC) (levonorgestrel or ethinyl estradiol) and implants (levonorgestrel or etonogestrel) and compared them to self-reported use.

*Results:* Among women reporting hormonal contraceptive use, 258/358 (72%) of samples were fully concordant with self-report, as were 642/744 (86%) of samples from women reporting no hormonal contraceptive use. However, 42/253 (17%) of samples from women reporting injectable use, 41/66 (62%) of samples from self-reported OC users and 3/39 (8%) of samples from self-reported implant users had no quantifiable hormones. Among self-reported nonusers, 102/744 (14%) had ≥1 hormone present. Concordance between self-reported method and exogenous hormones did not differ by HIV status.

*Conclusion:* Among African women with and at risk for HIV, testing of exogenous hormones revealed agreement with self-reported contraceptive use for most women. However, unexpected exogenous hormones were identified among self-reported hormonal contraceptive users and nonusers, and an important fraction of women reporting hormonal contraceptive use had no hormones detected; absence of oral contraceptive hormones could be due, at least in part, to samples taken during the hormone-free interval. Misreporting of hormonal contraceptive use could lead to biased results in observational studies of the relationship between contraceptive use and health outcomes.

*Implications:* Research studies investigating associations between hormonal contraceptive use and HIV should consider validating self-reported use by objective measures; because both overreporting and underreporting of use occur, potential misclassification based on self-report could lead to biased results in directions that cannot be easily predicted.



* Corresponding author. Tel.: +1 206 520 3808; fax: +1 206 520 3831.
*E-mail address:* jbaeten@uw.edu (J.M. Baeten).

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**Table 1**
Classification of quantifiable hormone results

| Self-reported method | Only expected hormones | Expected & unexpected hormones | Only unexpected hormones | No hormones |
|---|---|---|---|---|
| Injectable | Only MPA or NET | MPA or NET, plus LNG, ENG or EE2 | Only LNG, ENG or EE2 | None |
| Oral | Only LNG or EE2 | LNG or EE2, plus MPA, NET or ENG | Only MPA, NET or ENG | None |
| Implant | Only LNG or ENG | LNG or ENG, plus MPA, NET or EE2 | Only MPA, NET or EE2 | None |
| None | None | – | Any detected | – |

## 1. Introduction

Associations between use of hormonal contraceptive methods and the transmission or acquisition of HIV [1–4], bacterial vaginosis [5,6] and other sexually transmitted infections [7–9] have been topics of substantial interest for decades. Of particular concern is a possible increase in HIV acquisition and transmission among women using the injectable contraceptive depot medroxyprogesterone acetate (DMPA) [10]. Such research in general has relied on self-reported hormonal contraceptive use, rarely validated by biomarkers [11]. However, like many sensitive topics, self-reported hormonal contraceptive use is subject to possible misclassification due to social desirability bias, a need for privacy from sexual partners, confusion about methods, recall difficulties and potentially intentional misreporting because of desire to participate in research studies in which contraceptive use is a requirement [12–14]. Misclassification of women with respect to their hormonal contraceptive use could produce biased results in epidemiologic studies. In this analysis, we examined the degree of discordance between self-reported hormonal contraceptive use and exogenous hormones in serum from a cohort of HIV-uninfected and -infected African women.

## 2. Materials and methods

Data for this analysis came from three prospective studies (Partners in Prevention HSV/HIV Transmission Study, Couples Observation Study and Partners PrEP Study) [15–20]. Briefly, women were members of HIV-serodiscordant heterosexual couples in seven African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia) who were followed between 2004 and 2013.

This analysis includes a randomly selected subset of HIV-uninfected women who did not acquire HIV and HIV-infected women who did not transmit HIV to their male partner but who had a risk profile similar to women who acquired/transmitted HIV during the study follow-up, thereby representing a high-risk population [21]. A total of 843 women were initially selected for this analysis; each woman contributed up to two samples. Of the initial 1419 samples, we excluded: 50 samples from women with surgical contraception or IUD use (only copper IUDs without hormones were available in these settings), 188 samples from women 40 years old or older and 79 samples from women who were pregnant at the time of sample collection. However, samples from the first visit at which the pregnancy was detected were not excluded as these women may have been particularly likely to misreport their contraceptive use.

Contraceptive use was not a study requirement, but all study sites offered multiple contraceptive methods on site, and women could choose to obtain methods from the site or other providers. Women self-reported contraceptive methods by standard interviewer-administered questionnaires at regular study visits, and women in the analysis could switch between methods.

Blood samples were taken at quarterly visits and stored at −80°C. We used a validated, high-performance liquid chromatography–heated electrospray ionization–tandem triple quadrupole mass spectrometry (LC-MS/MS) assay to simultaneously test for five exogenous hormones, as well as progesterone (P4) [22]. We expected the following exogenous hormones for each self-reported method (Table 1): medroxyprogesterone acetate (MPA) or norethisterone (NET), components of two different injectable contraceptives; levonorgestrel (LNG) or ethinyl estradiol (EE2), components of oral contraceptives (OC); and LNG or etonogestrel (ENG), components of contraceptive implants. The lower limit of quantification (LLQ) for MPA, ENG and LNG was 0.02 ng/ml; for EE2 and P4, 0.01 ng/ml; and for NET, 0.04 ng/ml. We set results below LLQ to half the LLQ value for analysis.

For each sample, we compared self-reported hormonal contraceptive use to exogenous hormones as quantified by LC-MS/MS; the quantified hormones were not used to assign contraceptive use. We categorized the quantified hormones as expected, unexpected, both expected and unexpected, or no exogenous hormones for each method, as described above (Table 1). We compared the quantification of any expected exogenous hormone (versus no expected exogenous hormone) as a binary outcome by HIV status using generalized estimating equation (GEE) models to account for repeated observations, with a Poisson distribution and exchangeable correlation matrix. We also calculated the proportion of samples with evidence of ovulation (P4 ≥3 ng/mL). Among all users and separately for all nonusers, we modeled ovulation by presence of expected exogenous hormones using the same GEE model as above; due to small samples sizes, we were unable to model

**Table 2**
Characteristics of 664 women contributing samples

| | Self-reported method | | | |
|---|---|---|---|---|
| | Injectable, % (*n*) | OC, % (*n*) | Implant, % (*n*) | None, % (*n*) |
| N samples | 23.0% (253) | 6.0% (66) | 3.5% (39) | 67.5% (744) |
| Age | | | | |
| <25 | 22.5% (57) | 30.3% (20) | 15.4% (6) | 32.3% (240) |
| 25–29 | 25.3% (64) | 28.8% (19) | 25.6% (10) | 28.5% (212) |
| 30–34 | 29.2% (74) | 30.3% (20) | 28.2% (11) | 26.6% (198) |
| 35–39 | 22.9% (58) | 10.6% (7) | 30.8% (12) | 12.6% (94) |
| Married | 87.7% (222) | 90.9% (60) | 100% (39) | 84.8% (631) |
| >8 years of education | 32.4% (82) | 21.2% (14) | 23.1% (9) | 37.0% (275) |
| Recent condomless sex | 19.4% (49) | 31.8% (21) | 28.2% (11) | 15.1% (112) |
| Sexual partners outside of study partner | 2.4% (6) | 1.5% (1) | 0% (0) | 3.9% (29) |
| Pregnant | 1.2% (3) | 1.5% (1) | 0% (0) | 3.2% (24) |
| HIV-infected | 35.6% (90) | 36.4% (24) | 10.3% (4) | 40.0% (295) |
| Study | | | | |
| Couples Observational Study | 2.0% (5) | 1.5% (1) | 0% (0) | 6.7% (50) |
| Partners in Prevention HSV/HIV Transmission Study | 42.7% (108) | 36.4% (24) | 2.6% (1) | 66.7% (496) |
| Partners PrEP Study | 55.3% (140) | 62.1% (41) | 97.4% (38) | 26.6% (198) |

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