Original research article

Could misreporting of condom use explain the observed association between injectable hormonal contraceptives and HIV acquisition risk?☆,☆☆,★

Jennifer A. Smitha, Renee Heffronb,* Ailsa R. Butlera, Connie Celumb,c,d, Jared M. Baetenb,c,d, Timothy B. Halletta

aDepartment of Infectious Disease Epidemiology, Imperial College London, London, UK
bDepartment of Global Health, University of Washington, Seattle, USA
cDepartment of Epidemiology, University of Washington, Seattle, USA
dDepartment of Medicine, University of Washington, Seattle, USA

Received 26 September 2016; revised 19 December 2016; accepted 22 December 2016

Abstract

Objective: Some observational studies have suggested an association between the use of hormonal contraceptives (HC) and HIV acquisition. One major concern is that differential misreporting of sexual behavior between HC users and nonusers may generate artificially inflated risk estimates.

Study design: We developed an individual-based model that simulates the South African HIV serodiscordant couples analyzed for HC–HIV risk by Heffron et al. (2012). We varied the pattern of misreporting condom use between HC users and nonusers and reproduced the trial data under the assumption that HC use is not associated with HIV risk. The simulated data were analyzed using Cox proportional hazards models, adjusting for the reported level of condom use.

Results: If HC users overreport condom use more than nonusers, an apparent excess risk could be observed even without any biological effect of HC on HIV acquisition. With 45% overreporting by HC users (i.e., 9 out of every 20 sex acts reported with condoms are actually unprotected) and accurate condom reporting by nonusers, a true null effect can be inflated to give an observed hazard ratio (HR) of 2.0. In a different population with lower overall reported condom use, artificially high HRs can only be generated if non-HC users underreport condom use.

Conclusion: Differential condom misreporting can theoretically produce inflated HR values for an association between HC and HIV even without a true association. However, to produce a doubling of HIV risk that is entirely spurious requires substantially different levels of misreporting among HC users and nonusers, which may be unrealistic.

Implications: Considerably differential amounts of condom use misreporting by HC users and nonusers would be needed to produce entirely spurious observed levels of excess HIV acquisition risk among HC users when there is actually no true association.

© 2016 Published by Elsevier Inc.

Keywords: DMPA; Injectable hormonal contraceptives; HIV; Condom use; Misreporting bias; Mathematical modelling

1. Introduction

One of the most significant successes in global health has been the development of safe and effective methods of family planning and the expansion of their use in low- and middle-income countries [1]. A major challenge to global health in many countries, especially those in southern Africa, remains high HIV incidence in women of reproductive age [2]. It is therefore of substantial concern that some evidence suggests that the use of hormonal contraceptives (HC),
particularly injectables, could increase women’s risk of acquiring HIV infection, with recent meta-analyses suggesting a 1.4- to 1.5-fold increase in risk for women using the injectable depot medroxyprogesterone acetate (DMPA) [3–6]. The totality of analyses from observational studies assessing the potential association has produced conflicting results that are difficult to reconcile [7–19]. A challenging issue for these studies has been to appropriately adjust for behavioral patterns in the groups of women exposed and unexposed to HC. In particular, differences in condom use, coital frequency and the self-reporting of these measures have been hypothesized to artificially elevate risk estimates and produce spurious observed associations between HC use and HIV acquisition. Additionally, reported levels of condom use have varied widely across HC users and non-HC users in the observational studies among different populations, and this could impact the magnitude of any effect, as there is more room for overreporting when reported condom use is high and vice versa.

Despite efforts to promote condom use in conjunction with the use of hormonal contraception, condoms may be used less frequently by HC users compared to nonusers, perhaps because they are not relied on as the primary strategy for pregnancy prevention [20,21]. Considering this trend and all else being equal, the unadjusted HIV incidence rate among these women would be higher than others even in the absence of a biological effect of injectable hormonal contraception on HIV risk. In order to determine whether there is evidence of an additional risk of HIV infection among HC users, condom use must be accounted for in statistical analyses. All observational studies to date have collected data on condom use via self-report, which is difficult to collect reliably [22,23]. Furthermore, the degree of social desirability and recall bias related to condom reporting could vary according to contraceptive choice.

One observational analysis found a statistically significant twofold increase in HIV acquisition risk for women using combined oral contraceptives (COC) or injectable HC (hazard ratio [HR]=1.98 [95% confidence interval (CI) 1.06–3.68]) [7]. Our objective was to use mathematical modeling to understand the patterns of misreported condom use that would be necessary to reproduce that risk estimate in the absence of a true biological risk.

2. Methods

2.1. Model structure and parameterization

We developed an individual-based simulation model that reproduces the behaviors of the subset of stable HIV serodiscordant heterosexual couples of the South African sites in the Partners in Prevention HSV/HIV Transmission Study that were analyzed in Heffron et al. [7] Partners HSV/HIV was a multinational prospective HIV prevention clinical trial among HIV serodiscordant couples in which the HIV-infected partner had CD4 >250 cells/mm³ and was not eligible for antiretroviral therapy (ART) by national guidelines at enrolment [24,25]. The full model specification is described in [26]; in brief, the model tracks HIV transmission, disease progression and treatment and includes the composition of couples by sex, age, current CD4 cell counts, variations in coital frequency within stable partnerships, outside sexual partners and HC use (Tables 1 and 2). We capture differences between HC users and nonusers with respect to condom use only and assume that all other characteristics are equivalently distributed across groups.

2.2. Misreporting condom use

The model records true and reported condom use, HC use and HIV acquisition to create a set of simulated data that is analogous to the epidemiological data, with oral (22% of HC users) and injectable (both DMPA and norethisterone enanthate, Net-En, together 78%) HC grouped together to replicate the primary analysis [7]. Crucially, the model distinguishes between the actual pattern of condom use (which affects HIV transmission in the model) and the pattern that is reported (used in the statistical analysis; Fig. 1). To simplify the model, we assume that there is no contraceptive switching through the 2-year follow-up period, with the exception of condom use, which may vary month to month. Condoms are assumed to reduce HIV transmission by 78% per sex act [27]. Each individual is simulated over the 2-year study.

Condom misreporting is modeled by manipulating the proportion of sex acts per month that are assumed to occur with and without condoms relative to the proportion of sex acts for which condom use is reported (Fig. 1). Independent misreporting parameters were set for HC users and non-HC users, varying between complete underreporting (labeled −100% misreporting) and complete overreporting (+100%). Accurate reporting is defined as 0% misreporting. Overreporting was implemented as 
\[ n_m = \frac{c \cdot n_c}{100} \] where \( n_m \) is the number of misreported sex acts per month, \( n_c \) is the number of sex acts with reported condom use and \( c \) is the proportion of condom use in the model.

| Table 1 |
| Sexual risk group (reported monthly coital frequency) | Proportion of population |
|----------|-------------------------|
| 0–1      | 0.221                   |
| 2–3      | 0.214                   |
| 4–6      | 0.201                   |
| 7–9      | 0.119                   |
| 10–14    | 0.124                   |
| 15–30    | 0.121                   |

Reported monthly coital frequency at each study interval was categorized into six groups to represent the heterogeneity in sexual risk behavior. Each couple is assigned to a category at the start of the simulation, and each month, the coital frequency in the model is randomly selected from within that group.
misreporting parameter. Underreporting was implemented as 

\[ n_m = \frac{|c| n_u}{100} \]

where \( n_m \) is the number of misreported sex acts, \( n_u \) is the number of reported unprotected sex acts and \( c \) is the misreporting parameter. For both, condom use in the misreported sex acts was then reassigned as appropriate.

### 2.3. Model scenarios

In the data, most couples reported either consistent condom use or none at all. The proportion that reported no unprotected sex was similar among HC users and nonusers (91.4% vs. 92.5%; \( p=0.47 \)). Therefore, in the model, we initially assigned the same proportion of couples in each group to always report using condoms at the start of each simulation, calculated to reproduce the observed proportion with no unprotected sex (91.1% consistent condom use, Scenario 1) and the null hypothesis of HR=1.0.

We then repeated the analysis in two additional scenarios with different assumptions (Table 2). In Scenario 2, we assumed the same level of reported condom use as Scenario 1 but added an underlying weak association between HC use and HIV acquisition risk (HR=1.2).

Serodiscordant couples in the Partners HSV/HIV Transmission Study reported a much lower level of unprotected sex than participants in many other observational studies of HC and HIV, including another study of serodiscordant couples [19]. Therefore, in Scenario 3, we investigated the impact of misreporting condom use under the assumption that 50% of couples report no unprotected sex and the null hypothesis of HR=1.0.

### 2.4. Statistical analysis

We varied the patterns of condom misreporting from 90% underreporting to 90% overreporting for HC users and nonusers separately in each model scenario. The model generates a simulated dataset that is analyzed in a Cox proportional hazards (PH) model, adjusting for any reported unprotected sex over the simulated study period. This gives an estimate of the HR for HIV acquisition risk for women due to HC use in the model (we designate the model-estimated HR as HR throughout) that is analogous to the primary statistical methods of Heffron et al. Although the observational evidence for an association between HC use and HIV acquisition is strongest for DMPA [6], we group oral and injectable HC together in the statistical analysis for consistency with the primary analysis and because both methods are effective against unintended pregnancy and not expected to generate different degrees of misreporting. HC use in the model is assumed to be consistent throughout the study period.

The model and statistical analysis is run varying misreporting in HC users and nonusers independently from −90% to 90% in 5% increments, repeated 100 times at each combination. A smooth surface is then fit to the geometric means of the HRs at each grid point using locally weighted scatterplot smoothing with a quadratic polynomial (LOESS). Reported point estimates refer to the fitted surface, and the uncertainty bounds represent 90% of the variation in model HRs at that point (the 5th and 95th percentiles in the distribution of model HRs). All simulations and statistical analyses were performed using MATLAB and Statistics Toolbox Release 2012b [28].

### 3. Results

#### 3.1. Scenario 1: reported condom use from the Partners in Prevention HSV/HIV transmission study

With the reported condom use and no misreporting, HIV incidence among the serodiscordant couples in the model is 3.9 per 100 person-years (py; 90% of model variability: 3.2–4.4) from linked and unlinked infections, similar to the 4.1 per 100 py observed in the epidemiological data.

Fig. 2a shows the distribution of observed HRs over the complete range of possible condom use misreporting assuming no true association between HC use and HIV acquisition risk (true HR=1.0) and an underlying pattern of reported condom use as described in the Partners HSV/HIV Study data analyzed by Heffron et al. With no misreporting by either HC users or nonusers, or equal misreporting by both, changing the level of condom misreporting does not materially affect the HR (HR close to 1 for \( X-Y \) diagonal, e.g., points 1: \( HR=1.0 \) [0.6–1.5] and 2: \( HR=1.0 \) [0.7–1.4]). Thus, in this population of serodiscordant couples, misreporting condom use per se is benign to the HC–HIV association if the magnitude of misreporting and direction of misreporting are similar for HC users and nonusers.

If there is a tendency to overreport condom use, but only among HC users, then increases in the apparent excess risk may be observed even without any true biological effect of HC on HIV risk (HR>1.0). With 45% overreporting among
HC users, the $\hat{HR}$ matches that observed by Heffron et al. (point 3: $HR = 2.0 [1.5–2.8]$). At higher levels of overreporting, the $\hat{HR}$ is more inflated — e.g., $HR = 2.8 [2.2–4.0]$ with 80% overreporting (point 4). However, to reach these levels of spurious results requires that there be completely accurate reporting among the HC nonusers. If HC nonusers also overreport condom use but by less than half as much as the HC group, the $\hat{HR}$ is still elevated but not to the level observed in Heffron et al. (point 5: $HR = 1.5 [1.0–1.8]$) [7].

Apparent $\hat{HR}$ values more extreme than 2.0 can emerge if HC nonusers tend to underreport condom use. For example, with 50% underreporting by nonusers, it is possible to generate a high $\hat{HR}$ with less overreporting by HC users (point 6: $HR = 1.9 [1.3–2.7]$). This artificial doubling in risk can be generated with a wide range of misreporting behaviors by nonusers but always requires a minimum of 20% overreporting by HC users.

3.2. Scenario 2: assuming a weak association between HC use and HIV acquisition risk

High observed point estimates are reproducible with less skewed patterns of misreporting when we instead assume a low level of excess HIV risk associated with HC use ($HR = 1.2$; Fig. 2b). The overall pattern of model-estimated HRs is the same as the scenario with $HR = 1.0$, but the contours have shifted toward the bottom left quadrant. For example, an HR of 2.0 could be generated by 30% overreporting among HC users only, or 40% overreporting among HC users and 10% among nonusers (Fig. 2b, point 1: $HR = 2.0 [1.5–3.1]$; point 2: $HR = 2.0 [1.2–2.8]$).

3.3. Scenario 3: cohort with 50% condom use

Fig. 2c and d (light gray) shows the distribution of $HR$s across the same parameter space as Fig. 2a and d (dark gray)
and with the same true HR=1.0 but with the underlying reported condom use reduced to 50% among both HC users and nonusers. Here, the direction of the relationship between condom misreporting and apparent HIV risk is unchanged, but more extreme misreporting behaviors are required to spuriously generate a large $\hat{HR}$. At point 3, the $\hat{HR}$ is 1.3 (0.9–1.7), much lower than the HR = 2.0 in the model parameterized with high reported condom use. Even with 80% overreporting by HC users and none by nonusers, the HR is 1.5 (1.1–2.2; point 4). Considerable levels of
underreporting by women who do not use HC are required to reproduce HR=2.0, e.g., accurate reporting by HC users and 80% underreporting by nonusers, or 80% overreporting by HC users and 40% underreporting by nonusers. Differential misreporting of coital frequency may also generate elevated risk estimates, but 60% overreporting by nonusers, or a combination of 40% underreporting by HC users and 40% overreporting by nonusers is required to reproduce HR =2.0 in the model (see Supplementary Appendix).

4. Discussion

Appropriate adjustment for sexual behavior is essential to accurately assess from observational data whether some excess risk of HIV acquisition is attributable to the use of HC. We hypothesized that particular patterns of misreporting sexual behavior could lead to a spuriously high HR even if there is no true association.

We found it possible to observe an artificial doubling in HIV risk — even with no true relationship — through residual confounding due to misreporting. However, this requires substantial and directional misreporting that may not be plausible.

With no overreporting by non-HC users, HC users must overreport condom use by 45% for the observed results to be consistent with no true HC–HIV association. With any overreporting by non-HC users, then even greater misreporting among the HC users would be required to generate HR=2.0. This degree of reporting bias, which is highly differential between HC users and nonusers, is not supported by biomarker validation studies which have found that HC users are equally [29,30] or less [31] likely to overreport condom use as women using nonhormonal methods — contrary to the expected trend. However, model variability is large, and risk estimates within the confidence limits of the primary findings are attainable with less extreme patterns of misreporting.

When HC use is associated with a small increase in HIV acquisition risk, smaller differences in misreporting patterns between the HC users and nonusers are needed to reproduce HR=2.0. A small but true HR is only likely to be detectable with statistical significance in a study with a very large sample size but could contribute to biased risk estimates in smaller analyses when combined with substantial misreported condom use.

For many studies of HC and HIV risk, overall condom use in the population was low. In the model scenario with lower overall condom use, with a large degree of misreporting and a strong tendency for HC users to overreport more than the control group, the HR does not reproduce the point estimate observed in the Heffron et al. study, but it can attain the point estimates from some, but not all, other observational studies with medium levels of reported condom use [11,15,17,32]. To artificially generate the higher reported risk estimates, we must assume that non-HC users underreport their true use of condoms. However, behavioral and epidemiological research indicates that responses tend to overstate condom use and other protective behaviors in questionnaires of sexual behavior [33,34], and underreporting of condom use seems unlikely in settings where HIV prevention activities emphasize condom use. Although the Heffron et al. analysis has the highest reported condom use of all the observational studies included in recent systematic reviews [3–6], this is likely to be at least partly related to the study group — serodiscordant couples with mutually disclosed HIV status who had motivation within the partnership to use condoms.

Recent analyses have suggested that DMPA may increase risk for HIV acquisition by 40%–50% [3,6–35]. Applying our modeled misreporting scenarios to this risk estimate, differential degrees of condom use misreporting could also produce apparent excess risk (Fig. 2a and c). For example, 20% overreporting by DMPA users and complete accurate reporting by HC nonusers would produce HR=1.5. With more modest increases in estimated HIV risk than seen in the Heffron et al. analysis, lower levels of differential reporting accuracy could be sufficient to fully account for the increased risk.

The model makes some key simplifications. Injectable and oral contraceptive use is grouped together, and our model assumes that the amount of misreporting among injectable and oral contraceptive users was the same. Over three quarters of our HC use (78%) represent injectables, and since oral and injectable contraceptives are both considered to be effective methods, social desirability bias that can lead to inaccurate condom use reporting is likely to act to the same degree among oral and injectable users. An additional limitation is that we modeled condom use as a “take” type behavior, where couples use condoms either consistently or never; this approach neglects the partial protection that some women may have received due to mixed condom use.

Sexual behavior data are notoriously difficult to capture accurately yet extremely important for understanding risk levels for HIV acquisition. Our analysis confirms that differences in the amount of misreporting among exposure groups can result in spurious associations but asserts that considerable differences in misreporting would be needed for observed levels of excess risk among HC users to be consistent with no true association between HC use and HIV acquisition risk. Future studies designed to address the question of hormonal contraception and HIV risk must be designed to incorporate multiple methods to assess and validate sexual behavior reports.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.contraception.2016.12.003.
References

[1] Cleland J, Bernstein S, Ezeh A, Faundes A, Glasier A, Innis J. Family planning: the unfinished agenda. Lancet 2006;368(9549):1810–27.

[2] UNAIDS. UNAIDS report on the global AIDS epidemic; 2010.

[3] Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women’s risk of HIV acquisition: a meta-analysis of observational studies. Lancet Infect Dis 2015;15(2):181–9.

[4] Brind J, Condy S, Mosher S, Morse A, Kimball J. Risk of HIV infection in depot-medroxyprogesterone acetate (DMPA) users: a systematic review and meta-analysis. Issues Law Med 2015;30(2):129–39.

[5] Morrison CS, Chen P-L, Kwok C, Baeten JM, Crook AM, Cook AM, et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. PLoS Med 2015;12(1):e1001778.

[6] Polis CB, Curtis KM, Hannaford PC, Phillips SJ, Chipato T, Kiarie JN, et al. Update on hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence, 2016. AIDS 2016 [Published Ahead of Print].

[7] Heffron R, Donnell D, Rees H, Celmur C, Mugo N, Were E, et al. Use of hormonal contraceptives and risk of HIV-1 infection: a prospective cohort study. Lancet Infect Dis 2012;12(1):19–26.

[8] Baeten JM, Benki S, Chohan V, Laverleys L, McClelland RS, Mandaliya K, et al. Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women. AIDS 2007;21(13):1771–7.

[9] Morrison CS, Chen P-L, Kwok C, Richardson BA, Chipato T, Mugerwa R, et al. Hormonal contraception and HIV acquisition: reanalysis using marginal structural modeling. AIDS 2010;24(11):1778–89.

[10] Reid SE, Dai JY, Wang J, Sichalwe BN, Akpomie C, Cowan FM, et al. Prospective study of hormonal contraception and women’s risk of HIV infection in South Africa. Contraception 2007;75(6):461–7.

[11] Kleinenschmidt I, Rees H, Delany S, Smith D, Dinit N, Nkala B, et al. Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort. Contraception 2007;75(6):461–7.

[12] Myer L, Denny L, Wright TC, Kuhn L, et al. Update on hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence, 2016. AIDS 2016 [Publish Ahead of Print].

[13] Heffron R, Parikh UM, Penrose KJ, Mugo N, Donnell D, Celmur C, et al. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. J Infect Dis 2012;205(3):358–65.

[14] MATLAB and Statistics Toolbox Release. computer program; 2012 [Natick, Massachusetts, United States].

[15] Gallo MF, Sobel JD, Rompalo AM. Cu-Uvin S, Schoenbaum E, Jamieson DJ. Discordance between spermatozoa detection and self-reported semen exposure. Sex Transm Dis 2011;38(10):909–12, http://dx.doi.org/10.1097/OLQ.0b013e32835da324.

[16] Heffron R, Parikh UM, Penrose KJ, Mugo N, Donnell D, Celmur C, et al. Objective measurement of inaccurate condom use reporting among women using depot medroxyprogesterone acetate for contraception. AIDS Behav. http://dx.doi.org/10.1007/s10461-016-1563-y [in press, Epub ahead of print].

[17] McCoy S, Ralph L, Padian N, Minnis A. Are hormonal contraceptive users more likely to misreport unprotected sex? Evidence from a biomarker validation study in Zimbabwe. AIDS Behav 2014;1–6.

[18] Feldblum PJ, Lie C-C, Weaver MA, Van Damme L, Halpern V, Adeva I, et al. Baseline factors associated with incident HIV and STI in four microbicide trials. Sex Transm Dis 2010;37(10):594–601.

[19] Gregson S, Sobel JD, Rompalo AM, Cu-Uvin S, Schoenbaum E, Jamieson DJ. Discordance between spermatozoa detection and self-reported semen exposure. Sex Transm Dis 2011;38(10):909–12, http://dx.doi.org/10.1097/OLQ.0b013e32835da324.

[20] Heffron R, Parikh UM, Penrose KJ, Mugo N, Donnell D, Celmur C, et al. Objective measurement of inaccurate condom use reporting among women using depot medroxyprogesterone acetate for contraception. AIDS Behav. http://dx.doi.org/10.1007/s10461-016-1563-y [in press, Epub ahead of print].

[21] McCoy S, Ralph L, Padian N, Minnis A. Are hormonal contraceptive users more likely to misreport unprotected sex? Evidence from a biomarker validation study in Zimbabwe. AIDS Behav 2014;1–6.

[22] Mathews C, Little F. Condom use and sexual behaviours among individuals procuring free male condoms in South Africa: a prospective study. Sex Transm Dis 2002;29(4):239–41.

[23] Ott M, Adler N, Millstein S, Tschann J, Ellen J. The trade-off between condom and women’s risk of HIV acquisition: a meta-analysis of observational studies. Lancet Infect Dis 2015;15(2):181–9.