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Assessing the effect of hormonal contraception on HIV acquisition in observational data: challenges and recommended analytic approaches

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Abstract

Introduction—Determining whether hormonal contraception (HC), particularly the injectable contraceptive depot-medroxyprogesterone acetate (DMPA), increases a woman's risk of HIV acquisition is a priority question for public health. However, assessing the relationship between various HC methods and HIV acquisition with observational data involves substantial analytic design issues and challenges. Studies to date have used inconsistent approaches and generated a body of evidence that is complex and challenging to interpret.

Methods—In January 2013, USAID and FHI 360 supported a meeting of epidemiologists, statisticians, and content experts to develop recommendations for future observational analyses of HC and HIV acquisition.

Results—Meeting participants generated recommendations regarding careful definition of exposure groups; handling potential confounders, mediators, and effect modifiers; estimating and addressing the magnitude of measurement error; using multiple methods to account for pregnancy; and exploring the potential for differential exposure to HIV-infected partners. Advantages and disadvantages of various statistical approaches to account for time-varying confounding and estimating total and direct effects were also discussed.

Conclusions—Implementing these recommendations in future observational HC-HIV acquisition analyses will enhance interpretation of existing studies and strengthen the overall evidence base for this complex and important area.

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Keywords

HIV acquisition; contraception; DMPA; injectable; observational epidemiology

Introduction

Determining whether use of hormonal contraception (HC) increases a woman's risk of HIV acquisition is a priority research question for women's health [1, 2]. HC prevents unintended pregnancy and contributes to reductions in maternal and infant morbidity and mortality [3]. Globally, over 150 million women use HC, including oral contraceptive pills, injectable contraceptives (depot-medroxyprogesterone acetate [DMPA], norethisterone enanthate [NET-EN], or combined injectables), contraceptive implants, rings, patches, or levonorgestrel-releasing intrauterine devices (IUD) [4]. In sub-Saharan Africa, nearly 60% of HC users rely on injectable contraception [4], a highly effective, long-lasting, reversible method which can be used discreetly and provided by community health workers [5]. Some observational studies have raised concerns of a potentially increased risk of HIV acquisition among users of HC, primarily DMPA, but results overall are inconsistent and study quality varies greatly [6]. The widespread use of injectables in sub-Saharan Africa, an area of high HIV prevalence and incidence, heightens these concerns. During a 2012 WHO technical consultation, 75 experts reviewed all available biological, epidemiological, and modeling data, and recommended that WHO continue to suggest no restriction on the use of any HC method; however, they noted that condom use and other HIV preventive measures should be strongly emphasized for women at high risk of HIV who choose progestogen-only injectable contraception [1].

Twenty observational cohort studies published from 1991 to 2012, and conducted among a range of populations (e.g., family planning clinic attendees, commercial sex workers, women with HIV-1 infected partners, etc.), have used varied methodological approaches and generated heterogeneous results [6]. At the 2012 WHO consultation, experts gave the collective body of epidemiological evidence on HC and HIV acquisition a GRADE rating of "low" [7-10], due in part to inconsistencies between study results. Greater consistency and rigor in analytic approaches may allow for clearer interpretation of individual study results and comparability across studies, strengthening the overall evidence base and improving the GRADE rating. The complete body of evidence, including studies published since the 2012 WHO consultation [11, 12] will be reviewed at the next WHO technical consultation, currently planned for 2014.

Formal discussion on how to improve the observational HC-HIV acquisition evidence base has been limited. In response to the need to strengthen and harmonize HC-HIV acquisition analytic approaches for observational data, USAID and FHI 360 supported a meeting entitled "*Best practices in analytic approaches to assess the effect of hormonal contraception on HIV acquisition with observational data*," in Seattle, WA on January 24-25, 2013. Epidemiologists, biostatisticians, and content experts discussed recommendations on best analytic practices for future observational analyses; this report summarizes those discussions and presents recommendations for future analyses.

Analytic design

Observational analyses to assess the HC-HIV acquisition relationship present multiple challenges in analytic design. Below, we highlight several key challenges of conducting these analyses and offer recommendations (summarized in Table 1) that should be considered prior to the initiation of a primary or secondary observational analysis of HC and HIV acquisition.

Defining HC exposure and HIV outcome

In HC-HIV acquisition analyses, the outcome of interest is HIV acquisition, the detection of which requires repeated HIV testing. Defining HC exposure is more complex. Each HC method induces different biological effects, therefore it is critical to disaggregate by HC method type (e.g., pills vs. injectables vs. implants vs. IUDs), and when possible, by formulation (e.g., DMPA vs. NET-EN, estrogen and progestin combined methods vs. progestin-only methods, etc.) and dosage (e.g., intramuscular DMPA vs. lower-dose subcutaneous DMPA, etc.). Some studies to date have disaggregated by HC type, and a few have disaggregated by formulation [6]. High rates of contraceptive discontinuation and switching [13] and imperfect adherence [14] lead to complex exposure patterns, necessitating frequently updated, prospectively collected HC exposure data. Sensitivity analyses can explore the impact of censoring follow-up time when women first switch their contraceptive method. Any induced informative censoring would have to be addressed using additional analytic approaches, such as inverse probability weighting. An additional question is whether the exposure of interest is current exposure to HC (which most studies have addressed) or some summary of cumulative HC exposure [15].

Defining the “no HC exposure” comparison group

To date, most studies have assessed whether a particular HC method increases HIV risk relative to using no HC, but the composition of the “no HC” unexposed comparison group has varied. Women not using HC may be using condoms, copper IUDs, withdrawal, spermicides, diaphragms, sterilization, hysterectomy, traditional methods, or nothing to prevent pregnancy (some of these women may be actively trying to become pregnant). Thus, women not using HC may be heterogeneous with respect to *any* contraceptive use or non-use, with accompanying differences in other important factors, such as coital frequency, exposure to sexually transmitted infections (STIs), and pregnancy intention; factors which have not always been measured in previous studies. Further, some of these methods (or lack thereof) may magnify or dilute HIV incidence in the comparison group. For example, women using condoms for pregnancy prevention without an HC method (who would thus be in the “no HC” group) typically report more consistent use of condoms than women using condoms for HIV/STI prevention (who could be in either group) [16-21]. This could induce bias in the effect estimate if consistency of condom use over time, a challenging variable to assess, is not adequately measured and controlled. Some studies have contained comparison groups composed largely of women using condoms [22], while others have had few or no condom users in the comparison group [23]. Differences in comparison groups between studies could lead to substantial differences in effect estimates. Thus, clear descriptions of

the composition of the comparison group, with these parameters in mind, are necessary for cross-study comparisons.

Alternate comparison groups

In addition to comparisons of HC users versus non-HC users, future observational analyses could compare HIV acquisition rates among women choosing various effective contraceptive methods, (e.g., DMPA versus IUD, DMPA versus NET-EN, etc.). Such comparisons have not been made to date, but would reframe the research question to identifying the safest method of HC (with respect to HIV acquisition) among contracepting women at risk of HIV infection. Many recent HIV prevention trials emphasized counseling and on-site provision of effective contraceptive methods for participants; in these trials, most women used HC. Thus, future analyses using these datasets may be best suited to answering questions that compare different HC methods against each other. An advantage to this comparison is that underlying HIV risk (as measured, for example, by report of sexual behaviors and condom use consistency) may be similar among groups of women choosing highly effective contraceptive methods, which would reduce potential confounding by these factors. However, without an established understanding of baseline HIV-related risk of the comparison for each method, interpreting risk estimates may be challenging. For example, a null effect may indicate that neither method impacts risk, or that both methods increase or decrease risk equally.

Confounding, time-varying confounding, mediation, and effect modification

Women who choose to use HC are different from women who do not, and these differences may also be related to underlying risks for HIV infection. Such differences will result in confounded estimates of the HC-HIV relationship if not appropriately controlled. In addition, mediating factors that result from the exposure (HC) and that cause the outcome (HIV acquisition) can also complicate analyses and the interpretation of results. Some confounders may simultaneously act as mediators. For example, DMPA use may be influenced by recent coital frequency, and DMPA use may also affect subsequent coital frequency. Such variables, known as time-varying confounders, must be addressed using appropriate analytic techniques, e.g., marginal structural models (MSM), which have been used in some studies.[11, 24-26] Several early HC-HIV studies did not adjust for important confounders [6], and to date, no published observational studies have assessed potential mediation.

Since it is not always clear if certain variables (for example, coital frequency or condom use) should be assessed as confounders, mediators, or both, it is important to consider how each variable is included in a statistical model. Conceptual models can be used to help specify *a priori* which factors are assumed to operate as potential confounders, mediators, or both. Meeting participants drafted a simplified conceptual model (Figure 1) to illustrate theoretical relationships between use of an HC method (exposure) and HIV acquisition (outcome), listing multiple important potential confounders and/or mediators [27-31]. While it was not feasible to specify one model, given uncertainty on how best to incorporate the large number of potential variables, participants agreed which key factors to consider, and that several time-varying factors have been demonstrated in previous studies to act

simultaneously as confounders and mediators, including condom use, participant behavioral risk, and primary partner risk [24]. Future analyses should consider factors shown in Figure 1, and provide a rationale if they are not included in statistical models.

Previous studies have assessed whether various factors such as age, country, or infection with herpes simplex virus type-2 (HSV-2), could potentially act as effect modifiers of the HC-HIV acquisition relationship, but results have been mixed. Future investigations should explain biologically plausible mechanisms for apparent effect modification, and also consider the potential for differential confounding across strata, which could generate spurious effect modification [32].

Total and direct effects

The terms “total effects” and “direct effects” are used to describe relationships between an exposure, an outcome, and other factors in the causal pathway [33, 34]. Figure 2 displays a simplified causal diagram for one hypothesized HC-HIV relationship, suggesting condom use as one potential mediator. In Figure 2, the “direct effect” of HC on HIV risk is *not* mediated through condom use, while the “indirect effect” of HC on HIV is the mediated pathway through condom use. In this simplified example, the “total effect” is the overall effect of HC use on HIV acquisition (after controlling for confounding factors) of the direct and indirect effects combined. All three types of effects – direct, indirect, and total – are assumed to be free of confounding.

At the meeting, opinions differed as to whether estimating a total effect or a direct effect of HC not mediated by behavioral factors (informally referred to as a “biological” effect) would be more relevant to the policy agenda. Total effects are useful when the interest is in the overall effect of an HC method (including consequent effects of HC on mediators) on HIV risk, while the direct effect attempts to isolate the effect of a HC method on HIV risk not mediated by other factors. The direct effect may be more generalizable if the biological response to HC differs less than socially, culturally, and behaviorally mediated responses. While direct effects may be valuable, they may be difficult to obtain given challenges in accurately measuring confounding and mediating factors, the requisite additional assumptions required for their estimation, and potential loss of statistical precision.[34, 35]

Regardless of the effect estimated, it will continue to be important to prioritize novel programs to increase condom use alongside highly effective contraceptive methods, develop multipurpose prevention technologies,[36, 37] and expand contraceptive method options. However, if DMPA is found to increase risk of HIV, and a large portion of that effect is “biological” (and of substantial magnitude) [38], then it would be particularly crucial to enhance access to *alternative* safe, acceptable highly effective contraceptive methods, particularly in areas where both DMPA use and HIV prevalence is high. Such an effort might be lower priority if the total effect of HC on HIV were due to behavioral factors rather than (for example) physiological changes caused on the body by HC. Future studies should be clear about the effect being estimated (total or direct; and if direct, with respect to what factors), and consider estimating both where possible.

Analytic challenges & considerations

Measurement error and missing data

Self-reported data about sexual behavior and HC use are subject to biases, including misreporting, recall, and social desirability. In addition, data on these important factors may be intermittently missing as a result of unattended follow-up visits. Methods to address measurement error and missing data, minimize bias and estimate its magnitude and direction, or examine the robustness of primary analytic results may help to interpret findings from observational analyses. For example, to examine the accuracy of self-reported condom use, investigators can compare HIV (or other STI) acquisition rates or pregnancy rates between women who report consistently using condoms and those who do not. HIV incidence rates among consistent condom users are expected to be lower than women who never use condoms. If female genital specimens are available, biologic markers of unprotected intercourse (for example, prostate specific antigen (PSA) or Y-chromosome testing) could provide a biomarker of this behavior to help to estimate over-reporting of condom use among women who report recent sex [39]. Investigators can also conduct sensitivity analyses among individuals who report no condom use (by censoring at initiation of condom use, though this may be informative), as these individuals may theoretically be less vulnerable to social desirability bias [40, 41]; similarly, studies that include a small proportion of condom users may be less prone to condom over-reporting. To examine the accuracy of self-reported HC use, pregnancy rates among women reporting different types of contraceptive methods can be compared. Pregnancy rates would be expected to be higher among women using more user-dependent methods (condoms, oral contraceptives) compared to user-independent methods (injections, implants, IUDs). If these trends hold, they are an indication that self-reported data are accurate on an aggregate level. Other sensitivity analyses may be possible to examine the extent of inaccuracy in other potentially confounding factors.

If confounding (including residual confounding due to misreporting) is suspected to impact the effect estimates, it is important to provide information on the likely magnitude and direction of bias. One recent mathematical modeling example assessed the magnitude of differential misreporting required to generate a spurious doubling of HIV risk with injectable HC use in a recent HC-HIV acquisition study [26], and suggested that underreporting of condom use would need to be unrealistically large to have generated the reported effect estimate if condom use were the only confounder.[42]

Accounting for pregnancy

Previous studies have addressed pregnancy in several ways: no reported adjustment for incident pregnancy, censoring at pregnancy, and treatment of pregnancy as a time-varying confounder. HC prevents pregnancy, and pregnancy has been associated with an increased risk of HIV acquisition in some, but not all, observational studies [22, 23, 43, 44]. Yet even if pregnancy acts as a confounder of the HC-HIV relationship, adjusting for pregnancy may be problematic, since becoming pregnant makes a woman “ineligible” for HC use, thereby violating the positivity assumption which requires that there are both exposed and unexposed participants at all values of the confounder(s) [45]. The meeting's participants

concluded that the most appropriate method to address pregnancy should depend on the question being asked. If analytic interest is in direct effects not influenced by pregnancy, then censoring at pregnancy may be appropriate, although such censoring may be informative. If interest is in the total effect, then pregnancy (as part of that total effect) should not be “controlled away” (although confounding by pregnancy status may still be an issue). The optimal approaches to address pregnancy in HC-HIV analyses require further study. At present, implementation of various approaches for pregnancy is recommended in order to gauge the range of results when different approaches are employed.

Accounting for HIV exposure and partner risk

A substantial proportion of women participating in HIV prevention studies may never be exposed to HIV [6, 46]. Heterogeneity in HIV exposure risk may introduce bias if HIV exposure is linked to decisions regarding contraceptive method choice. If HIV exposure differs by HC method, this could impact results. Characterization of the level of HIV exposure could be achieved by assessing serodiscordant couples (ideally with information on male partner HIV viral load), by testing of female genital samples for viral HIV-1 DNA from male partners, or by testing partners for HIV. In the absence of data on partner risk, composite variables of sociodemographic factors related to partner risk could be considered, but proxy measures of partner risk may have limited utility [47] and should be validated. Further research would be useful for improving our understanding of HIV exposure in different populations, and whether HC use is associated with the likelihood of HIV exposure.

Statistical model considerations in the presence of time-dependent confounding

The majority of prospective HC-HIV studies have used Cox proportional hazards regression models, which can induce bias in the presence of time-varying confounders that are also mediating factors [48-50]. For example, if coital frequency (which changes over time) affects both use of DMPA and HIV acquisition risk (and so is a confounder), but is also affected by DMPA use (and so is also a mediator), then traditional regression approaches such as Cox models can give a biased effect estimate. This may happen even if there is no uncontrolled confounding (see also previous section entitled *Confounding, time-varying confounding, mediation, and effect modification*). Several alternative methods can estimate unbiased effects in such data (subject to assumptions including no uncontrolled confounding): the parametric g-formula [51-53], g-estimation of structural nested models [54, 55], and marginal structural models (MSM) [48, 49] fit with inverse probability weights (IPW) [56]. Collectively, these are referred to as “the g-methods.” These methods can also estimate either total or direct effects in specific situations in which traditional regression approaches cannot [34].

Of these methods, MSM fit with IPW are technically easiest to implement, and several recent HC-HIV analyses have used this approach [11, 24-26, 57]. In contrast to MSM, neither g-estimation nor the parametric g-formula has been widely implemented. The parametric g-formula is technically and computationally intensive, and has the disadvantage

of requiring numerous parametric assumptions. A notable advantage of this approach, however, is that the assumptions of the parametric g-formula complement those of IPW MSM [52]: the sets of relations modeled are complementary between the two methods. As such, the g-formula may make a good sensitivity analysis for HC-HIV acquisition analyses. More statistical details regarding MSM [48, 49, 58] and the g-formula [51, 53] can be found elsewhere.

Despite theoretical advantages of g-methods (including MSMs), over traditional regression approaches, if strong time-dependent confounding is absent from a dataset being used to estimate an HC-HIV acquisition relationship, then g-methods are unlikely to provide markedly different results from traditional methods [26]. The absence of strong time-dependent confounding could occur because current HC use has little or no effect on the mediator/confounder or because the mediator/confounder has little effect on the probability of future exposure to HC use; such assumptions could be tested prior to employing g-methods [59].

Theory shows that g-methods are the more statistically appropriate methods for longitudinal HC-HIV acquisition analyses. However, it is critical to note that their use does not *guarantee* an unbiased answer. The g-methods, like all statistical approaches, require a number of assumptions to be met. The aforementioned measurement issues, such as the failure to measure all relevant confounders or to appropriately account for measurement error, are likely to yield biased estimates from any analytic approach, including the g-methods. In addition, there are numerous practical and technical issues with the implementation of g-methods, and MSM specifically, that are not currently addressed in the epidemiologic or biostatistical literature. Descriptions of these challenges and suggested solutions would be helpful in framing future HC-HIV acquisition analyses (as well as other subjects).

Conclusions

Despite the challenges described here, future secondary analyses using existing high-quality datasets could inform our understanding of the HC-HIV acquisition relationship. Several analyses are on the horizon, including those from both individual and combined datasets. Furthermore, new HIV prevention studies that will collect information on contraceptive use will provide additional relevant data (including trials of tenofovir gel and a dapivirine-containing vaginal ring). Future studies that do not address the issues listed in Table 1 are less likely to meaningfully contribute to the existing evidence base.

This paper aims to contribute to an evolving discussion on observational HC-HIV acquisition evidence. We hope to spur conversations that build upon the recommendations in this paper. Methodological progress on addressing pregnancy in HC-HIV acquisition analyses is needed, as is dialogue with investigators conducting longitudinal cohort studies in areas of high HIV incidence, to ensure inclusion of relevant data collection tools into ongoing trials. Additionally, in light of a growing evidence base, discussions on how best to systematically assess this complex body of literature should also continue. We hope our recommendations might assist in interpreting existing studies; by outlining major challenges

of observational HC-HIV analyses, systematic assessment across studies is more straightforward. A recent HC-HIV acquisition systematic review specified minimum quality criteria for more in-depth analysis of higher quality studies [6]. As the evidence base continues to change and improve, these criteria should be continually refined. Finally, given the interdisciplinary nature of HC-HIV acquisition analyses, collaborative efforts between specialists of various disciplines are urgently needed.

Moving from data to policy regarding HC and HIV acquisition requires clearly framing the pertinent question(s) that can be answered with robust methods that assess necessarily imperfect data. Randomized trial data do not currently exist and animal model results have not always had clear implications for human female reproductive biology. Discussions about the feasibility of a randomized trial in this area are ongoing, but results would not be available for at least 5 years. In this vein, observational analyses from ongoing and planned epidemiologic studies, performed with robust analytic techniques and applied to high quality datasets, may be the most efficient and cost-effective means to contribute further understanding of this problem, especially in the near-term. Policy guidelines must consider the important contributions of HC to reducing maternal and infant morbidity and mortality and balance this with a robust estimation of the magnitude of how specific HC methods may or may not increase HIV acquisition risk. Resolution of this question is a high priority on the global health agenda, for women at risk of HIV, their partners, contraceptive and HIV care providers, women's health advocates, and the global health community.

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Note: Other key variables may include: participant behavioral risk, number of sex partners, education, marital status, parity, breastfeeding, various STIs, commercial sex work, vaginal washing, anal sex, etc. Furthermore, some variables, such as age, country, or HSV-2 status could potentially operate as effect modifiers, and should be assessed where possible.

Figure 1. Factors that may confound or mediate the relationship between depot-medroxyprogesterone acetate (DMPA) use and HIV acquisition

*A “biologic effect” of HC on HIV risk would be defined as the effect of HC on HIV risk in the absence of all confounding and mediation.

Note: this figure may not represent the true underlying relationships since the directionality of the relationship between HC use and reduced condom use is unclear. Condom use is depicted as a mediator for illustrative purposes only. Other potential mediators, including biologic mediators, are not specified.

Figure 2. Conceptual model to illustrate the difference in total and direct effects for a simplified potential relationship of hormonal contraceptive use, condom use, and HIV acquisition*

Table 1
Considerations and recommendations for future observational analyses of hormonal contraception and HIV acquisition

Considerations for observational analyses of HC and HIV acquisition	Recommendations for design, analysis, or reporting to minimize potential limitations and improve study quality
Multiple types of hormonal contraception	<ul style="list-style-type: none"> Disaggregate hormonal contraceptive methods by distinguishing between pills, injectables, implants, IUDs, etc. Where possible, further distinguish by hormonal content and formulation (e.g., DMPA vs. NET-EN, progestin-only methods (pills, injectables, implants, hormone-releasing IUDs) vs. combined methods (pills, patches, rings, injectables, etc.)) Where possible, further distinguish by dosage (e.g., standard intramuscular DMPA vs. lower-dose subcutaneous DMPA)
Contraceptive switching between study visits	<ul style="list-style-type: none"> Treat contraceptive exposure as time-varying factor; use appropriate analytic techniques to deal with time-varying confounding Distinguish between short-term (recent) exposures and cumulative exposures Conduct sensitivity analyses censoring at first switch in contraceptive method
Interval length between study visits	<ul style="list-style-type: none"> Given the need for frequent capture of information on HC exposure, outcome, and other variables, the shortest possible intervals are preferable
Comparison group	<ul style="list-style-type: none"> Clearly describe the composition and characteristics of the comparison group Consider assessing both a non-HC comparison group and a comparison group of another highly effective contraceptive method, if sample size and study power permit
Effect assessed	<ul style="list-style-type: none"> Clearly describe whether the study aims to assess total effects or direct effects
Potential confounding	<ul style="list-style-type: none"> Restrict or control for potential confounders, such as consistency of condom use over time (rather than any condom use, or condom use at last sex), age, and others listed in Figure 1
Potential effect modification	<ul style="list-style-type: none"> Specify <i>a priori</i> factors to consider as effect modifiers based on available literature, especially age, country/site, and HSV-2 infection
Measurement error in self-reported sexual behavior data	<ul style="list-style-type: none"> Compare pregnancy, HIV, and STI rates among women reporting different sexual behaviors to determine if consistent condom use is associated with reduced rates; report results within main paper to describe possible degree of measurement error Consider testing stored female genital swab specimens for semen exposure (Y-chromosome or PSA testing) to assess the frequency of condom use over-reporting during recent sex Consider sensitivity analyses among individuals who report no condom use (by censoring at initiation of condom use), given that individuals reporting no condom use may be less vulnerable to social desirability bias
Measurement error in self-reported contraceptive use data	<ul style="list-style-type: none"> Validate self-report with study clinic chart notes or concomitant medications logs Assess whether reported contraceptive use is associated with decreased pregnancy rates. Expect longer-acting, user-independent methods to have lower rates; report results within main paper to describe possible degree of measurement error
Pregnancy	<ul style="list-style-type: none"> Ideal approaches remain unclear; sensitivity analyses using multiple approaches are recommended to examine if primary results are robust

Considerations for observational analyses of HC and HIV acquisition	Recommendations for design, analysis, or reporting to minimize potential limitations and improve study quality
	<ul style="list-style-type: none"> Describe the rationale for analytic choices made regarding pregnancy
Level of HIV-1 exposure	<ul style="list-style-type: none"> Conduct studies among serodiscordant couples when possible If data are available on male partner HIV status (and HIV viral load), consider adjusting for this in the analysis Test stored female genital swab specimens for HIV DNA to determine exposure to HIV If serodiscordant data are unavailable, consider adjusting for behavioral data (conducting subgroup analyses) on partner risk, recognizing that such measures may have limitations and should be validated to the extent possible
Statistical techniques	<ul style="list-style-type: none"> Determine whether Cox proportional hazards modeling, marginal structural modeling with IPWs, or alternate g-methods are appropriate for the data and question of interest Analytic methods should be clearly pre-specified to avoid data-dredging Multiple approaches can act as sensitivity analyses; e.g., MSM and g-formula
Missed study visits and missing data	<ul style="list-style-type: none"> Ideal approaches for handling missing data due to women who are not lost to follow up but who miss specific follow up visits remain unclear; sensitivity analyses using multiple approaches are recommended to examine if primary results are robust
Loss to follow up	<ul style="list-style-type: none"> Compare contraceptive use and sexual behavior characteristics at enrollment between women retained and lost to follow up Determine whether loss to follow up is differential by arm If loss to follow up exceeds 20%, consider whether the data are appropriate for the analysis
Study power	<ul style="list-style-type: none"> Determine study power for each outcome <i>a priori</i> and report it in the manuscript If study power is low, consider whether the data are appropriate for analysis, or focus on interpretation of direction and magnitude of point estimates, rather than emphasizing statistical significance or lack thereof
Publication bias	<ul style="list-style-type: none"> Both significant and non-significant results should be published in the scientific literature