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Hormonal contraceptive use and HIV acquisition in women: a systematic review of the epidemiological evidence

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SUMMARY

Studies examining the relationship between hormonal contraceptive use and HIV acquisition have generated mixed results. We systematically searched the literature and identified twenty relevant prospective studies. Most of these studies found no statistically significant association between use of oral contraceptive pills and HIV acquisition. No studies reported statistically significant associations between use of norethisterone enanthate and HIV acquisition, but few studies assessed this method. Studies assessing use of depot medroxyprogesterone acetate or non-specified injectable contraceptives and HIV acquisition had heterogeneous methods and results. Factors that may contribute to this heterogeneity include analytical handling of condom use, length of inter-survey interval, and whether analysis focused on serodiscordant couples. Available epidemiologic data do not establish a clear causal association between injectable contraceptive use and HIV acquisition, nor do they definitively rule out the possibility of an effect. Concerns remain about the potential for residual confounding, even within otherwise high-quality studies.

BACKGROUND

Hormonal contraceptive methods are among the most highly effective, reversible methods of pregnancy prevention. The World Health Organization (WHO) has emphasized the need to understand whether hormonal contraception (HC) affects HIV acquisition in HIV-negative women, HIV progression in HIV-positive women, HIV transmission from an HIV-positive woman to an HIV-negative male sexual partner, and potential interactions with antiretroviral therapy.[1] This systematic review examines prospective studies assessing the relationship between HC use and HIV acquisition in HIV-negative women.

Several biological mechanisms by which HC use could theoretically increase the risk of HIV acquisition have been postulated.[2] Endogenous estrogen and progesterone impact immune processes in the female reproductive system which might affect susceptibility to HIV; exogenous contraceptive hormones may induce similar changes.[3] Use of oral contraceptive pills (OCPs) is associated with cervical ectopy,[4] which is associated with HIV acquisition in some studies.[5] In monkeys, progesterone thins the vaginal epithelium and increases acquisition of simian immunodeficiency virus (SIV),[6, 7] while in ovariectomized macaques, topical estrogen cream protects against SIV infection.[8, 9] Increased susceptibility to SIV infection may be mediated by active suppression of SIV-specific cellular immune responses,[9-11] and pre-treatment with depot medroxyprogesterone acetate (DMPA) increases susceptibility of macaques to SIV infection. However, SIV/macaque model findings cannot be easily applied to humans, given differences in doses of DMPA and challenge virus, delivery medium, and biology.[3, 12-14] HC use may be associated with disruption of colonization with H_2O_2-producing lactobacilli or other protective vaginal microorganisms.[14] Like pregnancy, HC may be associated with immunological changes, such as increased expression of CCR5 co-receptors on $CD4^+$ T cells or reduction in immune protection.[15, 16] Some studies suggest potential associations between HC use and other sexually transmitted infections (STI) that could also enhance susceptibility to HIV.[17, 18]

Previous systematic reviews concluded that the overall epidemiological data do not suggest an association between HC use and HIV acquisition in the general population.[17, 19] Given the availability of new data, we aimed to update previous systematic reviews.

METHODS

We searched PubMed and Embase for articles in any language either published or in press by December 15, 2011 (search strategy available on request, see Appendix A), and hand-searched reference lists. We used Early Review Organizing Software (EROS) during article selection.[20] We considered prospective studies of HIV-negative women either using HC (injectables, OCPs, implants, patch, ring, or levonorgestrel IUDs) or not using HC, but excluded cross-sectional studies. One author (CBP) conducted the literature search and identified studies for full-text review, and both authors determined study inclusion. When necessary, we attempted to contact study authors for clarifications. If multiple publications were based on the same study, we considered previous publications, but refer to the most recent publication unless otherwise indicated.

Abstraction forms underwent expert review and pilot testing. Both authors independently abstracted evidence for all included studies. To focus on evidence most likely to provide useful information on our question of interest (Does HC biologically alter risk of HIV acquisition?), we first determined whether studies met minimum quality criteria for further consideration. Studies failed to meet minimum quality criteria if they contained at least two of the following three concerns, or if authors noted that their data were unlikely to provide information on the biological effect of HC on HIV acquisition.[21]

- *Unclear definitions of exposure*: did not present separate estimates for different HC methods, included other HC methods in the comparison group, or did not use time-varying exposure information.
- *High loss to follow-up*: ≥20% loss to follow-up at twelve months.[22]

- *Lack of consideration of important potential confounders*: did not conduct multivariate analyses including, at minimum, assessment of some measure of condom use.

Among studies that met minimum quality criteria, we considered multiple methodological features, including:

- *Potential for confounding*. HC users and non-users may differ in ways which may also affect exposure to HIV; for example, HC users may have higher coital frequency, less consistent condom use,[23-25] or be in longer-term relationships.[26, 27] Since it is unknown whether HC users and non-users are equally likely to have HIV-infected sexual partners, analyzing serodiscordant couples (ideally incorporating viral load of the infected partner) or adequately controlling for partner risk may provide a methodological advantage, though proxy measures of partner risk may have limited utility.[28] HC users may differ from non-users on other important factors that may relate to HIV risk, such as age, parity, education, marital status, participant behavioral risk, or pregnancy status. Pregnancy is strongly associated with not using HC, and may be associated with HIV acquisition,[29] so could act as a confounder, but it is unclear whether censoring at or controlling for pregnancy is analytically superior. HC users using different HC methods may have unequal distributions of other potentially important factors; for example, injectable contraceptive users may be more likely than OCP users to be postpartum, breastfeeding, to use contraception covertly, or to use vaginal drying materials (J. Stanback, personal communication, 2011) [30] -- factors with unknown but potential effects on HIV risk.

Statistical adjustment is not always sufficient to eliminate confounding. For example, information on self-reported condom use is often inaccurate,[31-33] and using inadequately measured information for statistical adjustment (or failing to adjust for important covariates) can leave residual confounding. Some authors argue that studies among sex workers or mutually disclosed serodiscordant couples may contain less potential behavioral confounding,[34] since these individuals are aware of their HIV exposure risk. While possible, this has not been empirically established.

Factors which vary over time could potentially result in time-dependent confounding affected by prior exposure. In such cases, marginal structural models (MSM) fit with inverse probability weights may be preferred, [35-37] but these models are complex and require multiple assumptions. As with traditional statistical approaches, causal inference relies on the assumption that all confounders have been adequately measured and controlled for, or addressed with study design.

- *Handling of condom use.* Condom use is one of many potential confounders, but is critical in considering potential associations between HC use and risk of HIV acquisition. Non-users of HC might use condoms for pregnancy prevention, HIV/STI prevention, or both. HC users already use an effective contraceptive method, and some studies suggest that patterns of using condoms for STI/HIV prevention are less consistent than patterns of using condoms for pregnancy prevention.[38-41] In some studies, consistent condom use is associated with reduced HIV risk while inconsistent condom use is not, potentially because condom use may be a marker for exposure to higher risk sex partners.[42]

Furthermore, women using condoms to prevent infection might use them with men perceived as "high-risk" [23, 43] whereas condom use for contraception might be used with any male partner perceived to be fertile.[44]

Success of statistical adjustment for differences in condom use depends upon accurate measurement and parameterization of this variable. If HC users and non-HC users have differential validity of self-reported condom use, results may be biased. The length of the recall period may also affect overall validity of self-reported information. Furthermore, asking participants about the entire inter-survey interval may produce different responses than asking about a selected or "typical" period of time and extrapolating to a longer interval.

Comparing HC users to women who use condoms as a primary contraceptive method may be problematic if condom use or consistency differs between the two groups, but is not adequately controlled. Comparing HC users against non-HC-users who also do not report condoms as a primary contraceptive method (and statistically adjusting for remaining differences in condom use for infection prevention) could potentially equalize dimensions of condom use that are difficult to measure accurately (e.g., consistency, use with partners of varied risk profiles), but reasons for condom use may not be clear and correlations between reason for condom use and patterns of condom use are unknown. Analyses stratified by condom use (to separately assess women who report no condom use) may help to minimize confounding by condom use, but in populations where condom use is common, such analyses may have limited statistical power. In sum, the

best approach to handling condom use is unclear and may depend in part on the population studied. Using multiple approaches may help to assess the robustness of results. Correlating self-reported consistent condom use with reductions in HIV or pregnancy may confirm response validity of self-reported data, thus enhancing confidence in successful adjustment for condom use.

- *Frequency and accuracy in measurement of exposure, outcome, and key variables:* If both HC use and HIV status are not measured repeatedly and frequently, and with respect to the same intervals of time, it is difficult to ascertain whether HC was used at HIV infection, or whether exposure misclassification occurred. Use of time-varying information, preferably in conjunction with short inter-survey intervals, can reduce misclassification. Longer inter-survey intervals increase the possibility of recall bias, make it more difficult to establish temporality, and may not capture contraceptive switching behaviors, unless other measures to establish consistent HC use are taken. We considered an inter-survey interval of <6 months a methodological advantage. Most contraceptive information is collected via self-report, but validation using clinic contraceptive records may increase accuracy. Collecting HC exposure information exclusively from medical chart notes may result in poor measurement; but correlating HC information with reduced pregnancy rates might enhance confidence.

- *Purpose of data collection*: Studies that prospectively collect information specifically to assess the relationship between HC and HIV acquisition may theoretically collect more comprehensive information on key variables. For secondary data analyses, the effects of

study inclusion and exclusion criteria, as well as the quality of information available on key factors, should be considered. Such studies should ideally specify analysis plans *a priori* to discourage selective reporting of results found to be significant in post-hoc analyses.

- *Study power and precision*: Studies may have limited statistical power to detect an effect if the sample size is small, the number of HC users is low, or few women contract HIV. In attempting to draw causal inference, particularly in observational data, caution is justified if 95% confidence intervals (CIs) are wide and p-values are marginal.[45]

We created summary graphics of relative risks, but due to between-study heterogeneity in design, analysis, and point estimates, we did not conduct statistical meta-analysis.[46] Instead, we qualitatively considered how various design or analytic factors may have contributed to heterogeneity. We also summarized available information on potential effect modifiers.

RESULTS

Of 634 references, we identified 20 studies eligible for inclusion (**Figure 1**)[21, 47-65]; all were observational. Of these, 17 used data from various African countries,[21, 47, 49-51, 54-65] two from Thailand,[52, 53] and one from Italy.[48] Sixteen included estimates specific to OCPs,[21, 47-49, 51-57, 61-65] 14 included estimates specific to injectable contraception,[21, 52-59, 61-65], and two did not distinguish between HC methods but noted that most HC users used injectables.[50, 60] None examined the contraceptive patch, ring, implant, or levonorgestrel IUD.

Table 1 provides basic descriptions of all studies and whether they met minimum quality criteria. **Figure 2** summarizes sixteen studies on OCPs and HIV acquisition, and **Figure 3** summarizes sixteen studies on injectables (or non-specified HC methods) and HIV acquisition. All studies are depicted, regardless of methodological quality, and are shown in decreasing order of relative risk magnitude. For both HC methods, study results are heterogeneous, and in several studies, power to detect an effect was limited due to few endpoints. Among the sixteen studies examining OCPs, two reported significantly elevated HIV risk.[47, 56] The remainder found no significant differences: six reported a nonsignificant relative risk above 1·0,[51, 53-55, 61, 62, 64] six reported a nonsignificant relative risk below 1·0,[21, 49, 52, 57, 63, 65] and one did not calculate a relative risk due to no seroconversions in the HC group.[48] Among the sixteen studies that examined injectables, six reported statistically significant increased risks of HIV associated with use of injectables [21, 52, 56, 59, 61, 64] (although one was not significant under an alternative statistical approach[27]), four reported nonsignificant relative risks above 1·0 [50, 53, 60, 62], four reported nonsignificant relative risks below 1·0, [54, 55, 57, 63] and two reported nonsignificant point estimates separately for norethisterone enanthate (Net-En) and DMPA.[58, 65]

Findings among studies that met minimum quality criteria

Of twenty studies, eight met minimum quality criteria (**Table 2**).[55-58, 61, 63-65] Among seven such analyses on OCPs (**Figure 4**), one reported a statistically significant elevated risk at p=0·05, but the 95% CI included 1·0 (adjusted hazard ratio [adjHR]: 1.5, 1. 0-2.1)[56]. Three reported nonsignificant point estimates above 1·0, ranging from 1·1 to 1·8,[55, 61, 64] and three reported nonsignificant point estimates below 1·0, ranging from 0·7-0·9.[57, 63, 65]

Among eight analyses on injectables that met minimum quality criteria (**Figure 5**), three reported statistically significant elevated risks ranging from 1.5 to 2.2: Baeten 2007 [56], Morrison 2010 [61], and Heffron 2012 [64]. Estimates in Morrison 2010 were statistically significant under an MSM model (adjHR: 1·5, 1·0–2·2), but not a Cox proportional hazards model (adjHR: 1·3, 0·9-1·8).[27] The other five studies reported nonsignificant findings, with estimates ranging from 0·8 to 1·3, including the largest study[65] which reported a point estimate for DMPA of 1·3 (95% CI, 0·9-1·8). **Figure 5** depicts estimates for "any injectable", for comparability with other estimates combining types of injectables, unless such estimates were unavailable. None of the three estimates specific to NET-EN were statistically significant.[57, 58, 65] Findings for NET-EN and DMPA did not demonstrate a consistent pattern of one method generating higher risk (adjusted risk estimates for Net-En and DMPA, respectively: Kleinschmidt 2007: 1.76, 0.46; Myer 2007: 0.79, 0.96; Morrison 2012: 0.92, 1.28).

All studies that met minimum quality criteria included (or assessed the need for) statistical control for some parameterization of condom use, age, number of sexual partners, and at least one genital symptom or infection (**Table 3**). Other factors, such as marital status, coital frequency, or partner risk, were considered only in some studies.

Consideration of findings on injectables, in relation to study characteristics

Among studies that met minimum quality criteria and assessed injectables, we considered how differences in study design or analysis may have contributed to heterogeneity in results. We examined several factors that did not appear explanatory, including recruitment population, HIV incidence, purpose of data collection, study size, number of seroconverters, statistical approach,

or manner of handling pregnancy information, but we identified three factors which merit consideration:

- *Length of inter-survey interval*: One study interviewed women approximately every month,[56] five studies every 2-4 months,[58, 61, 63-65] and two studies every 8 or 10 months.[55, 57] The three studies with statistically significant findings had inter-survey intervals of ≤4 months, including one that interviewed women approximately every month.[56, 61, 64] Three other studies with inter-survey intervals <4 months reported no significant differences in risk. Two studies with intervals >4 months did not observe significant associations.[55, 57]
- *Manner of handling condom use*: Six studies addressed condom use via statistical adjustment alone,[56-58, 61, 64, 65] including all three that reported significantly increased risk.[56, 61, 64] The remaining two studies, neither of which reported increased risks, addressed condom use differently.[56,63] Reid 2010 compared HC users to women who did not report use of HC or condoms as a primary contraceptive method, and statistically adjusted for unprotected sex and other factors.[63] In Kiddugavu 2003, no HIV seroconversions occurred among self-reported consistent condom users, but self-reported inconsistent condom use was a marker for HIV acquisition and most condom use (70%) was inconsistent.[56] In multivariate analysis, investigators compared HC users to non-HC users who reported no condom use. The latter group had a lower crude HIV incidence than non-HC users who used condoms. The effect of using this reference group is unclear; it could theoretically dilute a potential adverse effect of HC, if HC users used condoms both concurrently and consistently (which may have occurred in a small minority of women), but may have been the most conservative approach since the reference group had the lowest crude HIV incidence rate.

In addition to main analyses, four studies also restricted analysis to those with no condom use [27, 55, 57, 58]; none found statistically significant increased risks associated with injectables, but approaches and estimates varied, and 95% CIs were wide. One study restricted to the subgroup of women who reported no condom use and adjusted for all covariates in the main Cox proportional hazards statistical model (adjHR DMPA: 1·6, 0·9-3·1),[27] another restricted to the subgroup of women who reported never or sometimes using condoms and adjusted for age (adjusted incidence rate ratio [adjIRR] DMPA 1·0, 0·6-1·7; adjIRR NET-EN 0·7, 0·3-2·0), (L. Myer, personal communication, 2012)[57] and two studies restricted to women who reported never using condoms but did not adjust for other covariates (crude IRR DMPA: 1·6, 0·9-2·7 [55]; crude IRR injectables: 0·8, 0·1-4·7).[58] None of the three studies that reported increased relative risks associated with injectables in the main model provided estimates stratified by condom use. Across studies that met minimum quality criteria, reporting on the correlation between self-reported (consistent) condom use and outcomes such as pregnancy or HIV varied, complicating assessment of the validity of self-reported condom use across studies.

- *Analysis of serodiscordant couples*: The only study among serodiscordant couples, in which potential confounding by differential exposure to HIV-positive partners may be less of a concern, suggested significantly increased risk of HIV associated with use of injectables.[64]

Effect modification

Below, we report results from studies that assessed for effect modification by particular factors; not all studies assessed each factor described.

- *Age:* Morrison 2010 reported that both DMPA and OCPs were associated with increased HIV acquisition in women aged 18-24 (DMPA MSM adjHR: 2·7, 1·6-4·7, OCP MSM adjHR: 2·0, 1·2-3·6), but not women aged ≥25 (DMPA MSM adjHR: 0·8, 0·5-1·4, OCP MSM adjHR: 0·7, 0·4-1·3).[61] Morrison 2012 reported a significant (p=0·03) interaction between age and NET-EN, with higher point estimates for younger NET-EN users compared to older NET-EN users, but did not report whether this interaction was significant for OCPs, DMPA, or non-hormonal methods.[65] Neither Kiddugavu 2003 nor Heffron 2012 detected effect modification by age,[55, 64] nor did Myer 2007, though this study was conducted among women aged 35-49.[57]
- *Herpes Simplex Virus type-2 (HSV-2) and other STIs*: Morrison 2010 reported that DMPA was associated with elevated HIV risk among HSV-2 negative (MSM adjHR: 4·5, 2·0-10·2), but not HSV-2 positive (MSM adjHR: 1·0, 0·7-1·6) women.[61] Neither Baeten 2007 nor Heffron 2012 found effect modification by HSV-2 status, though both included few HSV-2 negative women.[56, 64] Morrison 2012 found no evidence of an interaction between HC and prevalent chlamydia or gonorrhea.[65]
- *Site in multi-site studies*: Morrison 2007 reported a significant interaction by study site (point estimates for both OCPs and DMPA were above 1·0 in Uganda, but below 1·0 in Zimbabwe),[27] but a reanalysis of these data did not assess this under a MSM approach.[61]
- *Condom use or participant behavioral risk:* Morrison 2012 found no evidence of effect modification between HC and condom use as reported at baseline, or by participant behavioral risk.[65]

DISCUSSION

Twenty prospective studies addressing HC use and risk of HIV acquisition have been published, and results were heterogeneous. We identified eight as most likely to provide insight into the potential biological association between OCPs or injectables and HIV acquisition.

Oral contraceptive pills

The preponderance of evidence does not suggest that OCPs are associated with an increased risk of HIV acquisition. Baeten 2007 reported that OCPs were associated with a 46% increase in risk among sex workers in Kenya. While statistically significant at p=0·05, the 95% CI did not rule out either a null effect or a doubling in risk (adjHR: 1·5, 1·0-2·1). Factors specific to sex workers could theoretically modify the effect of OCPs on HIV acquisition, but the authors note that some factors in this study population, such as sexual frequency, were similar to other African women.[34] Heffron 2012 reported point estimates (1·6-1·8) slightly higher than Baeten 2007 for OCPs, but contained only three seroconverters who used OCPs, resulting in limited statistical power and precision.[64] Morrison 2010 assessed the largest number of seroconverters using OCPs, and reported no increase in risk for OCPs.[61] The marginally significant findings on OCPs reported in Baeten 2007 might be related to factors specific to this study population, to shorter inter-survey intervals, to chance, or to residual confounding.

Injectables

For injectable contraceptive users, available data do not rule out the possibility of increased risk of HIV acquisition, but data are inconsistent and do not establish a clear causal relationship.

Residual confounding could generate spuriously elevated risks or mask a real effect. We attempted to discern whether specific methodological factors could help to explain the heterogeneity. Failure to adequately control for differences in patterns of condom use is likely to generate spuriously elevated risks. Longer inter-survey intervals may increase exposure misclassification, which is generally likely to bias results towards the null, although the effect of contraceptive discontinuation, initiation, and switching on estimates is unclear. Long inter-survey intervals might be more problematic for OCP analyses versus injectables given the shorter duration of effect with OCPs. Additional evidence from serodiscordant couples may help to determine whether exposure to an HIV-infected partner confounds the relationship between HC and HIV acquisition.

Critiques of studies generating non-significant estimates generally relate to length of the inter-survey intervals, measurement of exposure to contraceptive use, and concern about potential differential exposure to HIV. For example, Kiddugavu 2003 and Myer 2007 had inter-survey intervals greater than 6 months, which could reduce accuracy in measurement of time-varying variables. Reid 2010 used self-reported contraceptive data captured in site chart notes and abstracted into a database at the end of the study, complicating assessment of how systematically exposure information was collected, however, use of HC was associated with reduced risk of pregnancy in this study. If HC users are less likely to have HIV-infected partners, this could mask a harmful effect of HC; none of the studies with nonsignificant findings assessed serodiscordant couples.

Critiques of studies generating significant estimates generally relate to whether potential differences in condom use or other sexual behaviors were adequately controlled for, and that elevated risk for multiple HC methods or outcomes might suggest potential residual confounding. While some studies with nonsignificant findings provided information that might bolster confidence in validity of self-reported behaviors (such as no seroconversions or decreased HIV risk among self-reported consistent condom users [55, 58] or women who reported using condoms for contraception)[63] others, such as Morrison 2007 (and thus the reanalysis in 2010 which indicated increased HIV risk with DMPA use) indicated that self-reported consistent condom use did not decrease HIV risk.[27, 61] This complicates assessment of the success of control for condom use, and in this study, the majority (84%) of non-HC users reported using condoms at baseline. Qualitative analyses of Partners in Prevention trial data included in the Heffron analysis note that even in serodiscordant couples, many individuals experience difficulties negotiating consistent condom use.[66] In the Heffron analysis, less than 8% of study intervals involved any self-reported unprotected sex, and despite low reported coital frequency, HIV incidence was 4·09/100 person-years, which may potentially suggest underreporting of unprotected sex.[67] If underreporting occurred, this could generate a spurious result if HC users underreported differentially, however, the magnitude of differential reporting may need to be large to account for the doubling in risk of HIV acquisition observed in the Heffron analysis (personal communication, Smith 2011). None of the studies with significant estimates of HIV risk for injectables asked women about condom use during the entire preceding inter-survey interval, which has unknown effects on response validity. Both Heffron 2012 and Baeten 2007 reported elevated point estimates for both OCPs and injectables, and Heffron 2012 reported elevated point estimates for both HIV acquisition in women and transmission to men. Such

patterns of elevated point estimates could reflect actual increases in risk for multiple methods and mechanisms, or systematic bias from uncontrolled differences between HC users and non-users.

In considering the totality of potentially informative evidence, data on injectables and risk of HIV acquisition are difficult to interpret. On one hand, plausible biological mechanisms and data from animal studies could suggest a potential for increased risk. Several high-quality epidemiological studies suggest significantly increased risks associated with use of injectable contraceptives, including the only published study assessing the association of injectables with HIV acquisition among serodiscordant couples [64] and two large studies designed to assess the relationship between HC and HIV acquisition.[56, 61] Each of these studies contains other important methodological strengths: all incorporated short inter-survey intervals (including the only study with monthly follow-up [56]), two addressed the potential for time-dependent confounding,[61, 64] and one validated reports of contraceptive method use using clinic records.[61] On the other hand, despite plausible biological mechanisms and animal data, it is not clear which mechanisms are relevant or how animal data applies to humans, and biological plausibility is only one of many standard criteria for considering causality.[68] Several high-quality epidemiological studies do not suggest significantly increased risk of HIV associated with use of injectables, including the largest study available,[65] a study in which condom use was so uncommon that it was unlikely to represent a major confounder,[57] and a study that excluded women reporting condoms as a primary contraceptive method from the referent population.[63]

Limitations

Several limitations of this body of evidence have been described above. All currently available studies are observational and could suffer from residual confounding. Evidence is limited for contraceptive methods other than OCPs and injectables, or for whether length of time using HC impacts risk. It is not known whether any potential increase in risk would be related to presence of hormones, or a dose-response to hormones. Thus, while diversification of method mix carries multiple advantages, recommendations that women switch to lower-dose hormonal methods given concerns about HIV acquisition are not evidence-based.

Systematically assessing risk of bias in individual studies is a difficult and necessarily subjective process, especially when evaluating observational studies.[69] Using scales to determine quality has not proven effective; we chose to use the "component approach," in which risk of bias items are specific to the topic of review.[70, 71] We examined the total body of evidence, and attempted to identify studies with lower risk of bias by developing minimum quality criteria. Other investigators may have chosen different minimum quality criteria and included a different subset of studies. For example, Reid 2010 has been criticized for measurement of contraceptive exposure and for having some proportion of missing data; but this study meets our minimum quality criteria, provided some evidence regarding validity of HC exposure information (HC reduced pregnancy risk), assessed missing data as a separate exposure, and included desirable components in terms of control for condom use. Similarly, we excluded Wand 2012, given personal communication with the authors who felt that their analysis was unlikely to provide information on the biological association between HC and HIV acquisition. However, Wand 2012 is similar to other secondary analyses from HIV prevention trials that met our minimum quality criteria, and an argument for inclusion could be made. Given the overall heterogeneity in

this body of evidence, we do not believe these decisions would impact overall conclusions regarding evidence available at the time of this review.

Competing risks of HIV infection and unintended pregnancy

HIV infection carries burdens beyond morbidity and mortality, and HIV prevention is an important public health priority. Highly effective contraception offers substantial benefits by preventing unintended pregnancies, decreasing recourse to abortion, reducing maternal morbidity and mortality, and providing non-health-related benefits.[72] Studies assessing the association between pregnancy and risk of HIV acquisition also show conflicting results, but raise concerns that pregnancy might potentially impact HIV-related risks.[29, 63, 73, 74] Injectable contraception is currently the most widely used hormonal method in sub-Saharan Africa, can be safely delivered by community-based health workers,[75, 76] offers several months of protection and the option of covert use, and is safe to use during breastfeeding. Programmatic efforts must be enhanced to expand method choice as access to other highly effective methods is severely limited in much of the developing world, and successful use of contraception is improved when women can obtain their method of choice.

WHO Technical Consultation

A draft of this systematic review was presented at a WHO Technical Consultation in Geneva in January 2012, along with other presentations on related issues. The GRADE system was used to evaluate the quality of all available studies,[77] rated "low" due to serious limitations and serious inconsistencies. A group of 75 experts discussed the implications of all information presented, and concluded by consensus that WHO should recommend no restriction on use of any HC

method for women at high risk of HIV, but added a strong clarification that, because of the inconclusive nature of the evidence, women using progestin-only injectables should be strongly advised to also always use male or female condoms and other HIV preventive measures (see technical statement for full clarification).[16]

Conclusions

Most currently available evidence does not suggest an association between OCP use and HIV acquisition. No currently available evidence suggests an association between NET-EN and HIV acquisition, but data are limited. Available data on DMPA or unspecified injectables neither establish a clear causal association with HIV acquisition, nor definitively rule out the possibility of an effect. It is imperative that women are informed that HC does not protect against HIV or other STIs, and that women at risk of HIV are advised to also use condoms correctly and consistently. However, negotiating condom use may be complex in some circumstances.[78-80] Many women at risk of HIV need safe and effective means of pregnancy and infection prevention. Pending availability of multipurpose prevention technologies, using an effective contraceptive method plus condoms can provide protection against both pregnancy and STIs, including HIV.

CONTRIBUTIONS OF AUTHORS

CBP conducted the literature search and identified studies for full-text review. CBP and KMC assessed included studies and wrote the manuscript.

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There were no external sources of support; USAID and CDC contributed staff time for conduct of this systematic review.

CONFLICTS OF INTEREST

None.

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Table 1: Description of studies, ordered by publication year

First author, publication year, location	Design, purpose, period of data collection	n enrolled, description of population	Results	Multivariate analysis included condom use?	Meets minimum quality threshold for further consideration?*
Plummer 1991[47] Nairobi, Kenya	Cohort; to determine incidence and risk factors for HIV acquisition 1985-1987	196 sex workers	crude OR OCPs: 3·1 (1·1-8·6) AdjOR OCPs: 4·5 (1·4-13·8) Stratified (no condom use) crude OR OCPs: 3·7 (1·1-11·4) crude HR OCPs: not reported, but log rank <0·05.	Yes	No. Large loss to follow-up (37% at 12 months). Association between HC and HIV was not primary objective of either data collection or data analysis. Referent group included other hormonal method users, complicating interpretation of estimates. No time-varying HC exposure in main analysis.
Saracco 1993[48] Italy	Cohort; to determine incidence and risk factors for male-to-female sexual HIV transmission in serodiscordant couples 1987-1991	368 women in stable, monogamous serodiscordant relationships	None of the 22 OCP users became infected vs. 19/283 non-users	No multivariate analysis	No. Association between HC and HIV was not primary objective of either data collection or data analysis; strong likelihood of confounding. Referent group unclear, inability to perform multivariate analysis due to small numbers of OCP users. No time-varying HC exposure. Loss to follow-up unclear (7% at six months, but median follow-up time was 24 months).
Laga 1993[49] Kinshasa, Zaire	Nested case-control; to determine if treatable ulcerative and non-ulcerative STD were risk factors for HIV 1988	431 female sex workers	crude OR ever OCP use: 0·6 (0·2-2·4); crude OR OCP use during study: 0·7 (0·1-3·4); crude OR OCP use during exposure interval: 0·9 (0-13·5)	No multivariate analysis	No. Association between HC and HIV was not primary objective of either data collection or data analysis; strong likelihood of confounding. No multivariate analysis; condom use not addressed. No time-varying HC exposure. Few OCP users and minimal OCP use during exposure interval. Information on total loss to follow-up not provided (mean monthly follow-up 76%).
Bulterys 1994[50] Southern Rwanda	Cohort; to determine incidence of HIV in young, sexually active women in Rwanda 1989-1993	1524 sexually active women <30 years old in mixed rural and urban population who were pregnant or attending a prenatal clinic	Crude OR ever HC use: 3·2 (1·6-6·5) Age-adj OR ever HC uses: 2·9 (1·4-6·2) adjOR ever HC use: 1·9 (0·8-4·6) Results not provided separately for OCPs and DMPA, but "incidence of HIV infection did not differ by the type of HC method used (data not shown)"	Multivariate analysis did not include condom use, but condom use was rare	No. HC use not collected prospectively (asked about use in past 24 months). Association between HC and HIV was not primary objective of either data collection or data analysis. Did not distinguish between HC methods, leading to lack of clarity on utility of estimates.

Sinei 1996[51] Nairobi, Kenya	Nested case-control; pilot study to demonstrate feasibility of larger study. 1990-1992	1537 women in a family planning clinic	Crude OR for OCP use in last 6 months: 3·5 (0·8-21·5) Attempted to adjust for multiple confounders including condom use, but association persisted	No, and estimates from multivariate analysis not provided	No. High loss to follow-up (71% at 12 months). Multivariate estimates not provided; condom use not addressed. No time-varying HC exposure.
Ungchusak 1996[52] Khon Kaen, Thailand	Cohort; to investigate risk factors of HIV 1990-1991	365 sex workers in 24 illegal brothels in Thailand	Crude IRR OCPs: 0·17 (p=0·11, 95% CI not provided) adjIRR OCPs: 0·22 (0·03-1·87) Crude IRR inj:2·90 (p=0·06, 95% CI not provided) adjIRR inj: 3·91 (1·29-11·82) (based on comment published after original publication)[81]	Multivariate analysis did not include condom use	No. Association between HC and HIV was not primary objective of either data collection or data analysis. Condom use not addressed. High loss to follow-up (34% at 3 months). No time-varying HC exposure.
Kilmarx 1998[53] Chiang Rai, Thailand	Cohort; to examine demographic, behavioral, and other STIs associated with HIV infection in FSWs 1991-1994	340 sex workers in STD clinic, medical clinic, or workplace	Crude RR OCPs: 2·5 (1·1-5·3) adjRR OCPs: 1·8 (0·8-4·0) crude RR DMPA: 1·5 (0·6-4·0) adjRR DMPA: N/A	Multivariate analysis did not include condom use	No. Association between HC and HIV was not primary objective of either data collection or data analysis. Condom use not addressed. High loss to follow-up (29% at 12 months, 46% at 24 months), and differential loss to follow-up.
Kapiga 1998[54] Dar Es Salaam, Tanzania	Cohort; to study HIV incidence in low-risk women and examine associations with contraceptive methods 1991-1995	2471 women in three family planning clinics in Dar es Salaam	Age-adjusted HR OCPs: 1·28 (0·58-2·81) adjHR OCPs: 1·01 (0·45-2·28) Age-adjusted HR injectables: 0·27 (0·06-1·12) adjHR injectables: 0·30 (0·07-1·26) Analyses on duration of HC use were not statistically significant for any method. Stratified on condom use: "adjusted results not altered"	Considered controlling for condom use in multivariate analysis	No. High loss to follow-up (44.5%, unclear at what time point), and differential loss to follow-up. Frequency of follow-up visits unclear and may have varied by participant. No time-varying HC exposure (ever/never during follow-up).
Kiddugavu 2003[55] Southwestern Uganda	Cohort; ongoing population-based cohort established as part of a community randomized trial 1994-1999	5117 sexually active women aged 15-49 years	adjIRR any HC: 0·94 (0·53-1·64) Crude IRR OCPs: 1·70 (0·85-3·04) adjIRR OCPs: 1·12 (0·48-2·56) Crude IRR injectable:1·47 (0·82-2·45) adjIRR injectable: 0·84 (0·41-1·72) Stratified by no condom use: Crude IRR any HC: 1·59 (0·90-2·66)	Yes	Yes

Baeten 2007[56] (update of Martin 1998 [82]and Lavreys 2004 [34]) Mombasa, Kenya	Cohort; to define HIV seroincidence in female CSWs and examine relationship between HC, STDs, and HIV incidence 1993-2003	1498 female sex workers attending clinic for STD	Crude HR OCPs: 1·58 (1·12-2·24) adjHR OCPs: 1·46 (1·00-2·13) Crude HR DMPA: 2·05 (1·56-2·70) adjHR DMPA: 1·73 (1·28-2·34)	Yes	Yes
Myer 2007[57] Cape Town, South Africa	Cohort; RCT to evaluate cervical cancer screening approaches 2000-2004	4555 women aged 35-65 enrolled in a cervical cancer trial	Crude IRR OCPs: 0·83 (0·20-3·40) adjIRR OCPs: 0·65 (0·16-2·66) Crude IRR NET-EN: 1·00 (0·40-2·49) adjIRR NET-EN: 0·79 (0·31-2·02) Crude IRR DMPA: 1·21 (0·73-2·02) adjIRR DMPA: 0·96 (0·58-1·59) adjIRR any injectable: 0·94 (0·59-1·49)	Yes	Yes
Kleinschmidt 2007[58] Orange Farm, South Africa	Cohort; to investigate prospectively if HIV incidence is higher among sexually active women using progestin 1999-2002	634 sexually active women aged 18-40	crude IRR injectables: 1·12 (0·45-2·78) crude IRR NET-EN: 1·77 (0·77-4·11) adjIRR NET-EN: 1·76 (0·64-4·84) crude IRR DMPA: 0·26 (0·03-1·97) adjIRR DMPA: 0·46 (0·06-3·79) Stratified analysis among "never" condom users: crude IRR injectables: 0·8 (0·1-4·7)	Yes	Yes
Kumwenda N 2008[59] Blantyre, Malawi	Cohort; RCT to assess effect of intravaginal antibiotic on genital tract infections 2003-2005	842 non-pregnant women of childbearing age attending general reproductive health services, enrolled at a central hospital or one of two health centers	Crude OR DMPA: 3·57 (1·37-9·31) adjOR DMPA: 2·84 (1·07-7·55)	Multivariate analysis did not include condom use	No. Association between HC and HIV was not primary objective of either data collection or data analysis; strong likelihood of confounding. Condom use not addressed. Referent group unclear; appears to include women using other methods of HC, complicating interpretation of estimates. No use of time-varying HC.

Watson-Jones 2009[60] Northwestern Tanzania	Cohort; RCT assessing effect of acyclovir on HIV incidence 2004-end date unclear	821 HSV2+ women aged 16-35 years working in bars, guesthouses, or other food and recreational facilities	Age-adjusted HR HC at baseline: 1·17 (0·71-1·93) Age-adjusted HR current HC: 1·63 (0·95-2·80) adjHR HC: 1·60 (0·93-2·76)	Multivariate analysis did not include condom use	No. Association between HC and HIV was not primary objective of either data collection or data analysis; strong likelihood of confounding. Condom use not addressed. Did not distinguish between HC methods. Potentially high loss to follow-up, unclear (20% did not complete follow-up defined as attending until seroconversion or end of study).
Morrison 2010 [61] (reanalysis of Morrison 2007)[27] Uganda, Zimbabwe	Cohort; to examine association between OCP and DMPA use and HIV 1999-2004	6,109 sexually-active, non-pregnant women in family planning clinics, plus some high-risk referral women from STI or primary healthcare clinics, sex worker networks, or military bases.	2010 MSM reanalysis: Crude HR DMPA: n/a adjHR DMPA: 1·48 (1·02-2·15) Crude HR OCPs: n/a adjHR OCPs: 1·19 (0·80-1·76) 2007 Cox PH analysis Crude HR DMPA: 1·24 (0·90-1·71) adjHR DMPA: 1·25 (0·89-1·78) Crude HR OCPs: 1·02 (0·72-1·43) adjHR OCPs: 0·99 (0·69-1·42) 2007 stratified analysis restricted to no condom use: adjHR OCPs: 1·47 (0·78-2·80) adjHR DMPA: 1·61 (0·85-3·06) Sensitivity analyses did not change results.	Yes	Yes
Feldblum 2010[62] Nigeria, Ghana, Benin, Uganda, India, South Africa	Cohort; data from four Phase III RCTs on microbicides 2004-2007	7364 women at "higher than average risk of HIV" (variably defined between studies)	Crude HR OCPs: 1·84 (0·83-4·05) Crude HR injectables: 2·51 (1·12-5·60) "Use of injectable contraception and condom use were significantly associated with incident HIV initial models, but dropped from the final model; only age and education were significantly associated with incident HIV in the final model."	Considered controlling for condom use in multivariate analysis	No. Association between HC and HIV was not primary objective of either data collection or data analysis. No use of time-varying information, all covariates assessed at baseline. High loss to follow-up in some but not all sites (up to 30% in Nigeria site).

Reid 2010[63] South Africa, Zambia, Zimbabwe	Cohort; HPTN 039 study, RCT to assess effect of acyclovir on HIV incidence 2003-2007	1358 (analyzed, n enrolled unclear) HSV2-positive women recruited from family planning, well-baby, and VCT clinics, and community venues.	Crude HR OCPs: 0·93 (0·48-1·82) adjHR OCPs: 0·91 (0·45-1·83) Crude HR injectables: 1·01 (0·51-1·98) adjHR injectables: 0·94 (0·46-1·92)	Yes	Yes
Heffron 2012[64] Seven countries in East and Southern Africa	Cohort; RCT assessing effect of acyclovir on HIV incidence 2004-2010	1314 (analyzed, n enrolled unclear) M+F-serodiscordant couples (83% of observations from an acyclovir RCT, 17% of observations from cohort study of immune correlates of HIV protection)	<u>HC</u> Crude HR (Cox): 1·73 (0·95-3·15) Adj HR (Cox): 1·.98 (1·06-3·68) Adj OR (MSM): 1·84 (0·98-3·47) <u>OCPs</u> Crude HR (Cox): 1·53 (0·48-4·90) Adj HR (Cox): 1·80 (0·55-5·82) Adj OR (MSM): 1·63 (0·47-5·66) <u>Injectables</u> Crude HR (Cox):1·80 (0·92-3·52) Adj HR (Cox): 2·05 (1·04-4·04) Adj OR (MSM): 2·19 (1·01-4·74) <u>Censoring at pregnancy</u> AdjHR HC: 1·84 (0·97-3·49)	Yes	Yes
Morrison 2012 [65] South Africa	Cohort; RCT assessing the effectiveness of the microbicide Carraguard, 2004-2007	5567 (analyzed, n enrolled unclear), recruited from community venues	<u>OCPs</u> Adj HR (Cox): 0·88 (0·49-1·30) Adj HR (MSM): 0·84 (0·51-1·39) <u>DMPA</u> Adj HR (Cox): 1·27 (0·93-1·73) Adj HR (MSM): 1·28 (0·92-1·78) <u>NET EN</u> Adj HR (Cox): 0·87 (0·60-1·25) Adj HR (MSM): 0·92 (0·64-1·32)	Yes	Yes

Wand 2012 [21] South Africa	Cohort; RCT assessing the effectiveness of vaginal microbicide, dates of data collection not provided	2236, recruited from community venues	OCPs Adj HR: 0·95 (0·62-1·46) Injectables Adj HR: 2·02 (1·37-3·00)	Yes	No; control for confounding weak, information on loss to follow-up not provided, and authors stated in personal communication (Dec. 11, 2011) that they "do not think that we can infer any biological conclusion between HC and HIV based on our data."

Abbreviations: Adj = adjusted; CSW = commercial sex worker; DMPA = depot medroxyprogesterone acetate; HC = hormonal contraception; HR = hazard ratio; HSV2+ = seropositive for herpes simplex virus 2; IRR = incidence rate ratio; MSM = marginal structural model; NET-EN = norethisterone enanthate; OCPs = oral contraceptive pills; OR = odds ratio; RCT = randomized control trial.

* Studies that had at least 2 of 3 problems failed to meet minimum quality criteria: lack of consideration of important potential confounders, high loss to follow-up, unclear definitions of exposure

Table 2: Comparison of studies that met minimum quality criteria.

Study, study population, and whether analysis is new since last Medical Eligibility Criteria (MEC) review	#n seroconverted/ #n analyzed, #n seroconverters using HC, overall HIV incidence	Interval between visits, length of follow-up, loss to follow-up and whether differential	Referent group Overall proportion of condom use in population	Handling of condom use	HC/non-HC differences noted at baseline or follow-up?	Results	Summary of strengths	Summary of weaknesses
Kiddugavu 2003 (Uganda)[55] Population-based cohort	202/5117 12 seroconverters using OCPs, 16 using injectables 1·5/100 person-years	10 months between visits. Median follow-up: ~31 months LTFU: Unclear, 15·5% of 6053 HIV-negative women had no follow-up blood sample. Unclear if differential.	Neither HC nor condoms During follow-up, 22·8% ever used condoms, mostly inconsistent use	In multivariate analysis, compared HC users to non-HC users who reported no condom use, control variable did not address consistency. Unadjusted analysis stratified by condom use (some vs. none).	Follow-up only.	adjIRR **any HC**: 0·94 (0·53-1·64) **OCPs**: Crude IRR: 1·70 (0·85-3·04) adjIRR: 1·12 (0·48-2·56) **Injectable (mostly DMPA)**: Crude IRR:1·47 (0·82-2·45) adjIRR: 0·84 (0·41-1·72) **Unadjusted analysis, restricted to those with no condom use:** Crude IRR **any HC**: 1·59 (0·90-2·66)	Large sample. Population-based cohort. No seroconversions among women who reported consistent condom use may suggest self-report reliability. Unclear if exclusion of condom users from non-HC group is a strength or weakness. Met minimum quality criteria.	Long inter-survey intervals. Assumes self-reported condom use in last six months reflects condom use in last 10 months. Lack of clarity on loss to follow-up. Unclear if exclusion of condom users from non-HC group is a strength or weakness. Potential for residual/unmeasured confounding.
Baeten 2007 (Kenya)[56] Sex workers	233/1206 seroconverted, 38 seroconverters using OCPs, 79 using DMPA 8·7/100 person-years	Median 35 days between visits. Median total follow-up: ~15 months LTFU: Unclear, Martin 1998, reported 18% at 7·5 months.[82] Unclear if	Used tubal ligation, used condoms, or used no method Overall condom use unclear, reported in Martin 1998 at enrollment as median 100%, range 0-100%[82]	Controlled for condom use, including consistency.	Neither provided.	**OCPs:** Crude HR: 1·58 (1·12-2·24) adjHR: 1·46 (1·00-2·13) **DMPA:** Crude HR: 2·05 (1·56-2·70) adjHR: 1·73 (1·28-2·34)	Primary objective of data collection. Monthly follow-up. Authors argue that behavioral confounding less of an issue among high-risk women. Met minimum quality criteria.	Assumes self-reported condom use in last week reflects condom use in last month. High loss to follow-up at 12 months (~45%, open cohort).[83] Potential for residual/unmeasured confounding.

		differential.						
Myer 2007 (South Africa)[57] Women older than 35	111/4200 18 seroconverters using DMPA, 5 using NET-EN, 2 using OCPs 2·2/100 person-years	Mean 7·8 months between visits Mean follow-up: 14·3 months LTFU: 11% at 6 months (subset with longer follow-up; 25% at 12 months and 32% at 24 months). Not differential by HC use.	No HC, could use condoms Overall condom use low,1% at enrollment, 8% during follow-up	Controlled for condom use, control may not have captured consistency. Age-adjusted analysis stratified by "no/some condom use," estimates not reported in publication (noted only that null association persisted) but provided by author in personal communication.	Both provided.	(Full study cohort) **OCPs**: Crude IRR: 0·83 (0·20-3·40) adjIRR: 0·65 (0·16-2·66) **NET-EN**: Crude IRR: 1·00 (0·40-2·49) adjIRR: 0·79 (0·31-2·02) **DMPA**: Crude IRR: 1·21 (0·73-2·02) adjIRR: 0.96 (0·58-1·59) **Any injectable**: adjIRR: 0·94 (0·59-1·49) **Restricted to those using condoms "never or some of the time" (instead of always or most of the time)** Age adjusted IRRs: **OCPs**: 0·45 (0·06-3·27) **NET-EN**: 0·72 (0·26-2·02) **DMPA**: 0·97 (0·56-1·67)	Large sample. Low condom use in study may have minimized potential for confounding by condom use. Met minimum quality criteria.	Control for condom use combined "always" users and "most always" users which may not address condom use consistency. Long inter-survey intervals. Subset had high loss to follow-up. Potential for residual/unmeasured confounding.
Kleinschmidt 2007 (South Africa)[58] Family planning clinic attendees	23/551 11 seroconverters using injectables 4·7/100 person-years	2-4 months between visits Total follow-up: 12 months LTFU: Unclear, at least 12% at 3 months (75/634). Unclear if differential.	Using non-hormonal methods or no contraception, could use condoms Overall condom use, 54·2% at enrollment (measured as use during last three months)	Controlled for condom use, including consistency. Unadjusted analysis stratified by condom use and no condom use during study.	Baseline only.	**Injectables** crude IRR: 1·12 (0·45-2·78) **NET-EN**: crude HR: 1·77 (0·77-4·11) adjHR: 1·76 (0·64-4·84) **DMPA**: crude HR: 0·26 (0·03-1·97) adjHR: 0·46 (0·06-3·79) **All injectables, restricted to "never" condom users:** crude IRR: 0·8 (0·1-4·7)	Primary objective of data collection. Frequent follow-up. Met minimum quality criteria.	Lack of clarity on loss to follow-up. Potential for residual/unmeasured confounding.
Morrison 2010 (reanalysis of Morrison 2007) (Uganda,	213/4435 71 seroconverters	3 months between visits. Mean total	At baseline, 84% used condoms, 13% used withdrawal, 10% used rhythm, 3% were sterilized,	2010 analysis: Controlled for condom use, but not consistency,	Both provided.	2010 MSM reanalysis: **OCPs**: Crude HR: n/a adjHR: 1·19 (0·80-1·76)	Primary objective of data collection. Large sample. Frequent	Self-reported condom use associated with increased HIV, and consistent condom

Zimbabwe)[27, 61] Family planning clinic attendees with subset of higher-risk women	using OCPs, 87 using DMPA 2·8/100 person-years	follow-up: 21·9 months LTFU: 8% at 24 months. Not differential by HC use.	5% used a non-HC method During follow-up, consistent condom use was 51% in non-HC, 13% in HC	authors noted via email that this did not impact results 2007 analysis controlled for condom use, addressed consistency (always condom use or no sex vs. none/some condom use) 2007 adjusted analysis stratified by condom use and no condom use during study		**DMPA**: Crude HR: n/a adjHR: 1·48 (1·02-2·15) 2007 Cox PH analysis **OCPs**: Crude HR: 1·02 (0·72-1·43) adjHR: 0·99 (0·69-1·42) **DMPA** Crude HR: 1·24 (0·90-1·71) adjHR: 1·25 (0·89-1·78) **2007 stratified analysis restricted to no condom use**: adjHR **OCPs**: 1·47 (0·78-2·80) adjHR **DMPA**: 1·61 (0·85-3·06)	follow-up and low loss to follow-up. Contraceptive self-report validated in clinic records. 2010 MSM analysis may have addressed time-dependent confounding. 2007 paper provided stratified analysis on never condom use. Met minimum quality criteria.	use did not decrease HIV, raising concern about response validity and success of statistical adjustment. Assumes self-reported condom use in "typical month in last 3 months" reflects condom use in last 3 months. Effect modification by study site (detailed in 2007 analysis), but a biological effect should be consistent. Potential for residual/unmeasured confounding.
Reid 2010 (South Africa, Zambia, Zimbabwe)[63] HSV-2 positive women in family planning or other clinics	72/1358 Unclear how many seroconverters using HC 4·0/100 person-years	3 months between visits. Total follow-up: up to 18 months. LTFU: Unclear, unclear if differential.	Women using no contraceptive method (excluded women using condom as a contraceptive method) At enrollment, 42% reported ever using condoms in last three months	Women reporting condoms as primary contraceptive method not in referent group. Addressed consistency by controlling for any unprotected sex.	Neither provided.	**OCPs**: Crude HR: 0·93 (0·48-1·82) adjHR: 0·91 (0·45-1·83) **Injectable (DMPA & NET-EN):** Crude HR: 1·01 (0·51-1·98) adjHR: 0·94 (0·46-1·92)	Frequent follow-up. Excluding women using condoms for contraception from referent group may equalize quality of condom use between groups. Met minimum quality criteria.	Self-reported contraceptive info during follow-up captured in site chart notes and abstracted into database at end of study, which may have impacted quality of exposure information. Lack of clarity on loss to follow-up. Potential for residual/unmeasured confounding.
Heffron 2012 (Seven countries in East and Southern Africa)[64] Women in a	73/1314 13 seroconverters using HC, 10 using injectables and 3 using	3 months between visits for HIV-partner. Median follow-up: 18	Had hysterectomy, tubal ligation, used condoms, or used no contraception During follow-up, self-reported condom use was high (only 7·6% of intervals	Controlled for unprotected sex (thereby incorporating information on self-reported condom use consistency).	Follow-up only.	**Any HC** Cox crude HR: 1·73(0·95-3·15) Cox adjHR: 1·98 (1·06-3·68) MSM adjOR: 1·84 (0·98-3·47)	Analysis of serodiscordant couples increases likelihood that all participants were equally exposed to sexual activity	Assumes self-reported condom use in last month reflects condom use in last three months. Possible condom over-reporting; only 8% of

serodiscordant couple	OCPs 4·09/100 person-years	months LTFU: Reported as 7% at 12 months, 13% at 24 months, unclear if differential.	included any self-reported unprotected sex)			**OCPs** Cox crude HR: 1·53(0·48-4·90) Cox adjHR: 1·80 (0·55-5·82) MSM adjOR: 1·63 (0·47-5·66) **Injectable (DMPA & NET-EN)** Cox crude HR:1·80 (0·92-3·52) Cox adjHR: 2·05 (1·04-4·04) MSM adjOR: 2·19 (1·01-4·74)	with an HIV-positive partner. Frequent follow-up. Low loss to follow-up. MSM analysis may have addressed time-dependent confounding. Met minimum quality criteria.	intervals involved any self-reported unprotected sex; yet HIV incidence was 4·09/100 person-years. Potential for residual/unmeasured confounding.
Morrison 2012 (South Africa) [65] Sexually active women aged 16-49, recruited from community venues	270/5567 21 seroconverters using OCPs, 103 using DMPA, 55 using NET-EN 3·7/100 person-years	Months 1, 3, and every 3 months thereafter Follow-up from 9-24 months LTFU not reported in manuscript (but 89·9% at 1 yr in Kaplan-Meier analysis), (C. Morrision, personal communication, 2012) unclear if differential.	No use of HC; excluded IUD users and women with hysterectomy; included women using male or female condoms, male or female sterilization, diaphragm, traditional methods, or not using any contraceptive method About 23% reported any condom use at enrollment; varied significantly by contraceptive method	Controlled for condom use, did not address consistency.	Baseline only	**OCPs** Cox adjHR: 0·88 (0·49-1·30) MSM adjHR: 0·84 (0·51-1·39) **DMPA** Cox adjHR: 1·27 (0·93-1·73) MSM adjHR: 1·28 (0·92-1·78) **NET-EN** Cox adjHR: 0·87 (0·60-1·25) MSM adjHR: 0·92 (0·64-1·32)	Large sample. Frequent follow-up. Low loss to follow-up. MSM analysis may have addressed time-dependent confounding. Met minimum quality criteria.	Analysis did not address consistency of condom use. Potential for residual/unmeasured confounding.

Abbreviations: Abbreviations: Adj = adjusted; DMPA = depot medroxyprogesterone acetate; HC = hormonal contraception; HR = hazard ratio; IRR = incidence rate ratio; LTFU = loss to follow-up; MSM = marginal structural model; NET-EN = norethisterone enanthate; OCPs = oral contraceptive pills; OR = odds ratio.

Table 3: Factors considered* and controlled for in multivariate analysis, among studies that met minimum quality criteria

		Kiddugavu 2003[55]	Baeten 2007[56]	Myer 2007[57]	Kleinschmidt 2007[58]	Morrison 2010[61]	Reid 2010[63]	Heffron 2012[64]	Morrison 2012[65]
Condom use	Considered	X	X	X	X	X	X	X	X
	Controlled	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Number of sex partners (or concurrent partners)	Considered	X	X	X	X	X	X	X	X
	Controlled	**X**	**X**	**X**	**X**	**X**	**X**		**X**
Age	Considered	X	X	X	X	X	X	X	X
	Controlled	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Education	Considered	X	X	X	X	X	X		X
	Controlled	**X**	**X**	**X**					
Married/lives with partner	Considered	X		X		X	X	X	X
	Controlled	**X**		**X**		**X**	**X**		**X**
Coital frequency	Considered					X	X	X	X
	Controlled					**X**			
Age at sexual debut	Considered				X				
	Controlled								
Parity	Considered		X		X	X		X	
	Controlled		**X**						
Pregnancy	Considered					X	X	X	
	Controlled							**X**	
Breastfeeding	Considered					X			
	Controlled								
Sex work	Considered		All CSW			X			X
	Controlled		All CSW			**X**			**X**
GUD	Considered	X	X				X	X	
	Controlled	**X**	**X**						
HSV2	Considered		**X**			X		X	
	Controlled		**X**						
HPV	Considered			X					
	Controlled			**X**					
BV	Considered		X	X	X	X			
	Controlled		**X**		**X**				
Chlamydia/Gonorrhea/ Trichomoniasis	Considered		X	X	X	X	X	X	X
	Controlled		**X**	**X**	**X**		**X**		
Vaginal discharge or discomfort, vulvitis, candida	Considered		X			X			X
	Controlled		**X**						**X**
Vaginal washing	Considered		X						
	Controlled		**X**						
Abnormal epithelial findings	Considered								X
	Controlled								**X**
Alcohol use	Considered			X					
	Controlled			**X**					
Partner risk	Considered					X		All HIV+	X
	Controlled					**X**		All HIV+	**X**
Male circumcision status	Considered							X	
	Controlled								
New partners recently	Considered					X	X		X
	Controlled					**X**	**X**		**X**
Recent HIV+ partner	Considered						X	All HIV+	
	Controlled							All HIV+	
Partner plasma VL	Considered	N/A	N/A	N/A	N/A	N/A	N/A	X	N/A
	Controlled	N/A	N/A	N/A	N/A	N/A	N/A	**X**	N/A
Partner CD4	Considered	N/A	N/A	N/A	N/A	N/A	N/A	X	N/A
	Controlled	N/A	N/A	N/A	N/A	N/A	N/A		N/A
Housing type	Considered			X					
	Controlled								
Site	Considered					X		X	X
	Controlled					**X**			**X**
Own income	Considered						X		
	Controlled								
Partner own income	Considered						X		
	Controlled						**X**		
Race	Considered								X
	Controlled								

Abbreviations: BV = bacterial vaginosis; CSW = commercial sex worker; GUD = genital ulcer disease; HPV = human papillomavirus; HSV2+ = seropositive for herpes simplex virus 2.
* Some confounders were considered but not controlled for due to a lack of confounding in those data; and some factors listed on this table are not relevant to all studies (i.e., site or race in homogeneous populations)

Figure 1: Article selection flow diagram.

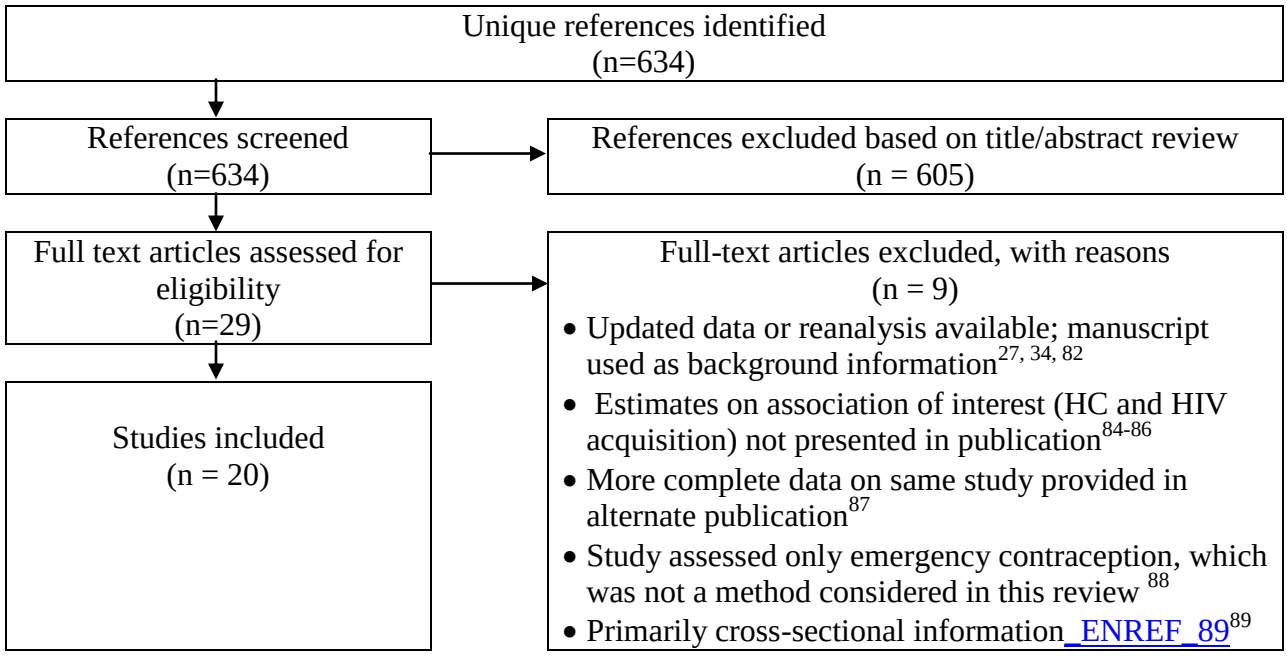
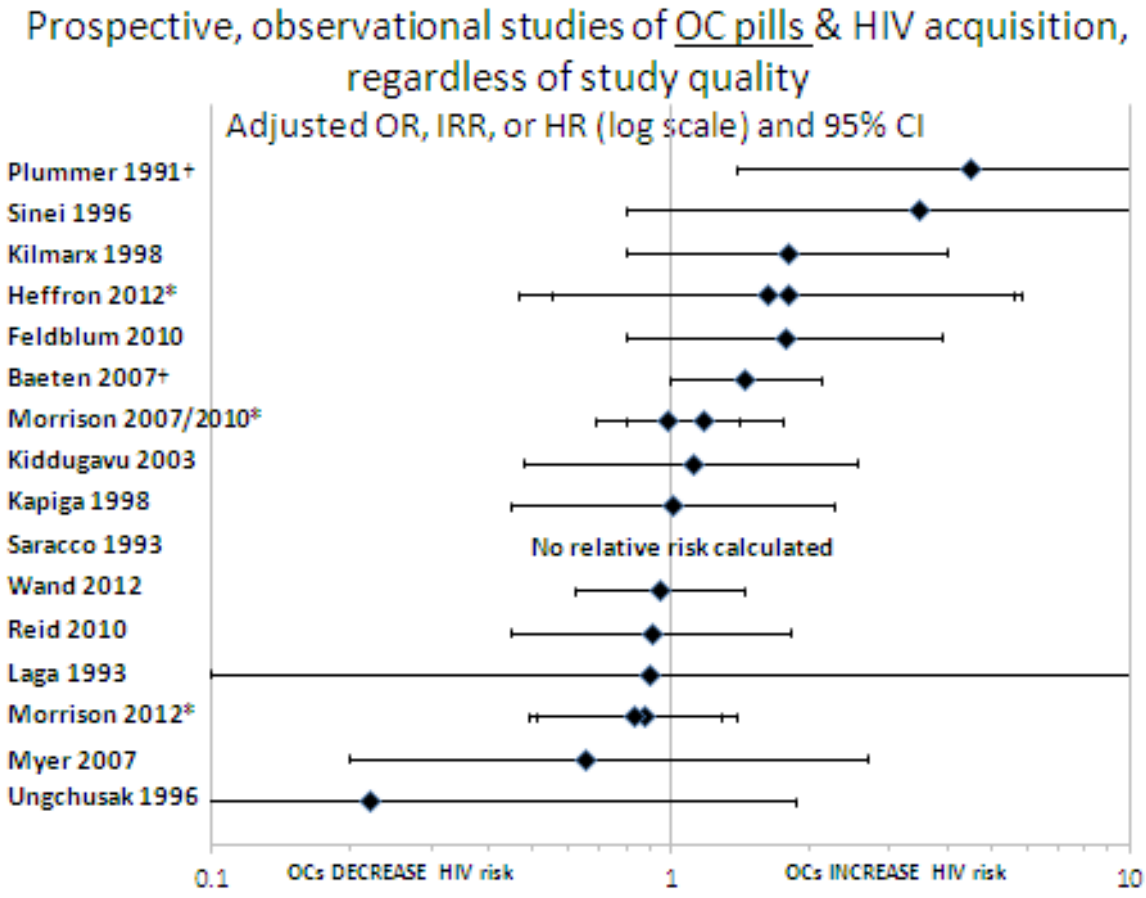
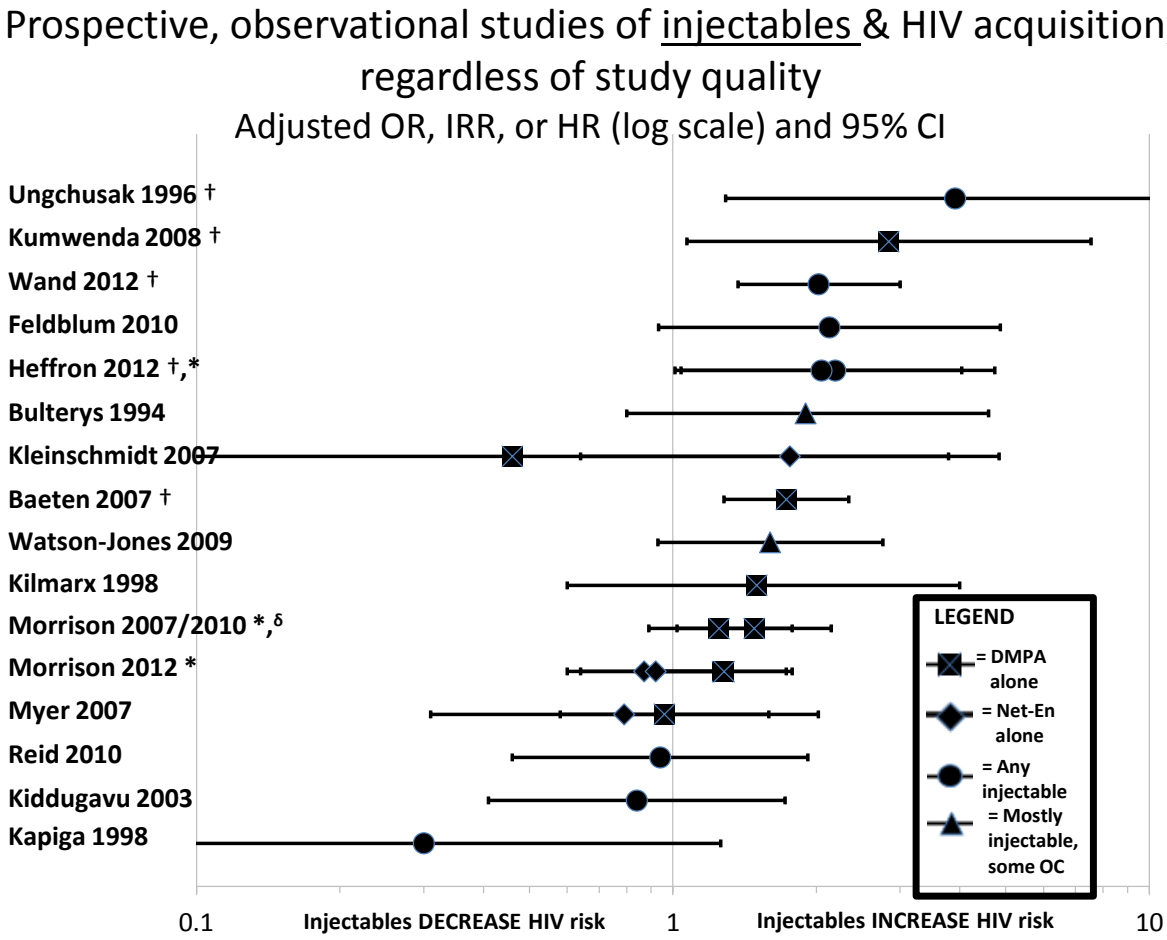


Figure 2.



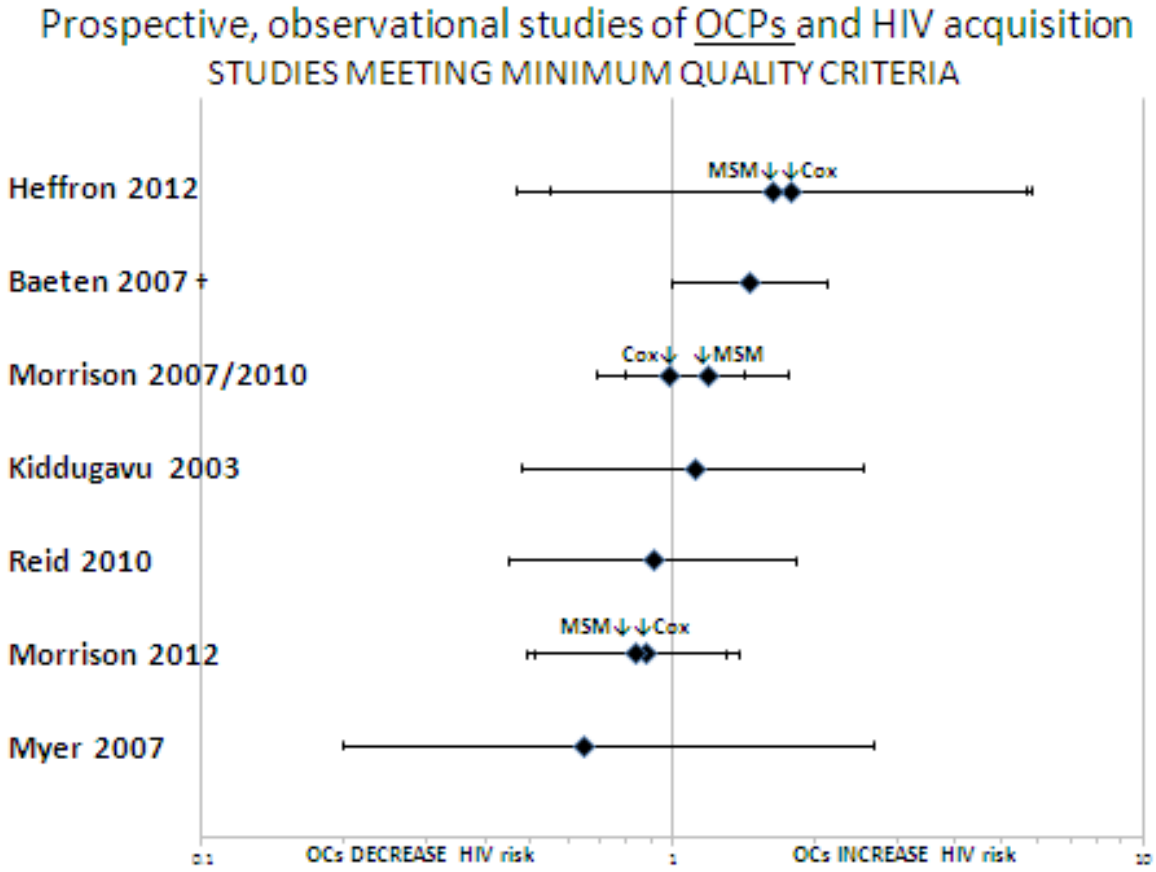
** study included both Cox and MSM estimates*
† study reported statistically significant findings
Abbreviations: OR=odds ratio, IRR=incidence risk ratio; HR=hazard ratio, OCs = oral contraceptive pills
Note: See Figure 4 for estimates of oral contraceptive use among studies that met minimum quality criteria.

Figure 3.



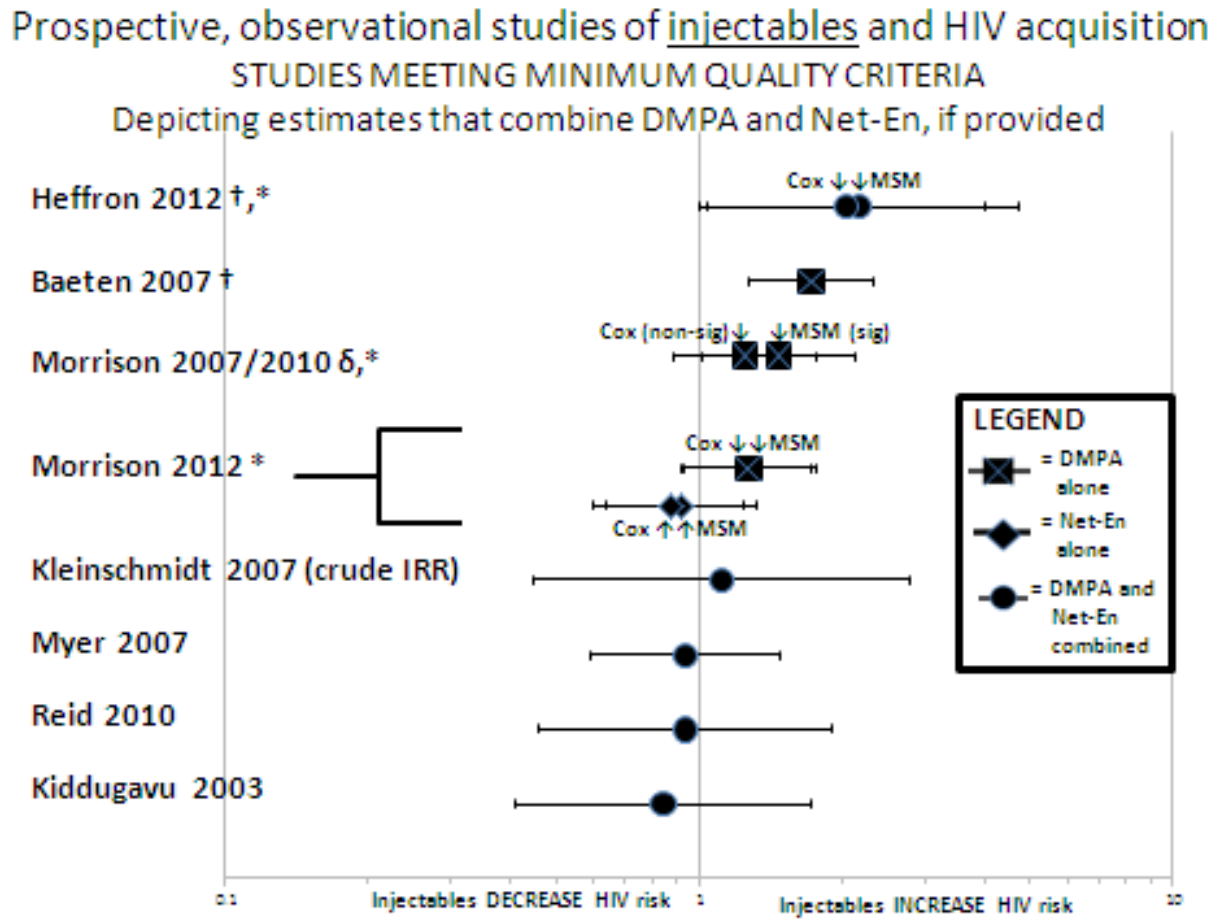
** study included both Cox and MSM estimates*
† study reported statistically significant findings
δ study reported statistically significant findings under one statistical approach, but non-significant findings under another statistical approach
Abbreviations: OR=odds ratio, IRR=incidence risk ratio; HR=hazard ratio, DMPA=Depot medroxyprogesterone acetate; Net-En= norethisterone enanthate; OC=oral contraception
Note: see Figure 5 for injectable estimates among studies that met minimum quality criteria

Figure 4.



† study reported statistically significant findings
Abbreviations: MSM = marginal structural modeling; Cox = Cox proportional hazards modeling, OCs = oral contraceptive pills

Figure 5.



** study included both Cox and MSM estimates*
† study reported statistically significant findings
δ study reported statistically significant findings under one statistical approach, but non-significant findings under another statistical approach
Abbreviations: MSM = marginal structural modeling; Cox = Cox proportional hazards modeling; DMPA=Depot medroxyprogesterone acetate; Net-En= norethisterone enanthate, sig = significant, non-sig = non-significant

Note: Adjusted estimates shown for all studies except Kleinschmidt 2007, which provided adjusted estimates for DMPA alone and for NET-EN alone (DMPA adjHR: 0·46 (0·06-3·79); NET-EN adjHR: 1·76 (0·64-4·84).

REFERENCES

1. WHO. Review of Priorities in Research on Hormonal Contraception and IUDs and HIV Infection: Report of a Technical Meeting. Geneva; 2007.
2. Blish CA, Baeten JM. Hormonal Contraception and HIV-1 Transmission. AmJ ReprodImmunol. 2010.
3. Hel Z, Stringer E, Mestecky J. Sex steroid hormones, hormonal contraception, and the immunobiology of human immunodeficiency virus-1 infection. Endocr Rev. 2010; **31**(1): 79-97.
4. Critchlow CW, Wolner-Hanssen P, Eschenbach DA, Kiviat NB, Koutsky LA, Stevens CE, et al. Determinants of cervical ectopia and of cervicitis: age, oral contraception, specific cervical infection, smoking, and douching. Am J Obstet Gynecol. 1995; **173**(2): 534-43.
5. Moss GB, Clemetson D, D'Costa L, Plummer FA, Ndinya-Achola JO, Reilly M, et al. Association of cervical ectopy with heterosexual transmission of human immunodeficiency virus: results of a study of couples in Nairobi, Kenya. J Infect Dis. 1991; **164**(3): 588-91.
6. Marx PA, Spira AI, Gettie A, Dailey PJ, Veazey RS, Lackner AA, et al. Progesterone implants enhance SIV vaginal transmission and early virus load. Nat Med. 1996; **2**(10): 1084-9.
7. Hild-Petito S, Veazey RS, Larner JM, Reel JR, Blye RP. Effects of two progestin-only contraceptives, Depo-Provera and Norplant-II, on the vaginal epithelium of rhesus monkeys. AIDS research and human retroviruses. 1998; **14 Suppl 1**: S125-30.
8. Mingjia L, Short R. How oestrogen or progesterone might change a woman's susceptibility to HIV-1 infection. Aust N Z J Obstet Gynaecol. 2002; **42**(5): 472-5.
9. Smith SM, Mefford M, Sodora D, Klase Z, Singh M, Alexander N, et al. Topical estrogen protects against SIV vaginal transmission without evidence of systemic effect. Aids. 2004; **18**(12): 1637-43.
10. Abel K, Rourke T, Lu D, Bost K, McChesney MB, Miller CJ. Abrogation of attenuated lentivirus-induced protection in rhesus macaques by administration of depo-provera before intravaginal challenge with simian immunodeficiency virus mac239. J Infect Dis. 2004; **190**(9): 1697-705.
11. Trunova N, Tsai L, Tung S, Schneider E, Harouse J, Gettie A, et al. Progestin-based contraceptive suppresses cellular immune responses in SHIV-infected rhesus macaques. Virology. 2006; **352**(1): 169-77.
12. Mauck CK, Callahan MM, Baker J, Arbogast K, Veazey R, Stock R, et al. The effect of one injection of Depo-Provera on the human vaginal epithelium and cervical ectopy. Contraception. 1999; **60**(1): 15-24.
13. Bahamondes L, Trevisan M, Andrade L, Marchi NM, Castro S, Diaz J, et al. The effect upon the human vaginal histology of the long-term use of the injectable contraceptive Depo-Provera. Contraception. 2000; **62**(1): 23-7.
14. Miller L, Patton DL, Meier A, Thwin SS, Hooton TM, Eschenbach DA. Depomedroxyprogesterone-induced hypoestrogenism and changes in vaginal flora and epithelium. Obstet Gynecol. 2000; **96**(3): 431-9.
15. Prakash M, Kapembwa MS, Gotch F, Patterson S. Oral contraceptive use induces upregulation of the CCR5 chemokine receptor on CD4(+) T cells in the cervical epithelium of healthy women. J Reprod Immunol. 2002; **54**(1-2): 117-31.
16. WHO. Hormonal contraception and HIV: technical statement. In: Research DoRHa, editor. Geneva, Switzerland; 2012.

17. Morrison CS, Turner AN, Jones LB. Highly effective contraception and acquisition of HIV and other sexually transmitted infections. BestPractResClin ObstetGynaecol. 2009; **23**(2): 263-84.
18. Morrison CS, Bright P, Wong EL, Kwok C, Yacobson I, Gaydos CA, et al. Hormonal contraceptive use, cervical ectopy, and the acquisition of cervical infections. Sex TransmDis. 2004; **31**(9): 561-7.
19. Curtis KM, Kapp N. Hormonal contraceptive use among women at high risk for HIV: A systematic review conducted in preparation for WHO's technical meeting on medical eligibility criteria for contraceptive use. Geneva, Switzerland: World Health Organization; 2008.
20. Ciapponi AG, D; Bardach, A; Garcia Marti, S; Comande, D. EROS: a new software for early stage of systematic reviews. ISPOR 3rd Latin America Conference. Mexico City, Mexico; 2011.
21. Wand H, Ramjee G. The effects of injectable hormonal contraceptives on HIV seroconversion and on sexually transmitted infections. Aids. 2012; **26**(3): 375-80.
22. Schulz KF, Grimes DA. Handbook of essential concepts in clinical research: Elsevier; 2006.
23. Cushman LF, Romero D, Kalmuss D, Davidson AR, Heartwell S, Rulin M. Condom use among women choosing long-term hormonal contraception. Fam Plann Perspect. 1998; **30**(5): 240-3.
24. Sangi-Haghpeykar H, Posner SF, Poindexter AN, 3rd. Consistency of condom use among low-income hormonal contraceptive users. Perspectives on Sexual and Reproductive Health. 2005; **37**(4): 184-91.
25. Polis CB, Gray RH, Lutalo T, Nalugoda F, Kagaayi J, Kigozi G, et al. Trends and correlates of hormonal contraceptive use among HIV-infected women in Rakai, Uganda, 1994-2006. Contraception. 2011; **83**(6): 549-55.
26. Beyeza-Kashesya J, Kaharuza F, Ekstrom AM, Neema S, Kulane A, Mirembe F. To use or not to use a condom: a prospective cohort study comparing contraceptive practices among HIV-infected and HIV-negative youth in Uganda. BMC Infect Dis. 2011; **11**: 144.
27. Morrison CS, Richardson BA, Mmiro F, Chipato T, Celentano DD, Luoto J, et al. Hormonal contraception and the risk of HIV acquisition. Aids. 2007; **21**(1): 85-95.
28. Warner L, Newman DR, Austin HD, Kamb ML, Douglas JM, Jr., Malotte CK, et al. Condom effectiveness for reducing transmission of gonorrhea and chlamydia: the importance of assessing partner infection status. American journal of epidemiology. 2004; **159**(3): 242-51.
29. Gray RH, Li X, Kigozi G, Serwadda D, Brahmbhatt H, Wabwire-Mangen F, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. Lancet. 2005; **366**(9492): 1182-8.
30. Smit J, McFadyen L, Zuma K, Preston-Whyte E. Vaginal wetness: an underestimated problem experienced by progestogen injectable contraceptive users in South Africa. Soc Sci Med. 2002; **55**(9): 1511-22.
31. Gallo MF, Warner L, Jamieson DJ, Steiner MJ. Do women using long-acting reversible contraception reduce condom use? A novel study design incorporating semen biomarkers. Infect Dis Obstet Gynecol. 2011; **2011**: 107140.
32. Minnis AM, Steiner MJ, Gallo MF, Warner L, Hobbs MM, van der Straten A, et al. Biomarker validation of reports of recent sexual activity: results of a randomized controlled study in Zimbabwe. American journal of epidemiology. 2009; **170**(7): 918-24.

33. Catania JA, Gibson DR, Chitwood DD, Coates TJ. Methodological problems in AIDS behavioral research: influences on measurement error and participation bias in studies of sexual behavior. Psychol Bull. 1990; **108**(3): 339-62.
34. Lavreys L, Baeten JM, Martin HL, Overbaugh J, Mandaliya K, Ndinya-Achola JO, et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. Aids. 2004; **18**(4): 695-7.
35. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000; **11**(5): 550-60.
36. Hernan MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. Stat Med. 2002; **21**(12): 1689-709.
37. Cole SR, Hernan MA, Robins JM, Anastos K, Chmiel J, Detels R, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. American journal of epidemiology. 2003; **158**(7): 687-94.
38. Magwali TL, Steiner MJ, Toms H, Brown JM. How are condoms used in a family planning setting: evidence from Zimbabwe. Cent Afr J Med. 2005; **51**(7-8): 79-84.
39. Aklilu M, Messele T, Tsegaye A, Biru T, Mariam DH, van Benthem B, et al. Factors associated with HIV-1 infection among sex workers of Addis Ababa, Ethiopia. Aids. 2001; **15**(1): 87-96.
40. Callegari L, Harper CC, van der Straten A, Kamba M, Chipato T, Padian NS. Consistent condom use in married Zimbabwean women after a condom intervention. Sexually Transmitted Diseases. 2008; **35**(6): 624-30.
41. Van Rossem R, Meekers D, Akinyemi Z. Consistent condom use with different types of partners: evidence from two Nigerian surveys. AIDS Educ Prev. 2001; **13**(3): 252-67.
42. Ahmed S, Lutalo T, Wawer M, Serwadda D, Sewankambo NK, Nalugoda F, et al. HIV incidence and sexually transmitted disease prevalence associated with condom use: a population study in Rakai, Uganda. Aids. 2001; **15**(16): 2171-9.
43. de Walque D, Kline R. Variations in condom use by type of partner in 13 sub-Saharan African countries. Studies in Family Planning. 2011; **42**(1): 1-10.
44. Maharaj P, Cleland J. Condom use within marital and cohabiting partnerships in KwaZulu-Natal, South Africa. Studies in Family Planning. 2004; **35**(2): 116-24.
45. Goodman SN. Toward evidence-based medical statistics. 1: The P value fallacy. Annals of Internal Medicine. 1999; **130**(12): 995-1004.
46. Egger M, Smith GD, Schneider M. Systematic reviews of observational studies. In: Egger M, Smith GD, Altman DG, editors. Systematic reviews in health care: meta-analysis in context. London: BMJ Publishing Group; 2001. p. 211-27.
47. Plummer FA, Simonsen JN, Cameron DW, Ndinya-Achola JO, Kreiss JK, Gakinya MN, et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. Journal of Infectious Diseases. 1991; **163**(2): 233-9.
48. Saracco A, Musicco M, Nicolosi A, Angarano G, Arici C, Gavazzeni G, et al. Man-to-woman sexual transmission of HIV: longitudinal study of 343 steady partners of infected men. Journal of Acquired Immune Deficiency Syndromes. 1993; **6**(5): 497-502.
49. Laga M, Manoka A, Kivuvu M, Malele B, Tuliza M, Nzila N, et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. Aids. 1993; **7**(1): 95-102.

50. Bulterys M, Chao A, Habimana P, Dushimimana A, Nawrocki P, Saah A. Incident HIV-1 infection in a cohort of young women in Butare, Rwanda. Aids. 1994; **8**(11): 1585-91.
51. Sinei SK, Fortney JA, Kigondu CS, Feldblum PJ, Kuyoh M, Allen MY, et al. Contraceptive use and HIV infection in Kenyan family planning clinic attenders. International Journal of STD and AIDS. 1996; **7**(1): 65-70.
52. Ungchusak K, Rehle T, Thammapornpilap P, Spiegelman D, Brinkmann U, Siraprapasiri T. Determinants of HIV infection among female commercial sex workers in northeastern Thailand: results from a longitudinal study. JAcquirImmuneDeficSyndrHumRetrovirol. 1996; **12**(5): 500-7.
53. Kilmarx PH, Limpakarnjanarat K, Mastro TD, Saisorn S, Kaewkungwal J, Korattana S, et al. HIV-1 seroconversion in a prospective study of female sex workers in northern Thailand: continued high incidence among brothel-based women. Aids. 1998; **12**(14): 1889-98.
54. Kapiga SH, Lyamuya EF, Lwihula GK, Hunter DJ. The incidence of HIV infection among women using family planning methods in Dar es Salaam, Tanzania. Aids. 1998; **12**(1): 75-84.
55. Kiddugavu M, Makumbi F, Wawer MJ, Serwadda D, Sewankambo NK, Wabwire-Mangen F, et al. Hormonal contraceptive use and HIV-1 infection in a population-based cohort in Rakai, Uganda. Aids. 2003; **17**(2): 233-40.
56. Baeten JM, Benki S, Chohan V, Lavreys 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.
57. Myer L, Denny L, Wright TC, Kuhn L. Prospective study of hormonal contraception and women's risk of HIV infection in South Africa. International Journal of Epidemiology. 2007; **36**(1): 166-74.
58. Kleinschmidt I, Rees H, Delany S, Smith D, Dinat 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.
59. Kumwenda NI, Kumwenda J, Kafulafula G, Makanani B, Taulo F, Nkhoma C, et al. HIV-1 incidence among women of reproductive age in Malawi. Int J STD AIDS. 2008; **19**(5): 339-41.
60. Watson-Jones D, Baisley K, Weiss HA, Tanton C, Changalucha J, Everett D, et al. Risk factors for HIV incidence in women participating in an HSV suppressive treatment trial in Tanzania. Aids. 2009; **23**(3): 415-22.
61. Morrison CS, Chen P, Kwok C, Richardson BA, Chipato T, Mugerwa R, et al. Hormonal contraception and HIV acquisition: reanalysis using marginal structural modeling. Aids. 2010; **24**(11): 1778-81.
62. Feldblum PJ, Lie CC, Weaver MA, Van DL, Halpern V, Adeiga A, et al. Baseline factors associated with incident HIV and STI in four microbicide trials. Sex TransmDis. 2010; **37**(10): 594-601.
63. Reid SE, Dai JY, Wang J, Sichalwe BN, Akpomiemie G, Cowan FM, et al. Pregnancy, contraceptive use, and HIV acquisition in HPTN 039: relevance for HIV prevention trials among African women. J AcquirImmuneDeficSyndr. 2010; **53**(5): 606-13.
64. Heffron R, Donnell D, Rees H, Celum C, Mugo N, Were E, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. Lancet Infect Dis. 2012; **12**(1): 19-26.

65. Morrison CS, Skoler-Karpoff S, Kwok C, Chen PL, van de Wijgert J, Gehret-Plagianos M, et al. Hormonal Contraception and the Risk of HIV Acquisition among Women in South Africa. Aids. 2012; **26**(4): 497-504.
66. Ngure K, Mugo N, Celum C, Baeten JM, Morris M, Olungah O, et al. A qualitative study of barriers to consistent condom use among HIV-1 serodiscordant couples in Kenya. AIDS Care. 2011.
67. Wawer MJ, Gray RH. Challenges in assessing associations between hormonal contraceptive use and the risks of HIV-1 acquisition and transmission. Future Microbiol. 2012; **7**(3): 315-8.
68. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965; **58**: 295-300.
69. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoSMed. 2009; **6**(7): e1000100.
70. Hodges JS. Are quality assessment methods any good? J Evid Base Dent Pract. 2004; **4**: 24-31.
71. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA : the journal of the American Medical Association. 1999; **282**(11): 1054-60.
72. Singh S, Darroch JE, Ashford LS, Vlassoff M. Adding It Up: The Costs and Benefits of Investing in Family Planning and Maternal and Newborn Health. New York: Guttmacher Institute and United Nations Population Fund; 2009.
73. Morrison CS, Wang J, Van Der Pol B, Padian N, Salata RA, Richardson BA. Pregnancy and the risk of HIV-1 acquisition among women in Uganda and Zimbabwe. Aids. 2007; **21**(8): 1027-34.
74. Mugo NR, Heffron R, Donnell D, Wald A, Were EO, Rees H, et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. Aids. 2011; **25**(15): 1887-95.
75. Stanback J, Spieler J, Shah I, Finger WR. Community-based health workers can safely and effectively administer injectable contraceptives: conclusions from a technical consultation. Contraception. 2010; **81**(3): 181-4.
76. Malarcher S, Meirik O, Lebetkin E, Shah I, Spieler J, Stanback J. Provision of DMPA by community health workers: what the evidence shows. Contraception. 2011; **83**(6): 495-503.
77. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011; **64**(4): 380-2.
78. Chersich MF, Rees HV. Causal links between binge drinking patterns, unsafe sex and HIV in South Africa: its time to intervene. IntJ STD AIDS. 2010; **21**(1): 2-7.
79. Shannon K, Csete J. Violence, condom negotiation, and HIV/STI risk among sex workers. JAMA. 2010; **304**(5): 573-4.
80. Williamson LM, Parkes A, Wight D, Petticrew M, Hart GJ. Limits to modern contraceptive use among young women in developing countries: a systematic review of qualitative research. ReprodHealth. 2009; **6**: 3.
81. Spiegelman D. Determinants of HIV Infection Among Female Commercial Sex Workers in Northeastern Thailand: Results From a Longitudinal Study. J Acquire Immune Def Syndromes Hum Retrovirol. 1998; **18**(2): 192.

82. Martin HL, Jr., Nyange PM, Richardson BA, Lavreys L, Mandaliya K, Jackson DJ, et al. Hormonal contraception, sexually transmitted diseases, and risk of heterosexual transmission of human immunodeficiency virus type 1. J Infect Dis. 1998; **178**(4): 1053-9.
83. Low N, Chersich MF, Schmidlin K, Egger M, Francis SC, van de Wijgert JH, et al. Intravaginal practices, bacterial vaginosis, and HIV infection in women: individual participant data meta-analysis. PLoS Med. 2011; **8**(2): e1000416.
84. Sagar M, Lavreys L, Baeten JM, Richardson BA, Mandaliya K, Ndinya-Achola JO, et al. Identification of modifiable factors that affect the genetic diversity of the transmitted HIV-1 population. Aids. 2004; **18**(4): 615-9.
85. Plourde PJ, Pepin J, Agoki E, Ronald AR, Ombette J, Tyndall M, et al. Human immunodeficiency virus type 1 seroconversion in women with genital ulcers. J Infect Dis. 1994; **170**(2): 313-7.
86. de Vincenzi I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. European Study Group on Heterosexual Transmission of HIV. N Engl J Med. 1994; **331**(6): 341-6.
87. Kumwenda JJ, Makanani B, Taulo F, Nkhoma C, Kafulafula G, Li Q, et al. Natural history and risk factors associated with early and established HIV type 1 infection among reproductive-age women in Malawi. ClinInfectDis. 2008; **46**(12): 1913-20.
88. Para MF, Schouten J, Rosenkranz SL, Yu S, Weiner D, Tebas P, et al. Phase I/II trial of the anti-HIV activity of mifepristone in HIV-infected subjects ACTG 5200. Journal of Acquired Immune Deficiency Syndromes. 2010; **53**(4): 491-5.
89. European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. European Study Group on Heterosexual Transmission of HIV. British Medical Journal. 1992; **304**(6830): 809-13.

Appendix A

The following search strategy was performed in PubMed: (((hormonal AND contracepti*) OR (“hormonal methods”)) OR ((progestin* OR progestins[MeSH] OR Progesterone[MeSH] OR progestogen* OR progestagen*) AND contracept*) OR (oral contracept*) OR ((((depo OR depot) AND medroxyprogesterone) OR depomedroxyprogesterone OR depo OR depot OR dmpa OR “net en” OR net-en OR “norethisterone enanthate” OR norethisterone-enanthate OR Medroxyprogesterone 17-Acetate[MeSH]) AND (contracept* OR inject*)) OR (((levonorgestrel OR etonogestrel) AND implant) OR (uniplant OR jadelle OR implanon OR norplant OR norplant2 OR sino-implant)) OR (contraceptives, postcoital[MeSH] OR (contracept* AND (emergency OR postcoital OR “post coital”)) OR “ulipristal acetate” OR “Plan B” OR mifepristone) OR ((levonorgestrel AND (intrauterine devices[MeSH] OR iud OR iucd OR ius OR “intrauterine system” OR “intra-uterine system” OR “intrauterine device” OR “intra-uterine device”)) OR mirena) OR ((combin* AND inject* AND contracept*) OR ((“once a month” OR monthly) AND inject* AND contracept*) OR (cyclofem OR lunelle OR mesigyna OR “cyclo provera” OR cycloprovera)) OR ((((contraceptive devices[MeSH] OR contraceptive agents[MeSH]) AND ring) OR nuvaring OR “nuva ring”)) OR ((((contraceptive devices[MeSH] OR contraceptive agents[MeSH]) AND patch) OR “ortho evra” OR orthoevra)) AND ("HIV Seropositivity"[MeSH] OR "HIV"[MeSH] OR "HIV Infections"[MeSH] OR "Acquired Immunodeficiency Syndrome"[MeSH] OR “HIV progression” OR “HIV disease progression” OR “HIV shedding” OR “viral shedding” OR “HIV transmission” OR “Virus Shedding”[MeSH]) AND Humans[MeSH]).

In Embase, we searched for (“Hormonal contraception”) AND HIV.

Supplemental items

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