Sexually Transmitted Diseases

Hormonal contraceptives and the acquisition of sexually transmitted infections: an updated systematic review

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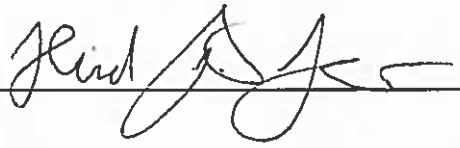
Corresponding Author Signature: 

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Hormonal contraceptives and the acquisition of sexually transmitted infections: an updated systematic review
Sexually Transmitted Diseases

Dear Dr. Miller,

Thank you for the careful review of our systematic review on the relationship between hormonal contraception and incident sexually transmitted infections. We have responded to each of the reviewers' comments as indicated in the attached document. We appreciate the reviewer's comments which have strengthened the manuscript.

Attached please find a revised version of the manuscript for your consideration.

With kind regards,

Heidi E. Jones, PhD MPH
Associate Professor, Dept. of Epidemiology & Biostatistics
CUNY School of Public Health

Reviewer #1:
The authors conducted a systematic review of recent studies of contraceptive use and acquisition of sexually transmitted infections. Overall, the product is good and the conclusions are balanced and forward-looking. Several comments:

1. Timing. My strongest question is why limit the data to 2009-2017 rather than update from all prior data. The authors note that reviews of HIV as an outcome have been routinely updated - and of course those built on prior data, not just took time-period chunks. The limiting of the time period, rather than updating, is central to the approach and needs a strong justification.

Thank you to the reviewer for this comment. As two previous systematic reviews had been implemented (Mohllajee et al., 2006; Morrison et al. 2009), we restricted our search to 2009-2017. The previous reviews found notable methodological limitations in the majority of articles identified, many of which were cross-sectional studies. In hindsight, however, we should have included prospective studies that met our criteria in our review. We have now reviewed the articles identified in the two previous studies, of which 8 met our criteria. These articles have been added to the tables, figures and text, as appropriate, based on our quality assessment.

2. Abstract and later. The use of "strong evidence" and "weak evidence" as terms is a bit guidelines-like, and standard definitions for such guidelines work do not seem to have been applied here (and probably would not be appropriate). Perhaps other descriptions could be used.

We have qualified the ‘strong’ and ‘weak’ evidence description of study results for DMPA on trichomoniasis and HSV-2. Instead we comment on the number of studies/consistency of findings and magnitude of effect size. This was done in the abstract and discussion/conclusions.

3. Abstract. The species name for Neisseria gonorrhoeae is misspelled.

This has been corrected.

4. Introduction. The statement that DMPA results in immune suppression is arguably an overreach; there may be immune modulation but "immune suppression" has a commonly-used sense (e.g., resulting in targeted or broad susceptibility to a host of infections, like in advanced AIDS, cancer therapy, etc.) which is obviously not appropriate.

We have revised the sentence accordingly (page 4).

5. Conclusions. Obviously, the question of contraceptive use and HIV risk has been much more in the spotlight than STIs. The HIV data has accumulated through secondary analysis of large HIV endpoint (observational or clinical trials of prevention interventions) studies and the ongoing ECHO randomized trial. It would not be too much, arguably, to advocate in this article for large studies of women such as these to include / analyze STI outcomes so the evidence base can grow.

We agree that more research is needed and have added a sentence highlighting the addition of STI outcomes to HIV research in lines 470-471 as follows:

"Existing large-scale prospective studies of HIV risk among women should incorporate well measured contraceptive use and STI outcomes to help address these gaps."

Reviewer #2:
Overall, this is a comprehensive and nicely organized and written systematic review on an important subject - the effect of hormonal contraception on STIs. There have been no published systematic reviews on this subject since 2008 (although another is in press) and thus it is important to update our understanding of these relationships - especially given the epidemiologic and biologic evidence suggesting a possible relationship between DMPA and HIV acquisition.

Specific Comments
Methods
1. The fact that the protocol was registered with PROSPERO and followed the PRISMA guidelines is appropriate for this systematic review and suggests rigorous methodology.

Thank you.

2. Important that the authors limited to prospective studies with outcomes defined by laboratory diagnostic tests.

Thank you.

3. Line 95-96. You say that a third reviewer resolved discrepancies. It appears that the third reviewer (HEJ/ELG) is one of the two original reviewers. Please clarify this.

To clarify, all studies were double reviewed. One reviewer extracted results from all studies [KM], while ELG and HEJ each independently reviewed half. Discrepancies were resolved by a third reviewer who had not originally reviewed the study (HEJ resolved discrepancies between KM and ELG; ELG resolved between KM and HEJ). This has been clarified in the text on page 6 as follows:

"Two independent reviewers [KJM & HEJ or ELG] screened each abstract or article using Covidence software; a third reviewer who had not previously reviewed the study [HEJ or ELG] resolved discrepancies."

4. Line 110-111. What happens if the two reviewers did not agree on their rating of study quality. How was this resolved?

Discrepancies were resolved through discussion between the reviewers. We have clarified this in the text in lines 130-131 as follows:

"Two reviewers [KJM & HEJ or ELG] independently rated study quality; discrepancies were resolved by discussion among all three reviewers."

5. The authors seemed to have used a comprehensive search strategy for hormonal contraception and STIs.

Thank you.

Results

1. Line 122. I think the authors should make it clearer that the analysis from the RCTs and nested case control are also observational analyses. They could make a blanket statement here that all analyses were observational and then break down the types of studies the data originated from.

Thank you for this suggestion, we have made the suggested revision on page 7 as follows:

"The 30 reviewed studies were all prospective and observational in design, most were longitudinal cohort studies (N=25), four were secondary analysis of a randomized control trial [23,24,34,35] and one used a nested case-control design [36]."

2. Line 136. It would be good to state what the non-hormonal methods are.

Non-hormonal methods were, for the large part, not specified in the reviewed studies. However, we revised to include example methods (e.g., condoms) in lines 181-184 as follows:

"Half of the studies (15 of 30) compared HC users to non-hormonal method users (e.g., condom), twelve studies compared two or more types of HCs [23,24,52,54,26–28,36,39,40,43,44], three compared HC use to women not using any method and/or women who were sterilized [21,22,46]."

3. Line 146. Not sure if it really makes sense to include articles that cannot distinguish between COC and POPs. There are important reasons to believe that these different pills could have different effects on STI acquisition. I would consider dropping these studies.

We agree that it is a large limitation when the type of OCP (COC or POP) is not specified as the biological mechanism involved is greatly different and has implications for STI susceptibility. We found that only 5 of the 24 studies which assessed STI risk following OCP use specified the type of OCP. Dropping studies without specification would therefore result in too few for analysis. We highlight this limitation in our Abstract conclusion as follows:

"Future studies should specify the type of injectable or OCP used to increase understanding of biological pathways.."

We also highlight this in our results section on page 8 as follows:

"Most studies (19 of 24) did not distinguish between combined or progestin only OCPs, and some did not distinguish between DMPA and Net-En injectable (3 of 19)."

Further we have updated our discussion on page 18 as follows:

"Further many of the studies of OCPs did not differentiate between combined or progestin-only OCPs and similarly some injectable studies did not differentiate between Net-En and DMPA. Given that biological responses to HC differ by class of drug as well as drug formulations, [5]

future research needs to distinguish between HC formulations when estimating risk of STI/HIV acquisition."

4. Line 177. Not only are the reference groups inconsistent but they could include users of other contraceptive methods in the reference group. This makes it even harder to interpret.

We agree and have added this as an additional complication on page 8 as follows:

"The reference group of non-users of a given HC was not defined consistently and sometimes included users of other forms of contraception."

5. Line 199. I would not say that the effect was 'attenuated'. Really there is little meaningful difference between the two effect estimates or confidence intervals.

We have revised our description of the results as follows:

"The other study found DMPA use relative to non-DMPA use was strongly associated with HSV-2 acquisition among women both living with and without HIV (aHR: 4.43, 95%CI: 1.90, 10.35), and when restricted to women living without HIV (aHR: 3.97, 95%CI: 1.64, 9.60) [54]."

6. Line 227: I would say a 'non-significant' reduced risk as you are specifying this in other places in the manuscript.

We have made the suggested change.

7. Line 235: I would say "injectable type unspecified' to be clear.

Thank you, we have made the suggested change.

8. Line 264: "Two studies … evidence of reduced risk". You already said this in line 261. Are these the same studies? Please clarify.

We have clarified that we intended to say 'Of the two studies which documented significant evidence of reduced risk…' and then to further describe results from the two studies. This has been corrected in the text, only now three studies are discussed (see revisions lines 385-391.

9. Line 293. 'weaker evidence of increased risk of HSV-2 incidence'. There may only be 3 studies for DMPA and HSV-2 as opposed to six studies for DMPA and Tv. However, the raised effect estimated for DMPA and HSV-2 are much stronger than the reduced effect estimates for DMPA and TV. I would mention that and consider that in your conclusions about the relative strength of evidence for these relationships.

The Reviewer raises an important point. and we clarify that by 'weak evidence', we were referring to the small number of studies that assessed the association and not the effect size or biological plausibility. We agree that the magnitude of effect is also an important consideration. We have qualified our description of the 'strength' of study findings by both these criteria, as suggested, in the abstract in lines 45-47 as follows:

"Depo-medroxyprogesterone acetate (DMPA) reduces the risk of trichomoniasis (consistent evidence) and may increase the risk of HSV-2 (strong effect, few studies."

We have also updated the discussion in lines 430-432 as follows:

"Among studies of sufficient quality, DMPA use is consistently associated with a reduced risk of *T. vaginalis* acquisition, with evidence of substantial (two times or higher) increased risk of HSV-2 incidence from a smaller number of studies."

10. Line 295 OC and Tv. I find the evidence for DMPA and increased HSV-2 to be stronger than the evidence for OC and reduced TV incidence. Please address the reasons why you say the evidence for HSV-2 is limited but do not say this for OCs and Tv.

See our response to comment 9 above.

11. Evidence Tables: Nice job here. I would add the reference number to the first column with the first author and date. This makes it easier for the reader to look something up.

We have added the reference number of cited studies to the data tables, as suggested.

12. Under the OCP column of the evidence table, I would make it clear whether you are referring to COC, POP, or type unspecified.

Results reported under the OCP column of the evidence tables specifies whether the type of pill was COC (if combined pill was specified by study authors), POP (progestin-only) or as OCP if otherwise unspecified (as generally few studies specified the type of pill). This was previously described in the table notes, which we have changed to footnote 'a'. This notation was adopted as few studies specified the type of OCP.

13. Figures: Nice job on the Forest Plots. However, is there some important reason why the estimated risk is on the log scale? Most readers are much more familiar with seeing effect estimates expressed as OR/ RR/HR with the null being 1.0 rather 0.0. Also, I take it you didn't include Forest Plots for other relationships because there are too few studies. Is that correct?

We plotted the estimated risk on the log scale for two reasons: 1. This approach ensures that the 95% confidence intervals are symmetrical around the point estimate; and 2. This approach ensures that preventive and causal effects are presented visually on the same scale, which is not the case when plotted on the OR/HR/RR scale. For example, a RR of 2 is not visually equivalent to a RR of 0.5 on the OR/HR/RR scale. However, these estimates are equivalent on the log scale. The reviewer is correct that we did not include forest plots for other examined associations because the number of studies was small (<5) and forest plots are most useful when interpreting results across several studies.

14. Nice supplemental tables. Why don't you put all the references together in the body of the paper? Is that a Sexually Transmitted Diseases rule that you can only have 30 references in the body of the paper?

The reviewer is correct, the journal does not permit more than 30 references in the body of the paper and we have included them in the Appendix to keep with the guidelines.

Hormonal contraceptives and the acquisition of sexually transmitted infections: an updated systematic review

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References = 59 (31-59 in supplemental table)

Tables = 6 / Figures = 5

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Short summary: A systematic review of the association between hormonal contraception and incident STIs found that DMPA and oral contraceptive pills decrease risk of trichomoniasis, and DMPA may increase risk of HSV-2.

Key words: Hormonal contraception, sexually transmitted infections, systematic review

Abstract

Background: Evidence suggests that some forms of hormonal contraception (HC) increase women's risk of non-HIV sexually transmitted infections (STIs), yet evidence has not been reviewed since 2008. We conducted an updated systematic review to incorporate studies published between January 2009 and June 2017 to examine the relationship between HCs and incident and/or recurrent STIs.

Methods: We searched PubMed and EMBASE to identify prospective studies comparing risk of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, human papillomavirus (HPV), herpes simplex virus type 2 (HSV-2), *Treponema pallidum*, or *Trichomonas vaginalis*, between women using HC vs. non-hormonal methods or no methods. We summarize results by type of STI and HC and study quality using an adapted Newcastle-Ottawa Quality Assessment Scale.

Results: Thirty articles met the inclusion criteria. Depo-medroxyprogesterone acetate (DMPA) reduces the risk of trichomoniasis (consistent evidence) and may increase the risk of HSV-2 (strong effect, few studies); inconclusive evidence exists for HPV, chlamydia, gonorrhea and syphilis. Data on oral contraceptive pills (OCPs; generally not differentiated whether combined or progestin-only pills) suggest use is associated with a reduced risk of trichomoniasis with inconclusive findings for HSV-2, HPV, chlamydia, gonorrhea, and syphilis. Very few studies included norethisterone enanthate (Net-En) injectable, implants or the levonorgestrel IUD.

Conclusions: DMPA and OCPs reduce the risk of trichomoniasis and DMPA may increase the risk of HSV-2. However, the potential for confounding cannot be ruled out. Future studies should specify the type of injectable or OCP used to increase understanding of biological pathways; more research is needed on implants and hormonal IUDs.

Introduction

While access to hormonal contraception (HC) reduces unwanted pregnancy and maternal morbidity and mortality, a body of evidence from recent systematic reviews, meta-analyses and in vivo and in vitro studies suggest that the progestin injectable depo-medroxyprogesterone acetate (DMPA) increases risk of HIV acquisition [1–5]. Comparatively less emphasis, however, has focused on the potential association of DMPA and other HC and other sexually transmitted infections (STIs).

Several biological mechanisms by which HC use may facilitate STI acquisition have been proposed including through changes in the protective cervicovaginal epithelial barrier from hypo-estrogenism induced by progestin-only methods [6,7]. A second mechanism is through weakening of immune defense [8]. For example, DMPA is known to bind to glucocorticoid receptors, which generally results in immune modulation [5,9]. Third, hypo-estrogenism induced by progestin-only methods could lead to changes in the vaginal microbiota composition, leading to vaginal dysbiosis and inflammation [10], which in turn could lead to epithelial breaches and mucus degradation [11,12]. At a behavioral level, HC use may result in decreased condom use, thereby increasing risk of STI exposure [13,14].

Two prior systematic reviews have examined the association between HCs and STI acquisition; evidence has not been synthesized since 2008 [15,16]. Both reviews found that OCP and DMPA users had a possible increased risk of chlamydia but concluded there was inconclusive evidence for gonorrhea, herpes simplex virus type 2 (HSV-2), trichomoniasis, syphilis and human

papillomavirus (HPV). Given the magnitude of women using HC globally and the negative health repercussions of many STIs, we conducted an updated systematic review to incorporate literature from longitudinal studies published between 2009 and 2017 on the association between the HC use and non-HIV STI acquisition; systematic reviews on HIV acquisition have been updated regularly [1–4].

Materials and Methods

The protocol was registered *a priori* with PROSPERO [Record 42017069357] and follows PRISMA guidelines (Supplemental Table 1). Articles were identified using key term searches of two electronic databases: PubMed and EMBASE (Supplemental Figure 1).

Inclusion/exclusion criteria

Included articles were peer reviewed, published in English, Spanish or French between 01 January 2009 and 30 June 2017 and measured incident/recurrent cases of cervicovaginal HPV, HSV-2, chlamydia, gonorrhea, syphilis, and/or trichomoniasis, with laboratory diagnostic tests, among HC users compared with non-users or users of non-hormonal methods. All HC methods were included except for emergency contraception, since it is typically used in combination with other contraceptive methods [17]. We also reviewed articles identified from two earlier systematic reviews [15,16]; articles from these reviews which met our criteria are also included.

We excluded cross-sectional studies, review articles, studies which relied on clinical exam or self-reported STIs, and studies which did not control for potential confounding variables. We

also excluded studies of HCs and HIV and bacterial vaginosis (BV), as both have been recently reviewed [18,19]. Two independent reviewers [KJM & HEJ or ELG] screened each abstract or article using Covidence software; a third reviewer who had not previously reviewed the study [HEJ or ELG] resolved discrepancies.

Data Extraction

One reviewer [KJM] extracted data, with independent review for accuracy [HEJ or ELG]. Extracted information included: participant characteristics, geographic location, sample size, sampling method, contraceptive method, duration of use, comparison group, STI, whether infection was incident or recurrent, STI diagnostic test, confounders in adjusted estimates, type of statistical analysis, treatment of missing data, length of time between exposure and outcome assessment, and the effect estimate, variance and significance level.

Study quality

Risk of bias was assessed using the Newcastle-Ottawa Quality Assessment Scale [20], adapted to reflect challenges identified previously for assessment of the relationship between HC use and STIs/HIV [3,15] (Supplemental Tables 2 and 3). Two reviewers [KJM & HEJ or ELG] independently rated study quality; discrepancies were resolved by discussion among all three reviewers.

Data synthesis

Our primary outcome is incident STI. We examined findings by HC method used (e.g., OCP, DMPA, levonorgestrel IUD, Net-En, Norplant) and type of STI. Forest plots were constructed using the forestplot package in R Studio (Version 1.1.383, Vienna, Austria).

Results

Our key term search resulted in 1,477 unique articles, 1,284 articles were excluded during abstract screening; 24 required full-text review of which two were excluded (Figure 1). An additional 13 prospective studies identified in the previous two systematic reviews were considered for inclusion. Of these eight met our study inclusion criteria and are included [21–28], five did not meet our criteria [29–33]. The 30 reviewed studies were all prospective and observational in design, most were longitudinal cohort studies (N=25), four were secondary analysis of a randomized control trial [23,24,34,35] and one used a nested case-control design [36].

The majority of articles assessed the incidence or recurrence of HPV (n=13) [26,27,43–45,28,36–42], followed by trichomoniasis (n=9) [21,24,34,37,46–50], chlamydia (n=9) [21–23,37,47,48,50–52], gonorrhea (n=7) [21–23,37,47,48,50], HSV-2 (n=4) [35,37,53,54], and syphilis (n=3) [24,37,47] (not mutually exclusive). Two studies combined incident chlamydia and/or gonorrhea [25,55]. Twelve studies included women ages 18-50 years [22–24,27,36,37,41,42,48,51,53,55], ten studies included adolescents (<age 18 years) [21,25,26,28,35,44,46,47,50,52], three included women older than age 49 years [34,45,47] and five did not report age range, but the majority of participants were of reproductive age [38–

40,43,49]. One-third of studies enrolled populations considered at increased STI risk: women reporting transactional sex (n=6) [21,22,37,51,53,54], injection drug use (n=1) [43], lower genital tract infection/partner with diagnosed STI (n=1) [52], or living with HIV (n=2) [22,55]. Three additional studies included women living with and without HIV [43,46,54].

Half of the studies (15 of 30) compared HC users to non-hormonal method users (e.g., condom), twelve studies compared two or more types of HCs [23,24,26–28,36,39,40,43,44,52,54], three compared HC use to women not using any method and/or women who were sterilized [21,22,46].

Study quality assessment and risk of bias

Most studies were considered high (n=8) or medium (n=19) quality (Supplemental Tables 2 and 3). Low quality studies (n=3) are presented in the data tables, but not included in forest plots or discussed [40,45,47].

Despite medium/high quality, a number of methodological challenges remained. Nearly all studies relied on self-reported HC exposure, despite known limitations [9]. Most studies (20 of 25) did not distinguish between combined or progestin only OCPs, and some did not distinguish between DMPA and Net-En injectable (3 of 19). The reference group of non-users of a given HC was not defined consistently and sometimes included users of other forms of contraception. Most studies employed empirically driven rather than theoretical adjustment for confounding.

Non-significant estimates were not always presented, prohibiting information on the direction of association. For some studies, incidence rates were low suggesting limited power.

HPV

Eleven studies evaluated the risk of HC on incident HPV infection and provide inconclusive evidence of association (Table 1, Figure 2). All diagnostic tests were DNA-based and five assessed one or more high-risk HPV (HR-HPV) types, one assessed one or more low-risk HPV (LR-HPV), while eight considered any HPV type; two disaggregated results more than one way. Four studies assessed the influence of injectables; two found that incidence of HR (one study) or any HPV (one study) was lower but not significantly lower compared to non-HC users [37,41]. A third study found recent DMPA users had increased incident HR-HPV (used in past six months aOR: 1.6; 95%CI: 0.7, 3.7) and long-term users (≥1 year of use aOR: 4.7; 95%CI: 1.4, 15.8) relative to non-users of DMPA [36]. Findings were in the same direction but not statistically significant among short term and former users. The fourth study found non-significant results in mixed directions, depending on HPV type [44]: DMPA use was associated with lower incidence of HR and increased risk of LR-HPV.

Ten studies evaluated OCP use. Three reported OCP use to be associated with increased HPV risk [27,42,44], two found non-significant increased risk, [37,41] one found significant decreased risk [26], two reported non-significant decreased risk [28,36], one found no effect [38] and one did not report the effect estimate for non-significant findings [43]. Only two studies specified combined OCP use (COC), both documented a non-significant association

[36,41]. Of the studies which documented evidence of increased risk, one was among OCP users vs. non-OCP users in the last three months among LR-HPV (aHR: 2.73; 95%CI: 1.52, 4.90) and all-HPV types (aHR: 2.0; 95%CI: 1.28, 3.15), but not HR-HPV types [44]. Another study which also assessed OCP users vs. non-OCP users on all-HPV types found a lower magnitude of increased risk (aHR: 1.40, 95%CI: 1.01, 1.80) [27]. The final significant finding of increased risk was documented in the longest exposure group only (7+ years) (aOR: 1.66; 95%CI: 1.17, 2.35), with attenuated evidence of marginal risk in lower exposure groups (5-6 year and 3-4 year groups) and null effects among users <2 years relative to nonusers of HC [42]. The one study that found significant decreased risk was among OCP using U.S. women attending a family planning clinic relative to non-current OCP users (aHR: 0.49, 0.28, 0.86) [26]. Overall, inconsistent exposure groups (current versus ever user), reference group (non-current versus never user) and differences in HPV-subtype may contribute to disparate findings.

Only one study assessed the risk of hormonal IUD use on incident HPV infection. This retrospective record review compared levonorgestrel IUD users to copper IUD users and documented a four-fold higher risk of HR-HPV among the former [39]. This effect was marginally significant and based on few incident cases.

HSV-2

Studies examining HSV-2 acquisition provide some evidence that injectable use increases risk [35,37,54] and inconclusive evidence regarding OCPs [35,37,53,54] (Table 2).

Three studies examined the risk of injectable use on HSV-2 incidence. Two studies reported evidence of a significantly increased risk following injectable use (one specifies DMPA, the other is unspecified) [35,54]. The remaining study reports evidence of non-significant increased risk (injectable type unspecified) [37]. The two studies that did not record the injectable type reported that DMPA was most common. Of the two studies that documented a significant effect, one study among HIV-negative women in Uganda reported increased risk (aOR: 2.26, 95%CI: 1.09, 4.69) among consistent DMPA users, but not those who discontinued use, relative to non-HC users [35]. The other study found DMPA use relative to non-DMPA use was strongly associated with HSV-2 acquisition among women both living with and without HIV (aHR: 4.43, 95%CI: 1.90, 10.35), and when restricted to women living without HIV (aHR: 3.97, 95%CI: 1.64, 9.60) [54]. The third study documented non-significant evidence of increased risk among HIV-negative women who engaged in sex work and used DMPA (aOR: 6.34, 95%CI: 0.25, 158.5) compared to non-HC users, [37] based on only five incident cases among DMPA users.

Three studies examined HSV-2 acquisition among OCP users: two documented a non-significant reduced risk of HSV-2 among OCP users relative to non-HC users [35,53]. The remaining study was in the harmful direction but was based on only two incident cases among OCP users [37].

Chlamydia

Seven studies provide inconclusive evidence of increased risk of chlamydia among injectable users [21,22,37,48,50–52] and three provide inconclusive evidence regarding OCP use [23,37,51] (Table 3, Figure 3).

Of the seven studies among injectable users, three documented a significant increased risk of acquisition among DMPA users [21,22,51]. The magnitude of increased risk ranged between 1.6 (95%CI: 1.1, 2.4) fold among DMPA users relative to women who were sterilized or using no contraception [21] to 3.1 (95%CI: 1.0, 9.4) among women living with HIV-1 who used DMPA compared to those who were sterilized or used IUD [22]. The latter effect was marginally significant (p=0.05). Four studies found a non-significant increased risk of acquisition among DMPA users relative to non-HC users [37,48,50]; the direction of effect varies by the reporting period in one study but remains non-significant [50]. An additional study documented a hazard ratio close to one among women who reported DMPA at any fourth month visit relative to non-DMPA users [52]. Only one study compared norethisterone enanthate (Net-En) users to non-HC users, and found a non-significant reduced risk of infection [48].

Six studies examined the incidence of chlamydia among OCP users [21–23,37,51,52], only one study specified combined or progestin-only pill use [23]. Three studies documented significant evidence of increased risk [21,23,37]. One study among HIV-negative women engaging in sex work in Rwanda compared OCP users to non-HC users (aOR: 6.13, 95%CI: 1.5, 23.8) [37]. Results from this study are based on few incident cases. The two other studies documented significant increased risk of similar magnitude. One study compared OCP users to women who were sterilized or using no contraceptive (aHR: 1.80, 95%CI: 1.10, 2.90) [21], the other compared OCP users to women who were sterilized or using IUD (aHR: 1.73, 95%CI: 1.08, 2.77) [23]. Three studies reported null findings. One study did not report the effect coefficient [52], and the

other found non-significant reduced risk (aHR: 0.2, 95%CI: 0.0, 1.7), among OCP users relative to non-HC users [51].

Gonorrhea

We found no significant prospective evidence that injectable use (five studies) [21,22,37,48,50], was associated with risk of gonorrhea. Only one of four studies of OCP use showed increased the risk of gonorrhea [21–23,37] (Table 4, Figure 4). Of the three studies which compared injectable users to non-HC users, two studies found non-significant evidence of increased risk among DMPA users [48,50], one found non-significant evidence of reduced risk among Net-En users [48], and one study found non-significant evidence of reduced risk (injectable type unspecified) [37]. Two additional studies which examined DMPA use relative to women who were sterilized or used no contraception found an association close to the null [21,22]. One of these was among women who were living with HIV-1 [22]. Information from the one study which found increased risk of gonorrhea following OCP use found nearly double risk (aHR 1.7, 95%CI: 1.05, 2.76) among COC users relative to women who used an IUD or were sterilized [23]. This was the only study to assess pill formulation and found that a higher ratio of progestin in COC had a nonsignificant, but positive correlation with the risk of gonorrhea acquisition. The other three studies evaluating OCP use found results in mixed directions and did not specify pill type.

Combined STI

Two studies evaluated a combined group of women who tested positive for either *C. trachomatis* or *N. gonorrhoeae* due to small sample sizes (Table 5) [25,55]. A study among American STI patients found significant increased risk among DMPA users (aHR: 3.6, 95%CI: 1.6, 8.5), and non-significant increased risk among COC users (aHR: 1.5, 95%CI: 0.6, 3.5) relative to non-HC users [25]. The second study was among HIV-1 positive women on antiretroviral therapy was unable to evaluate OCP use due to no incident infections among users. However, women who used DMPA had more than five times the incident risk of *N. gonorrhoeae* or *C. trachomatis* (combined) (aOR: 5.83, 95%CI: 0.90, 37.7), relative to non-HC users [55].

Syphilis

Two studies assessed HC use on syphilis incidence (Table 6), both which found non-significant results. One study found non-significant evidence of increased risk among Kenyan women who engaged in commercial sex work and used OCPs (aHR: 0.40, 95%CI: 0.10, 1.50) and DMPA (aHR: 0.50, 95%CI: 0.20, 1.40), relative to women who used no contraception or were sterilized [21]. The other study found non-significant evidence of increased risk among HIV-negative sex workers in Rwanda who used any injectable relative to non-HC users (aOR: 1.43, 95% CI: 0.11, 19.1) [37]. The finding, however, is based on only four incident cases.

Trichomoniasis

Studies of HC use on risk of trichomoniasis suggest injectables and OCPs are associated with reduced risk while findings are mixed regarding implant use (Table 7, Figure 5) [21,24,34,37,46,48–50].

All seven studies that measured incident trichomoniasis suggest that injectable use reduced incidence by a magnitude ranging from 0.35 (95%CI: 0.12, 1.01) to 0.70 (95%CI: 0.50, 1.0), though some results were not statistically significant. Three studies found significant reduced risk following injectable use (two specified DMPA and one was unspecified) [21,34,46] and two documented reduced risk that approached significance (one specified DMPA, one was unspecified but DMPA use was most common) [37,48]. Two of the studies which documented significant evidence of reduced risk compared HIV-1 negative injectable users (type unspecified) to non-HC users (aHR: 0.60, 95%CI: 0.47, 0.78), and DMPA users (aHR: 0.60, 95%CI: 0.4, 1.0, p=0.04) to women who were sterilized or did not use contraception [21,34]. The third study found women in Uganda who reported DMPA use in the past 12 months were at decreased risk compared to women who used neither HC nor condoms (aIRR: 0.54, 95%CI: 0.30, 0.98) [46]. Notably, the same study found non-significant findings of a similar magnitude among women who reported consistently using only DMPA at baseline and follow-up (aIRR: 0.59, 95%CI: 0.28, 1.26). Only one study reported results for Net-En relative to non-HC use and found non-significant reduced risk [48].

Six of seven studies that assessed OCP use and trichomoniasis documented reduced risk, although only two were significant. One significant finding was reported in a study among OCP users in five countries (Malawi, South Africa, the United States, Zambia and Zimbabwe) who were significantly less likely to acquire *T. vaginalis* relative to non-HC users (aHR: 0.64, 95%CI: 0.47, 0.89) [34]. The other was among OCP using women attending a STI clinic in the U.S.

relative to those who used IUD or were sterilized (aHR: 0.56, 95%CI: 0.39, 0.81) [24]. Only one study specified COC use [46]. This study documented null findings among women in Uganda who reported COC use in the past twelve months (aIRR: 1.02, 95%CI: 0.40, 2.59), or consistently using COCs in the past 12 months (aIRR: 1.07, 95%CI: 0.25, 4.56) relative to no method (neither hormonal nor condom).

One of three studies which assessed implant use on incident trichomoniasis found a three-fold increased risk of trichomoniasis (aIRR: 3.01, CI: 1.07, 8.49) among Norplant users relative to women who used no contraception method (hormonal or condoms) and slightly higher risk among consistent users of Norplant for 12 months (aIRR: 3.13, 95% CI: 1.08, 9.07) [46]. The two remaining studies found no relationship between implant use (type unspecified) and trichomoniasis [34,49].

Discussion

Among studies of sufficient quality, DMPA use is consistently associated with a reduced risk of *T. vaginalis* acquisition, with evidence of substantial (two times or higher) increased risk of HSV-2 incidence from a smaller number of studies. The results for HPV, chlamydia, gonorrhea and syphilis were inconclusive. Net-En was only assessed in one study [48]. Data on OCP use suggest reduced incidence of trichomoniasis, with inconclusive findings for HPV, HSV-2, chlamydia, gonorrhea and syphilis. Implant use was less studied (n=3), and only one specified type (Norplant). This study documented increased risk of trichomoniasis, but did not assess other

STIs [46]. Only one study assessed the levonorgestrel IUD and found a higher risk of HR-HPV incidence compared to the copper IUD; however, findings were marginally significant [39].

Findings from our study differ somewhat from two previous systematic reviews, which found inconclusive results for DMPA and OCPs on incident trichomoniasis, and increased risk of incident chlamydia [15,16]. However, one previous review primarily synthesized cross-sectional research [16]. In the second review, half of the studies (2 of 4 for trichomoniasis; 3 of 6 for chlamydia) did not include statistical adjustment for confounding [15]. Those studies that reported adjusted *T. vaginalis* analyses also found decreased risk [21,24]. Prior prospective evidence of incident HPV from four studies [26–28,31] also suggest mixed results regarding the influence of OCPs and DMPA [26],Figure without clear trends by HPV type or exposure time.

This review provides limited evidence that DMPA is associated with increased risk of HSV-2; we identified no prior review of HC use on incident HSV-2. Notably, our findings are based on a small number of studies. However, findings correspond with studies in mice which show heightened susceptibility to HSV-2 following prolonged (>2 weeks) treatment with DMPA [56,57]. These findings align with the one study that examined multiple exposure periods to DMPA and found a two-fold increased risk of HSV-2 in consistent DMPA users relative to non-HC users but not among those who initiated, or discontinued use [35]. A recent study in mice demonstrated that both DMPA and levonorgestrel, another progestin, increase mucosal epithelial permeability by acting on epithelial cell junction proteins (DSG1α), enhancing access of inflammatory and infectious viral molecules to the genital tissue, a possible biological

mechanism [7]. Given substantial evidence that HSV-2 increases risk of HIV infection, [58] if the finding that DMPA increases the risk of HSV-2 is substantiated, this could be a mechanism for the association between DMPA use and HIV acquisition.

Further prospective research is warranted in several areas. Very few studies have explored the prospective association between HC use and syphilis (n=3) or HSV-2 (n=4) incidence. Similarly, few prospective studies have explored the potential risk of Net-En (n=1), levonorgestrel IUD (n=1) or implants on STIs (n=3), while use of these methods is increasing [59]. No reviewed studies evaluated Sayana Press, the Nuva Ring, or patch. Current large-scale prospective studies of HIV risk among women should incorporate well measured contraceptive use and STI outcomes to help address these gaps. Further many of the studies of OCPs did not differentiate between combined or progestin-only OCPs and similarly some injectable studies did not differentiate between Net-En and DMPA. Given that biological responses to HC differ by class of drug as well as drug formulations,[5] future research needs to distinguish between HC formulations when estimating risk of STI/HIV acquisition.

This updated systematic review of prospective evidence published between 2009 and 2017 suggests that DMPA and OCP use are associated with a reduced risk of incident trichomoniasis, with evidence of increased substantial risk of HSV-2 acquisition with DMPA use from a small number of studies. Our review findings are tempered by notable methodological limitations. Prospective evidence regarding the STI risk of hormonal contraceptive methods are extremely limited or non-existent, highlighting an urgent research need.

References

1. Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies. Lancet Infect Dis. 2015;15: 181–189. doi:10.1016/S1473-3099(14)71052-7

2. Morrison CS, Chen P-L, Kwok C, Baeten JM, Brown J, Crook AM, et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. PLoS Med. Public Library of Science; 2015;12: e1001778. doi:10.1371/journal.pmed.1001778

3. Polis CB, Phillips SJ, Curtis KM, Westreich DJ, Steyn PS, Raymond E, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. Contraception. 2014;90: 360–390. doi:10.1016/j.contraception.2014.07.009

4. Polis CB, Curtis KM, Hannaford PC, Phillips SJ, Chipato T, Kiarie JN, et al. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. AIDS. 2016;30: 2665–2683. doi:10.1097/QAD.0000000000001228

5. Hapgood JP, Kaushic C, Hel Z. Hormonal contraception and HIV-1 acquisition: biological mechanisms. Endocr Rev. Oxford University Press; 2018;39: 36–78. doi:10.1210/er.2017-00103

6. 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: 431–9.

7. Quispe Calla NE, Vicetti Miguel RD, Boyaka PN, Hall-Stoodley L, Kaur B, Trout W, et al. Medroxyprogesterone acetate and levonorgestrel increase genital mucosal permeability and enhance susceptibility to genital herpes simplex virus type 2 infection. Mucosal Immunol. 2016;9: 1571–1583. doi:10.1038/mi.2016.22

8. Wira CR, Fahey J V., Ghosh M, Patel M V., Hickey DK, Ochiel DO. Sex hormone regulation of innate immunity in the female reproductive tract: The role of epithelial cells in balancing

reproductive potential with protection against sexually transmitted pathogens. Am J Reprod Immunol. 2010;63: 544–565. doi:10.1111/j.1600-0897.2010.00842.x

9. Achilles SL, Hillier SL. The complexity of contraceptives: understanding their impact on genital immune cells and vaginal microbiota. AIDS. 2013;27 Suppl 1: S5-15. doi:10.1097/QAD.0000000000000058

10. Jespers V, Kyongo J, Joseph S, Hardy L, Cools P, Crucitti T, et al. A longitudinal analysis of the vaginal microbiota and vaginal immune mediators in women from sub-Saharan Africa. Sci Rep. 2017;7: 11974. doi:10.1038/s41598-017-12198-6

11. Straub RH. The Complex Role of Estrogens in Inflammation. Endocr Rev. 2007;28: 521–574. doi:10.1210/er.2007-0001

12. Ghanem KG, Shah N, Klein RS, Mayer KH, Sobel JD, Warren DL, et al. Influence of sex hormones, HIV status, and concomitant sexually transmitted infection on cervicovaginal inflammation. J Infect Dis. 2005;191: 358–66. doi:10.1086/427190

13. Ott MA, Adler NE, Millstein SG, Tschann JM, Ellen JM. The trade-off between hormonal contraceptives and condoms among adolescents. Perspect Sex Reprod Health. 34: 6–14.

14. Mullinax M, Sanders S, Dennis B, Higgins J, Fortenberry JD, Reece M. How condom discontinuation occurs: interviews with emerging adult women. J Sex Res. 2017;54: 642–650. doi:10.1080/00224499.2016.1143440

15. Morrison CS, Turner AN, Jones LB. Highly effective contraception and acquisition of HIV and other sexually transmitted infections. Best Pract Res Clin Obstet Gynaecol. 2009;23: 263–284. doi:10.1016/j.bpobgyn.2008.11.004

16. Mohllajee AP, Curtis KM, Martins SL, Peterson HB. Hormonal contraceptive use and risk of sexually transmitted infections: a systematic review. Contraception. 2006;73: 154–65. doi:10.1016/j.contraception.2005.08.012

17. Jones R, Darroch J, Henshaw S. Contraceptive use among U.S. women having abortions in 2000–2001. Perspect Sex Reprod Health. 2002;34: 294–303.

18. van de Wijgert JHHM, Verwijs MC, Turner AN, Morrison CS. Hormonal contraception decreases bacterial vaginosis but oral contraception may increase candidiasis. AIDS. 2013;27: 2141–2153. doi:10.1097/QAD.0b013e32836290b6

19. Vodstrcil LA, Hocking JS, Law M, Walker S, Tabrizi SN, Fairley CK, et al. Hormonal contraception is associated with a reduced risk of Bacterial Vaginosis: a systematic review and meta-analysis. PLoS One. 2013;8: e73055. doi:10.1371/journal.pone.0073055

20. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. In: Ottawa Hospital Research Institute [Internet]. [cited 30 Nov 2017]. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

21. Baeten JM, Nyange PM, Richardson BA, Lavreys L, Chohan B, Martin HL, et al. Hormonal contraception and risk of sexually transmitted disease acquisition: Results from a prospective study. Am J Obstet Gynecol. 2001;185: 380–385. doi:10.1067/mob.2001.115862

22. Lavreys L, Chohan V, Overbaugh J, Hassan W, McClelland RS, Kreiss J, et al. Hormonal contraception and risk of cervical infections among HIV-1-seropositive Kenyan women. AIDS. 2004;18: 2179–84.

23. Louv WC, Austin H, Perlman J, Alexander WJ. Oral contraceptive use and the risk of chlamydial and gonococcal infections. Am J Obstet Gynecol. 1989;160: 396–402.

24. Barbone F, Austin H, Louv WC, Alexander WJ. A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. Am J Obstet Gynecol. 1990;163: 510–4.

25. 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 Transm Dis. 2004;31: 561–7.

26. Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. JAMA. 2001;285: 2995–3002.

27. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol. 2003;157: 218–26.

28. Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyn A, Chong S, et al. Incidence, clearance and predictors of human papillomavirus infection in women. CMAJ. 2003;168: 421–5.

29. Avonts D, Sercu M, Heyerick P, Vandermeeren I, Meheus A, Piot P. Incidence of uncomplicated genital infections in women using oral contraception or an intrauterine device: a prospective study. Sex Transm Dis. 17: 23–9.

30. Rahm VA, Odlind V, Pettersson R. Chlamydia trachomatis in sexually active teenage girls. Factors related to genital chlamydial infection: a prospective study. GenitourinMed. 1991;67: 317–321.

Table 1. Prospective associations between hormonal contraceptive use and Human Papillomavirus (HPV) (N=13).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
Borgdorff, 2015 [37]	166, HIV negative sex workers in Kigali Rwanda ages 18-49; *N=47 incident HPV (any type) cases*	24M; 0M, 6M, 24M	Linear Array HPV genotyping test (Roche)	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time between assessments	Non-pregnant non-hormonal user	OCP on HPV (any type) aOR: 1.08 (0.21, 5.44)	HPV (any type) Injectable (any type[b]) aOR: 0.79 (0.34, 1.83)	NA
Harris, 2009 [36]	257, HIV negative women with no history of cervical neoplasia in the United States seeking routine care at family planning clinics, ages 18-50; *N=152 cases, N=107 controls*[c]	Median follow-up: 60D; 0M, and colposcopy biopsy visit	PCR amplification, line blot assay (Roche) and histology assessment	Age at colposcopy-biopsy, lifetime number of male partners, and parity	Cases: women with positive oncogenic HPV type; Controls: HPV-negative women with negative histology and cytology at both visits: HC reference group: never user of specific method	Oncogenic HPV COC recent user: aOR: 0.6 (0.3, 1.5); COC ≥1Yr: aOR: 0.8 (0.3, 2.0); <1Yr: aOR: 0.5 (0.2, 1.2); COC former user aOR: 0.9 (0.3, 2.3)	Oncogenic HPV DMPA recent user[d] aOR: 1.6 (0.7, 3.7); ≥1Yr DMPA: aOR: 4.7 (1.4, 15.8)*; <1Yr DMPA user: aOR: 0.7 (0.3, 2.1); Former DMPA user[d] aOR: 1.3 (0.6, 3.1)	NA
Gosvig, 2013 [38]	604, women with CIN2 or worse at four hospitals in Denmark, age range NR; *N=18 cases of reappearance (2.2%)*	8-12M follow-up duration; 4-6M; 8-12M	Hybrid Capture 2; HPV genotype testing via line probe assay (INNO LiPAv2 Innogenetics)	Age, HPV viral load at baseline, condom use since last visit, # partners since last visit, time since last visit	Non-user of oral contraception in last 4-6M	OCP on re-appearance of any HPV: aOR 1.00 (0.21, 4.82)	NA	NA
Lekovich, 2015 [39]	302, HIV negative women with IUD placement between 2005 and 2012 and	Mean time b/w pre-IUD and post IUD HR-HPV test: 555 days (Copper	Hybrid Capture 2 test	Study groups matched on: age, high-risk HPV infection, rate of	Non-pregnant Copper IUD user	NA	NA	HR-HPV: Levonorgestrel vs. Copper IUD

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
	pre/post insertion HPV testing at participating U.S. institution, Mean age 33; *N=8 /152 cases Levonorgestrel IUD, 2/150 cases Copper IUD*	IUD), 534 days (Levonorgestrel IUD); IUD placement and repeat HR-HPV test: 356 (Copper IUD), 349 (Levonorgestrel IUD)		abnormal cytology and proportion of smokers				OR: 4.11, p=0.056
Louvanto, 2011 [40]	255, postpartum women in Finland, Mean age 26 (SD 3.1); *N=203 incident cases, 133 for HPV- species α7 and α9 included in analyses*	6Y; 0M, 2M, 12M, 24M, 36M, 6Y	Multiplex-HPV genotyping kit (Progen Biotechnik GmbH)	Age, HR-HPV seropositive at baseline, seroconverted to HR-HPV, # sexual partners until age 20, lifetime # sex partners, age initiation of OC use, marital status, employment status, age of onset of sexual activity, baseline PAP smear results, baseline oral HR-HPV DNA status, frequency of sex, # of births, oral sex, ever had STD, history of genital warts, history of oral warts, age initiation of smoking, pregnancy during follow-up, change in marital status during follow-up Final model (empirical strategy): age, seroconverted to HR-	Never used OC pills	OCP (ever use) on Species α7 and α9 HR- HPV: aIRR: (ns) NR (respectively)	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
				HPV, # sexual partners until age 20, lifetime # sexual partners, age initiated OC use, smoking, pregnancy during follow-up, change in marital status during follow-up				
Marks, 2011 [41]	1135, HIV-negative women ages 20-37 in Thailand, reporting no commercial sex work in past 6M and willing to adhere to self-selected contraceptive method for at least 1Y; *N=269 (8%) incident cases for any HPV, 157 (4.7%) incident HR-HPV cases*	18M; 0M, 6M, 12M, 18M	QIAamp DNA Blood Kit (Qiagen), HPV Linear Array, PCR assay (Roche Diagnostics)	Age, study site, # live births, male condom use P6M, age sexual debut, # lifetime partners, # partners P6M, smoking P6M, cervical cytology at enrollment and follow-up, BV at enrollment, prior STI infection, cervical ectopy Final model (empirical strategy): age, study site, # of lifetime and recent sexual partners, new sexual partner, concurrent BV, duration of HC use	Non-hormonal user during same interval of assessment	COC on HPV (any type) aOR: 1.27 (0.93, 1.74); HR-HPV aOR: 1.22 (0.81, 1.83)	DMPA on HPV (any type) aOR: 0.90 (0.63, 1.31), HR-HPV aOR: 0.87 (0.55, 1.35)	NA
Moscicki 2001 [26]	105, women aged 13 to 21 attending 2 family planning clinics in San Francisco, USA; *N=54 incident cases*	Median follow-up: 50M [IQR: 23-79M]; ~4-6M (9 median visits, IQR: 4-15)	PCR assay; B-globin control; dot blot and Roche reverse blot method (Roche Molecular Systems)	Rate of new partners per month since last visit, history of HSV, history of vulvar warts, lifetime sexual partners, marijuana use	Non-current OCP user	OCP on HPV (any type) aHR 0.49 (0.28, 0.86)*	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
				Final model: rate of new partners per month since last visit, history of HSV, history of vulvar warts.				
Nielsen, 2009 [42]	6246, women aged 20-29 in Copenhagen, Denmark, randomly sampled from general population; *N*= 798 *(12.8%) HR-HPV incident cases*	2Y; 0M and 2Y[e]	Hybrid Capture 2 and LiPA V2 PCR assay (Innogenetics); B-globin control	Age, # sexual partners, marital status, self-reported history of chlamydia, self-reported history of genital warts, parity, current condom use, amount of smoking Final model (empirical strategy): age, # of sexual partners during follow-up, marital status, interaction between marital status and number of sexual partners during follow-up	Current non-hormonal user	OCP on HR-HPV: ≤2Yr aOR: 1.01 (0.68, 1.50), 3-4Yr aOR: 1.39 (0.98, 1.99); 5-6Yr aOR: 1.44 (1.00, 2.07); 7+Yr aOR: 1.66 (1.17, 2.35)*, Per Yr): 1.04 (0.98, 1.10)	NA	NA
Phelan, 2009 [43]	220, HIV+ and HIV women ages 18+ who reported injection drug use in past 10 years in Baltimore, USA; Mean age 37 (SD 6.6); *Detection of new type-specific HPV cases 22% of 775 visits*	5Y; 0M and every 6M	PCR assay; B-globin controls, oligonucleotide dot blot hybridization	Age, HIV status and CD4 category, smoking in P6M, injection drug use P6M, marijuana use P6M, any STD P6M, # male sex partners P6M, # male sex partners P10Y, # live lifetime births Final model (empirical and theoretical approach): age, HIV	Never user of OC (lifetime)	OCP (ever): Not significant at univariate level (among HIV+ or HIV- women) so multivariate not reported	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
				status and CD4 level, crack use in P6M, # of male sex partners in P10Y				
Sellors, 2003 [28]	253, Canadian women ages 15 to 49 in selected physician practices; *28 incident HPV cases (11.1%)*	1Y; 0M and 12M	PCR assay with HPV-genotyping; HCII assay for HR-HPV detection	Age, median number of sex partners in the last year, median number of lifetime sex partners, marital status, smoking status	Non-OCP user	OCP on HR-HPV aOR: 0.70 (0.20, 2.0)	NA	NA
Shew, 2015 [44]	150, adolescents ages 14-17 in Indianapolis, U.S. visiting one of 3 primary care clinics	Mean follow-up: 5.8Y (3.9-9.2); Every 3M	Linear array HPV genotyping test (Roche Diagnostics) and PCR assay with B-globin control	STIs (clinic test): CT, NG and TV; contraceptive use, condom use, coital frequency, number of partners	Non-user of OCP in last 3M, Non-user of DMPA in last 3M, respectively	OCP on HPV (all types) aHR: 2.0 (1.28, 3.15)*; HR-HPV aHR: 1.31 (0.73, 2.35); LR-HPV aHR: 2.73 (1.52, 4.90)*	DMPA on HPV (all types) aHR: 0.96 (0.67, 1.38); HR-HPV aHR: 0.80 (0.54, 1.19); LR-HPV aHR: 1.57 (0.90, 2.75)	NA
Winer, 2003 [27]	553, university women in Seattle, USA ages 18-20; *incident cases (all HPV type) among OCP users: 92 per 503 PY vs. 56/553 PY among non-OCP users*	5Y; 4M intervals	PCR assay and dot-blot hybridization with B-globin control	Time interval, current smoking, history of non-genital warts, history of tampon use, being delivered by cesarean section, length of time having known a partner, partner's ethnicity, partner's age, partner's educational level, partner's lifetime number of partners, partner's circumcision status, condom use with a new partner.	Non-OCP user	OCP on HPV (all types) aHR: 1.40 (1.01, 1.80)*	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
				Whether partner had ever had a STI, subject/partner alcohol use during sex. Final model: no. sex partners, condom use with new partners, sex partner's no. of other partners, new partner in past 12 M, time knowing partner before sex, current smoker				
Winer, 2016 [45]	420, women aged 25-65 in the USA sampled from internet dating group; *cumulative incidence of HR-HPV: 25.4%*	Mean follow-up: 12.5M +/- 5M; Mean interval b/w assessment: 5.1M +/- 1.4M	PCR assay with B-globin controls, Roche Linear Array genotyping test	Age at first sex, (time dependent variables): age, marital status, smoking history, abnormal PAP history, current HC use, menopausal status, sex with ≥1 male partner in past 6M, lifetime # sex partners Final model (empirical strategy): lifetime # of male sex partners, and male sex partners in the P6M (women with ≥1 partner in P6M)	Current non-hormonal user	NA	NA	Any HC use on HR-HPV, all women aHR: 1.82 (1.17, 2.83)*; Women with no sex partners in P6M aHR: 4.16 (1.27, 13.63)*; Women with ≥ 1 partner in P6M aHR: 1.65 (1.05, 2.59)*

Notes: PY: person-years at risk; aOR: adjusted odds ratio; aHR: adjusted hazard ratio. HR-HPV: high-risk HPV, LR-HPV: low-risk HPV. *p<0.05; #p=0.056;

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate (NE-ENT) use.

[c] Case control study.

[d] Former user defined as having stopped using method at least one year before colposcopy-biopsy. Recent use defined as having used that method within 6 months of biopsy.

[e] Contraceptive use exposure period retrospectively recalled, exceeds study follow-up duration.

Table 2. Prospective associations between hormonal contraceptive use and herpes simplex virus type 2 (HSV-2) (N=4).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Length of follow-up; frequency STI assessment	Covariates	Reference group	OCP[a]	Injectable	Combined HC
Borgdorff, 2015 [37]	163, HIV-negative sex workers in Kigali, Rwanda ages 18 to 49, *N=21 HSV-2 incident cases*[c]	24M; 0M, 3M, 6M, 12M, 24M	HerpeSelect 2 ELISA (index ≥3.5 defined as positive)	24M; 0M, 3M, 6M, 12M, 24M	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	OCP aOR: 4.28 (0.07, 262.1)	Injectable (type not specified[d]) aOR: 6.34 (0.25, 158.5)	NA
Chohan, 2009 [53]	297, HIV-negative sex workers in Mombasa, Kenya ages 18 to 46, N=*115 HSV-2 incident cases (23 cases per 100 PY)*[b]	13Y; every 1M (median time b/w visits: 33d [IQR 28-48]	HSV-2- type-specific HSV-2 gG based ELISA (index value of >1.1 defined as positive)	13Y; every 1M (median time b/w visits: 33d [IQR 28-48]	Education, parity, alcohol and tobacco use, vaginal washing practices, bar vs. night club work. Time-dependent variables: age, duration of sex work, presence of other genital tract infections, # sex partners per week, condom use during past working week Final model: duration of sex work, bar (vs. night club) work, # sex partners per week, percentage condom use past week, presence of BV	Non-hormonal user	OCP aHR: 0.50 (0.23, 1.08)[#]	NA	aHR Norplant/ DMPA (combined): 0.92 (0.53, 1.61)

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Length of follow-up; frequency STI assessment	Covariates	Reference group	OCP[a]	Injectable	Combined HC
Grabowski, 2015 [35]	682, HIV-negative women in Rakai, Uganda ages 15 to 49 who had a HIV-negative male partner, N=*52 HSV-2 incident cases*[e]	3Y; 0M, 12M & 24M	HSV-2 ELISA test	3Y; 0M, 12M & 24M	Age, education of woman and male partner, # of lifetime sexual partners. Time-varying variables: male circumcision, coital frequency, and female and male self-report of any condom use and non-marital partners in the past year. Final model: did not include coital frequency or male circumcision based on model fit	Non-pregnant non-hormonal user	OCP aHR: 0.49 (0.08, 3.01)	Consistent DMPA users aHR: 2.26 (1.09, 4.69)*; Initiated DMPA aHR: 0.75 (0.29, 1.92); Discontinued DMPA use aHR: 0.58 (0.13,2.51)	NA
Socias, 2017 [54]	149, HIV-positive (N=13) and HIV-negative (N=136) sex workers in Vancouver, Canada ages 14+, *N=39 HSV-2 incident cases;* 17.1 cases per 100 PY (12.4, 23.6)	4Y; every 4M	Serum samples via non-specific EIA HSV IgG. If reactive, anti-HSV-2 using TSS Focus HerpeSelect-2 IgG EIA (Focus Diagnostics)	4Y; every 4M	Time invariant: Age, indigenous ancestry, education. Time-varying: HIV status, incident STIs (*T. pallidum*, NG and CT), average # of clients per week, # male non-commercial partners, inconsistent use of condoms by clients and non-clients, respectively, type of sex work venue Final model (stepwise selection): type of sex work venue	Non-DMPA user in prior 6M	NA	HIV positive and negative DMPA users aHR: 4.43 (1.90, 10.35)*; HIV negative DMPA users aHR: 3.97 (1.64, 9.60)*	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05. # Marginally significant at p=0.08;

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] *10 women seroconverted to HSV-2 & HIV-1 at same visit; PY: person-years; NA: not assessed by study.*

[c] Women censored after first incident infection.

[d] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate use.

[e] Excluding incident cases among pregnant women.

Table 3. Prospective associations between hormonal contraceptive use and *Chlamydia trachomatis* (CT) (N=9).

Study	N, study sample, *N of incident cases or incident rate*	Length of follow-up; frequency STI assessment	STI Diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Borgdorff, 2015 [37]	397, HIV-negative sex workers in Kigali, Rwanda ages 18-49; *N=30 incident cases*[b,e]	12M; 0M, 6M, 12M	Endocervical swabs via Amplicor CT/NG PCR test (Roche Diagnostics)	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	OCP aOR: 6.13 (1.5, 23.8)*	Injectable (type not specified[d]) aOR: 2.24 (0.69, 7.29)	NA
Baeten, 2001 [21]	948, HIV-1 negative sex workers in Mombasa, Kenya ages 16-48; N=175 incident cases (11.1/100 PY)	Range 15 to 2366 days (median: 421 days); median time b/w visits: 35 days	Enzyme-linked immunoabsorbent assay (ELISA) (Microtrak)	Age, years of education, years of prostitution, parity, number of sexual partners, place of work (ie, bar vs. nightclub), number of sexual contacts, and condom usage	No contraceptives or tubal ligation	OCP aHR: 1.8 (1.1, 2.9)*	DMPA aHR: 1.6 (1.1, 2.4)*	NA
Kapiga, 2009 [47]	958, HIV negative women ages 16 to 62 in Lusaka, Zambia (ZA), Moshi Tanzania (TZ) and Durban/Hlabisa, South Africa (SA); *Incidence rate*[b]*: 19.5/100 PYAR (SA); 4.9/100 PYAR (TZ, ZA)*	12M, every 3M	TZ/ZA site: endocervical swabs via enzyme-linked immunosorbent assay (ELISA), (Murex Biotech); SA site: urine samples via BD Probe Tec ET assay[c]	Age, site, partner earns income, # sex partners, frequency vaginal sex in past 1W, anal sex in past 3M, other STIs, bacterial vaginosis, candida, abnormal vaginal discharge on exam, abnormal cervical discharge on exam, incident HIV Final model (empirical approach): site, age, # sex partners, incident HIV infection and *N. gonorrhoeae* infection (SA model); site, presence of candida and abnormal vaginal discharge on exam (TZ/ZA model)	Not specified	OCP Durban/Hlabis ,SA aOR: NR (ns); Moshi TZ/Lusaka ZA site aOR: NR (ns)	DMPA Durban/Hlabis, SA aOR: 1.8 (1.0, 3.3)*; DMPA Moshi TZ/Lusaka ZA site aOR: NR (ns)	Norplant Durban/Hlabis,SA aOR: NR (ns); Norplant Moshi TZ/Lusaka ZA site aOR: NR (ns)
Louv, 1989 [23]	818, U.S. women ages 19 to 29 attending a STI clinic in Birmingham Alabama; *N=214 incident cases*[b]	6M; Monthly	Fluorescein-tagged antibody; Microtrak Culture confirmation (Syva CO)	Age, mean number of sex acts per month, mean number of partners during follow-up period, parity, gravidity	Tubal ligation or IUD user	COC: aHR: 1.73 (1.08, 2.77)*	NA	NA

Study	N, study sample, *N of incident cases or incident rate*	Length of follow-up; frequency STI assessment	STI Diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Lavreys, 2004 [22]	242, HIV-1 positive commercial sex workers attending STI clinic in Mombasa, Kenya; *N=26 incident cases, incidence rate: 7.7/100 PY*	Median follow-up 35M (IQR: 11-62M); Every 1M	Antigen test by ELISA (Microtrak, Syva)	Age, years of education, years of sex work, parity, workplace, number of sexual partners per week, condom use	No contraception or tubal ligation	OCP: aHR 2.20 (0.70, 7.30)	DMPA: aHR 3.10 (1.0, 9.4)[#]	NA
Masese, 2013 [51]	865, HIV positive and HIV-negative women who report engaging in transactional sex, ages 18 to 50 in Mombasa, Kenya; *N=101 incident cases[b], incidence rate = 5.0/100 PY*	4Y, every 1-3M	Endocervical swab via Gen-Probe Aptima GC/CT Detection System	Age, vaginal microbiota, place of work (bar vs. nightclub or home based/ other), educational level, marital status, unprotected intercourse in past wk, # of sex partners in past wk, vaginal washing, presence of other genital tract infections (*T. vaginalis*, *C. albicans*, *N. gonorrhoeae*), HIV-1 serostatus, and cervical ectopy Final model (empirical approach): Age, unprotected sex with >1 sex partner in past week, HIV status, *N. gonorrhoeae* infection	Non-hormonal user	OCP aHR: 0.2 (0.0, 1.7)	DMPA aHR: 1.8 (1.1, 3.0)*	NA
Pettifor, 2009 [48]	567, HIV-negative women ages 18 to 40 recruited from family planning clinics in Orange Farm, South Africa; *N=119 incident cases[b], incident rate: 28.2 per 100 PY*	1Y; every 3M	Urine sample via ligase chain reaction (LCx®; Abbot Laboratories)	Age, relationship status, education, frequency of sex in the past 3M, # partners in the past 3M, condom use in the past 3M, vaginal douching past 3M, age of first sex Final model (empirical and theoretical approach): Age, education, condom use consistency in past 3M	Non- pregnant, non-hormonal user	NA	DMPA aIRR: 1.24 (0.80, 1.94); NET-EN aIRR: 0.91 (0.59, 1.43)	NA

Study	N, study sample, *N of incident cases or incident rate*	Length of follow-up; frequency STI assessment	STI Diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Romer, 2013 [50]	342, adolescent girls ages 14-17 attending clinics in inner-city areas of Indianapolis, USA; *N=165 incident cases*[b]	Originally 27M, extended to 5Y for some participants; every 3M	Clinician obtained cervical samples or self-obtained vaginal swabs via nucleic acid amplification tests (NAATs) (Amplicor PCR, Roche Diagnostics)	Age, positive STI test at start of period, # of partners in past 3M, # of lifetime partners, # of sexual events in last 3M (diary period), # of unprotected sexual events in last 3M (diary period)	Non-hormonal user	NA	DMPA, use in past 3M aOR: 0.76 (0.45, 1.31); DMPA used 3-6M ago aOR: 1.17 (0.69, 1.96)	NA
Russell, 2016 [52]	225, HIV-negative women recruited from outpatient clinics ages 15-35 who had lower genital tract infection or were biologically at risk of STI infection from Pittsburgh PA, USA; *Incidence rate: 48 women tested positive, 28 per 100 PY*[c] *incident rate*	Median 12M FU; 0M, 1M, 4M, 8M, 12M	Endocervical swab via nucleic acid amplification tests (NAATs)	Age, education, site of *C. trachomatis* (CT) infection at enrollment (cervix vs. cervix/endometrium, or uninfected), GN infection during follow-up, STI diagnosis among partner during follow-up, # of male partners since last visit, new male partners since last visit, sex with uncircumcised male in last 3M, condoms (reported at any visit) Final model (empirical approach): age, *N. gonorrhoeae* during follow-up, site of CT infection, CT infection by partner during follow-up, new male partner since last visit, sex with uncircumcised male last 3M	Non-user of OCP or DMPA, respectively	OCP aHR: NR (ns)	DMPA aHR: 1.03 (0.59, 1.78)	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05. # p=0.05

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only) is noted.

[b] Multiple incident cases per woman were allowed, i.e., incident cases defined as a positive test following a negative test.

[c] Incident infection defined as any positive test during follow-up.

[d] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate (NE-ENT) use.

[e] Excluding cases among pregnant women.

Table 4. Prospective associations between hormonal contraceptive use and *Neisseria gonorrhoeae* (NG) (N=7).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Borgdorff, 2015 [37]	381, HIV-negative sex workers in Kigali, Rwanda ages 18 to 49, *N=42 incident cases* [b,d]	12M; 0M, 6M, 12M	Endocervical swab via Amplicor CT/NG PCR test (Roche Diagnostics)	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	OCP aOR: 2.57 (0.78, 8.45)	Injectable (type not specified[c]) aOR: 0.80 (0.28, 2.31)	NA
Baeten, 2001 [21]	948, HIV-1 negative sex workers in Mombasa, Kenya ages 16-48; N=272 incident cases (16.5/100 PY)	Range 15 to 2366 days (median: 421 days); median time b/w visits: 35 days	Culture on Thayer-Martin media	Age, years of education, years of prostitution, parity, number of sexual partners, place of work (ie, bar vs. nightclub), number of sexual contacts per week, and condom usage	No contraception or tubal ligation	OCP aHR: 1.4 (0.9, 2.1)	DMPA aHR: 1.1 (0.8, 1.6)	NA
Louv 1989 [23]	818, U.S. women ages 19 to 29 attending a STI clinic in Birmingham Alabama; *N=155 incident cases* [b]	6M; Monthly	Gram stain or oxidase reagent (Marion Scientific), confirmation by Rapid NH system (Innovative Diagnostic Systems)	Age, mean number of sex acts per month, mean number of partners during follow-up period, parity, gravidity	Tubal ligation or IUD user	COC: aHR: 1.70 (1.05, 2.76)*	NA	NA
Lavreys 2004 [22]	242, HIV-1 positive commercial sex workers attending STI clinic in Mombasa, Kenya; *N=119 incident cases, incidence rate: 14.9/100 PY*	Median follow-up 35M (IQR: 11-62M); Every 1M	Antigen test by ELISA (Microtrak, Syva)	Age, years of education, years of sex work, parity, workplace, number of sexual partners per week, condom use	No contraception or tubal ligation	OCP: aHR 0.6 (0.3, 1.3)	DMPA: 1.0 (0.6, 1.7)	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Kapiga, 2009 [47]	958, HIV negative women ages 16 to 62 in Lusaka, Zambia (ZA), Moshi Tanzania (TZ) and Durban/Hlabisa, South Africa (SA), *Incidence rate[a]: 16.5/100 PYAR (SA); 5.3/100 PYAR (TZ, ZA)*	12M; every 3M	TZ and ZA: culture methods used. SA: urine sample via BD Probe Tec ET assay	Age, site, partner earns income, # sex partners, frequency vaginal sex past 1W, anal sex past 3M, other STIs, BV, candida, abnormal vaginal discharge on exam, abnormal cervical discharge on exam, incident HIV Final model (empirical approach): site and incident HIV infection (SA model); age (TZ/ZA model)	Not specified	OCP Durban/Hlabisa SA site: aOR: NR (ns); Moshi TZ/Lusaka ZA site aOR: NR (ns)	DMPA Durban/Hlabisa SA site: aOR: NR (ns); Moshi TZ/Lusaka ZA site aOR: NR (ns)	Norplant Durban/Hlabisa SA site: aOR: NR (ns); Moshi TZ/Lusaka ZA site aOR: 4.7 (1.3, 16.5)*
Pettifor, 2009 [48]	567, HIV-negative women ages 18 to 40 recruited from family planning clinics in Orange Farm, South Africa; *N=45 incident cases [b] incident rate: 9.9 per 100 PY*	1Y; 0M, 2M, 6M, 8M and 12M (NET-EN users) or 0M, 3M, 6M, 9M and 12M (DMPA users and controls)	Urine sample via ligase chain reaction (LCx®; Abbot Laboratories)	Age, relationship status, education, frequency of sex past 3M, # sex partners past 3M, condom use past 3M, vagina douching past 3M, age of first sex Final model (empirical and theoretical approach): Age, education and condom use consistency in past 3M	Non-pregnant non-hormonal user	NA	DMPA aIRR: 1.30 (0.58, 2.98); NET-EN aIRR: 1.11 (0.55, 2.25)	NA
Romer, 2013 [50]	342, adolescent girls ages 14-17 attending clinics in inner-city areas of Indianapolis, USA; *N=65 incident cases [b]*	Originally 27M, extended to 5Y for some participants ; every 3M	Nucleic acid amplification tests (Amplicor CT/NG PCR; Roche Diagnostics). Positive results confirmed by Gen-Probe	Age, positive STI test at start of period, # of sexual partners in past 3M, # of lifetime sexual partners, # of sexual events in last 3M (diary period), # of unprotected sexual events in last 3M (diary period)	Non-hormonal user	NA	DMPA use in current 3M period aOR: 1.19 (0.57, 2.48); DMPA use in prior 3M aOR: 1.12 (0.54, 2.32)	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05.
[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.
[b] Multiple incident cases per woman were allowed, i.e., incident cases defined as a positive test following a negative test.
[c] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate use.
[d] Excludes cases among pregnant women.

Table 5. Prospective associations between hormonal contraceptive use and *Chlamydia trachomatis* (CT) or *Neisseria gonorrhoeae* (NG) (combined) (N=2).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Low 2014 [55]	172, HIV-1 positive women on antiretrovirals who engage in transactional sex in Bobo-Dioulasso Burkina Faso, ages 18 to 50, *N=11 incident cases GN; rate of 2.76 cases per 100 PY; 3 incident cases CT, rate of 0.75 per 100 PY* [b]	4Y; 0M, ~3-6M	Cervical swab via PCR (Amplicor CT/NG PCR assay, Roche) using pooling approach	Age, education, tobacco use, # sex acts past wk, alcohol use, sex work, condom use, vaginal washing, antibiotic use past 1M, abnormal vaginal discharge on exam, genital ulcers on exam, abnormal cervical exam, genital warts, concurrent BV, *T. vaginalis*, *Candida albicans*, or HSV-2 DNA, presence of Y-PCR, HIV-1 plasma viral load, HIV-1 eCVL RNA detected, CD4 count, time since sample collection, antiretroviral status Final model (empirical and theoretical approach): # sex acts past wk, CD4 count, education	Non-hormonal user	OCP aOR: ns (NR)	DMPA on NG/CT aOR: 5.83 (0.90, 37.70)	NA
Morrison 2004 [25]	819, women attending 2 reproductive health clinics in Baltimore, USA ages 15 to 45. N=45 incident cases of CT or GN; 6.2 per 100 PY.	3, 6 and 12M	CT by ligase chain reaction (LCx; Abbott Laboratories). GN by Gram stain, oxidase reaction, lactamase and production. Confirmation by Gonocheck II (E-Y Laboratories).	Age, race, and site and measures of contraceptive exposure.	Non-hormonal user	COC aHR: 1.5 (0.6, 3.5)	DMPA: aHR: 3.6 (1.6, 8.5)	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05.

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] Incidence is new cases of NG or CT during study period, divided by number of women at risk; cases at baseline excluded.

Table 6. Prospective associations between hormonal contraceptive use and *Treponema pallidum* (syphilis) (N=3).

Study	(N), study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Borgdorff, 2015 [37]	354, HIV-negative sex workers in Kigali, Rwanda ages 18 to 49, *N=4 incident cases* [b]	12M; 0M, 6M, 12M	Spinreact Raplid Plasma Reagin test, confirmation by Spinreact T. pallidum Haemagglutination test	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	NA	Injectable (type not specified[b]) aOR: 1.43 (0.11, 19.1)	NA
Baeten, 2001 [21]	948, HIV-1 negative sex workers in Mombasa, Kenya ages 16-48; N=48 incident cases (2.9/100 PY)	Range 15 to 2366 days (median: 421 days); median time b/w visits: 35 days	Hemagglutination assay (Biotech Laboratories)	Age, years of education, years of prostitution, parity, number of sexual partners, place of work (ie, bar vs. nightclub), number of sexual contacts per week, and condom usage	Non-hormonal user or tubal ligation	OCP aHR: 0.40 (0.10, 1.50)	DMPA aHR: 0.50 (0.20 1.4)	NA
Kapiga, 2009 [47]	958, HIV negative women from general population ages 16 to 62 in Lusaka, Zambia (ZA), Moshi Tanzania (TZ) and Durban/Hlabisa, South Africa (SA), Incidence rate [b]: 7.5/100 PY (all sites)	12M; every 3M	Positive serum reaction after both a rapid plasma reagin card test and treponema pallidum haemagglutination assay (TPHA) or microhaemagglutination assay-treponema pallidum (MHA-TP)	Age, site, partner earns income, # sex partners, frequency vaginal sex in past wk, anal sex in past 3M, other STIs, bacterial vaginosis, candida, abnormal vaginal discharge on exam, abnormal cervical discharge on exam, incident HIV infection Final model (empirical selection): site, age, husband/partner earns income, frequency of vaginal sex past wk, T. vaginalis	Not specified	OCP All sites aOR: NR (ns)	All sites, DMPA: aOR: NR (ns)	All sites, Norplant aOR: NR (ns)

Notes: PY: person-years at risk. * Statistically significant at p<0.05.

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] Multiple incident cases per woman were allowed; included positive serology results from baseline, incident cases defined as a positive test following a negative test.

Table 7. Prospective associations between hormonal contraceptive use and *T. vaginalis* (TV) (N=9).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant or combined HC
Balkus, 2014 [34]	2920, HIV-negative women ages 18+ with no-drug use in past 12M in Blantyre, Lilongwe Malawi; Durban, Hlabisa, South Africa; Philadelphia USA; Lusaka Zambia; Harare, Chitungwiza, Zimbabwe, Detection at *N=400 of 16,259 visits*[d]	12 to 30 M; 0M, 12M, 30M (or study exit)	Vaginal wet mount via saline microscopy	Age, marital status, unprotected sex in the last week, T. vaginalis at baseline, intermediate Nugent score, BV at prior visit	Non-pregnant non-hormonal user	OCP aHR: 0.64 (0.47, 0.89)*	Injectable (type not specified) aHR: 0.60 (0.47, 0.78)*	Implant (type not specified) aHR: 0.57 (0.20, 1.60)
Baeten, 2001 [21]	948, HIV-1 negative sex workers in Mombasa, Kenya ages 16-48; N=435 incident cases (26.4/100 PY)	Range 15 to 2366 days (median: 421 days); median time b/w visits: 35 days	Vaginal wet mount	Age, years of education, years of prostitution, parity, number of sexual partners, place of work (ie, bar vs. nightclub), number of sexual contacts per week, and condom usage	Non-hormonal user or tubal ligation	OCP aHR: 0.90 (0.70, 1.30)	DMPA aHR: 0.60 (0.40 1.0)*	NA
Barbone [24]	818, U.S. women ages 19 to 29 attending a STI clinic in Birmingham Alabama; *N=171 incident cases*[e]	6M; Monthly	Vaginal wet mount	Spermicide use, sexual activity, age, race	Tubal ligation or IUD user	OCP: aHR 0.56 (0.39, 0.81)*	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant or combined HC
Borgdorff, 2015 [37]	381, HIV-negative sex workers in Kigali, Rwanda ages 18 to 49, *N=89 incident cases*[b]	24M; 0M, 6M, 12M, 24M	Vaginal swab via culture kit (InPouch, BioMed Diagnostics) and Gram stain (presence of >20% clue cells and Nugent criteria). Considered positive if tested positive on either test.	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	OCP aOR: 0.61 (0.20, 1.84)	Injectable (type not specified[f]) aOR: 0.44 (0.17, 1.10)	NA
Brahmbhatt, 2014 [46]	2374, HIV+ (304) and HIV- (2070) women ages 15 to 49 in rural Rakai, Uganda[c]; N=96/2374 cases; 2.4/100 PY	12M; 0M, 12M	Self-collected vaginal swab via culture kit (InPouch, TV, BioMed Diagnostics)	10-year age group, marital status, education, # sex partners past 12M, SES (home building materials), Nugent score for BV, condom use, syphilis result, HIV status Final model (empirical and theory informed): age, marital status, education, SES, condom use and other STIs, interaction b/w HC use and HIV status	No method (neither hormonal or condom)	COC past 12M aIRR: 1.02 (0.40, 2.59); Consistently used COC (at baseline and follow-up) aIRR: 1.07 (0.25, 4.56)	DMPA past 12M aIRR: 0.54 (0.30, 0.98)*; Consistently used DMPA only (at baseline and follow-up) aIRR: 0.59 (0.28, 1.26)	Norplant past 12M aIRR: 3.01 (1.07, 8.49)*; Consistently used Norplant only (at baseline and follow-up) aIRR: 3.13 (1.08, 9.07)*

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant or combined HC
Kapiga, 2009 [47]	958, HIV negative women ages 16 to 62 in Lusaka, Zambia (ZA), Moshi Tanzania (TZ) and Durban/Hlabisa, South Africa (SA), Incidence rate: 31.9/100 PY (all sites)	12M; every 3M	Vaginal swab via Gram stain using Nugent criteria	Age, site, partner earns income, # sex partners, frequency vaginal sex in past 1W, anal sex in past 3M, other STIs, bacterial vaginosis, candida, abnormal vaginal discharge on exam, abnormal cervical discharge on exam, incident HIV infection Final model (empirical selection): site and incident HIV infection included in SA model and only age in TZ/ZA model	Not specified	OCP All sites aOR: 0.6 (0.3, 1.0)	All sites DMPA aOR: 0.7 (0.5, 1.0)	All sites Norplant aOR: NR (ns)
Pettifor, 2009 [48]	567, HIV-negative women ages 18 to 40 recruited from family planning clinics in Orange Farm, South Africa; *N=47 incident infections[b], incident rate: 10.2 per 100 PY*	1Y; 0M, 2M, 6M, 8M and 12M (NET-EN users) or 0M, 3M, 6M, 9M and 12M (DMPA users and controls)	Vaginal swabs via culture in Diamond's media	Age, relationship status, education, frequency of sex past 3M, # partners in past 3M, condom use in past 3M, vagina douching past 3M, age of first sex Final model (empirical and theoretical selection): Age, education, condom consistency in past 3M	Non-pregnant non-hormonal user	NA	DMPA aIRR: 0.35 (0.12, 1.01); NET-EN aIRR: 0.63 (0.30, 1.29)	NA
Pintye, 2017 [49]	1271, HIV-negative women enrolled during pregnancy and followed until 9M postpartum in western Kenya, median age 22 (IQR: 19-27),	~14M; 20, 24, 32 and 36 weeks gestation and post partum (2, 6, 10 and 14 weeks; 6 and 9 months)	Self-collected vaginal swabs treated with metronidazole, detection via wet mount microscopy	Final model (empirical selection): employment, male partner circumcision status, pregnancy status and other non-TV curable STIs (CT, NG, *T. pallidum*, BV or candidas) detected at enrolment.	Non-hormonal user	OCP aHR: NR (ns)	Injectable (type not specified) aHR: NR (ns)	Implant (type not specified) aHR: NR (ns)

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant or combined HC
	N=112 incident infections[b]; 10.4 per 100 PY							
Romer, 2013 [50]	342, adolescent girls ages 14-17 attending clinics in inner-city areas of Indianapolis, USA; *N=80 incident cases*[b]	Originally 27M, extended to 5Y for some participants; every 3M	Detection of T vaginalis DNA was performed using a modification of the Amplicor CT/NG PCR assay that included primers and probes specific for T vaginalis.	Age, positive STI test at start of period, # of partners in past 3M, # of lifetime partners, # of sexual events in last 3M (diary period), # of unprotected sexual events in last 3M (diary period)	Non-hormonal user	NA	DMPA use in current 3M period aOR: OR: 0.66 (0.32, 1.36); DMPA use in prior 3M aOR: 1.04 (0.52, 2.08)	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05.

[a] OCP type was unspecified unless COC (combined oral contraception)) or POP (progestin-only pill) is noted.

[b] Multiple incident cases per woman were allowed, i.e., incident cases defined as a positive test following a negative test.

[c] All women tested negative for T. vaginalis at baseline. Incident cases were number of T. vaginalis positive women at follow-up (only 1 follow-up).

[d] Women censored after first T. vaginalis incident, or if became pregnant, acquired HIV or tested positive for CT or NG. N=211 women who tested positive for T. vaginalis at baseline were included and prescribed treatment; N=39 [18%] of these women were also infected at the subsequent visit.

[e] Women censored after first T. vaginalis incident.

[f] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate use.

Figure 1. PRISMA Flow Chart

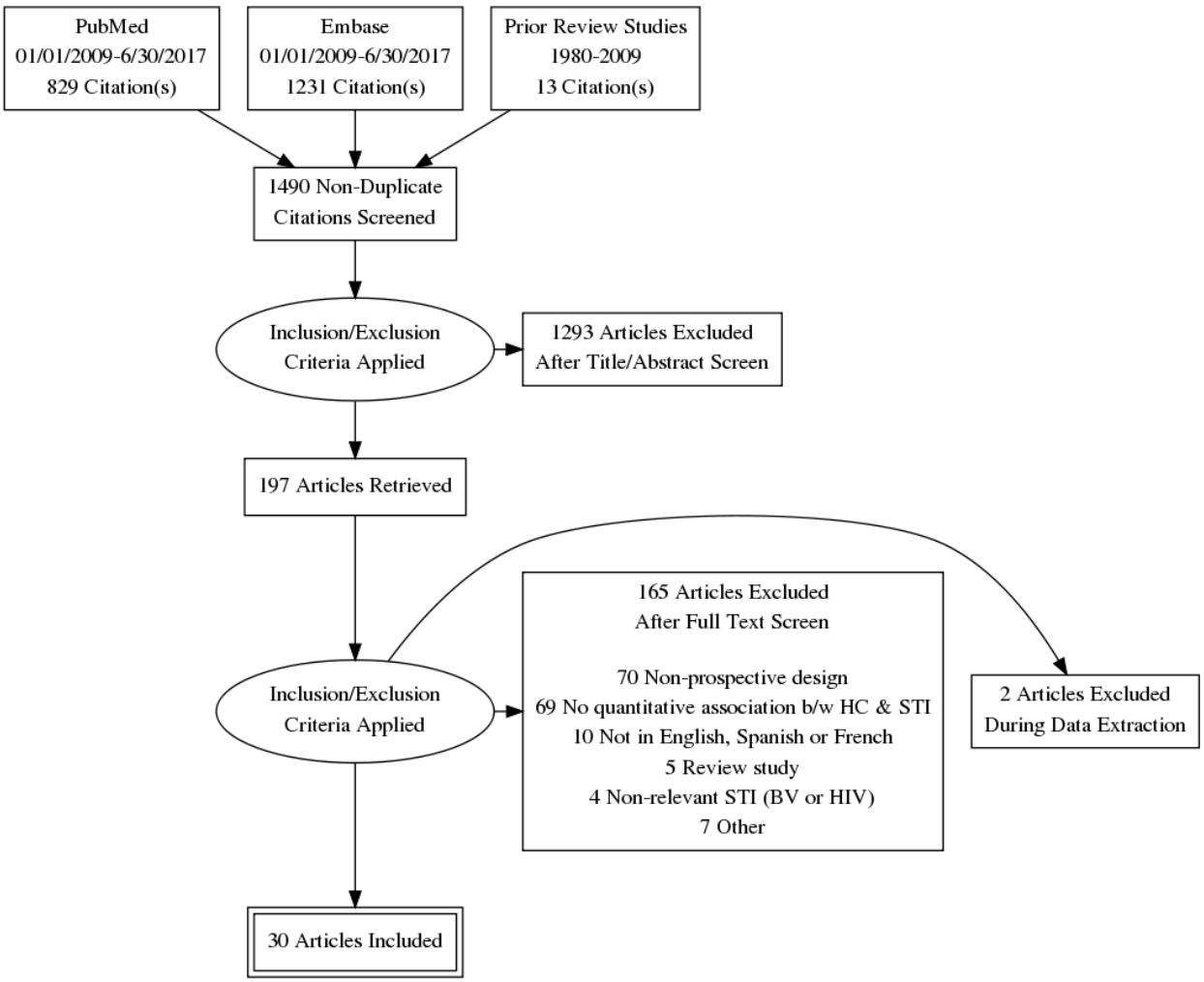
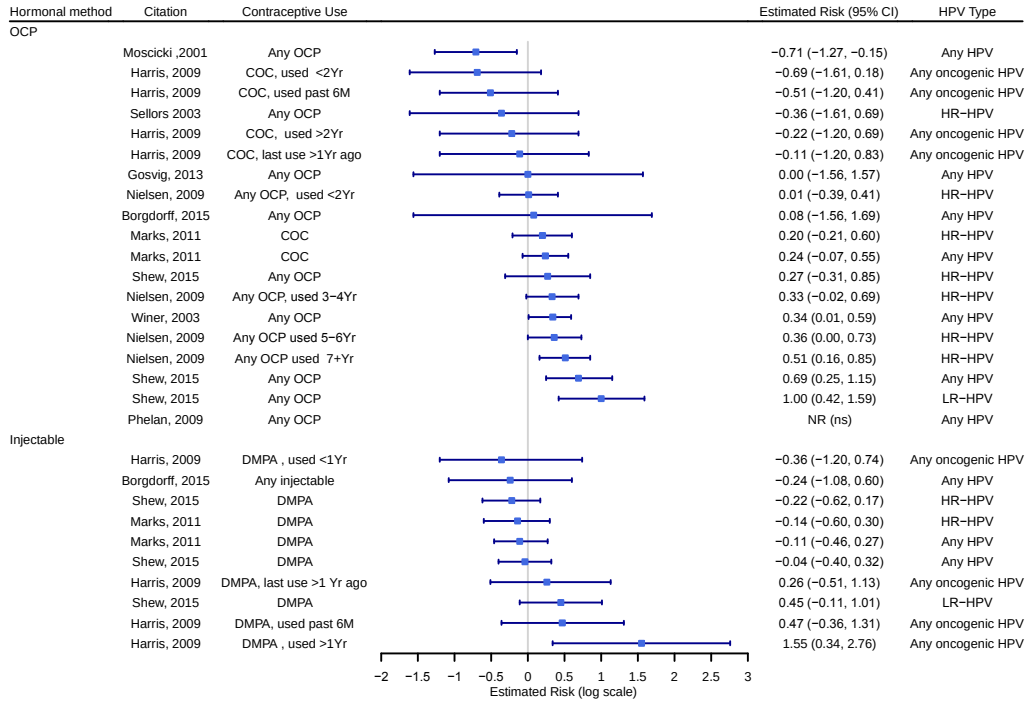


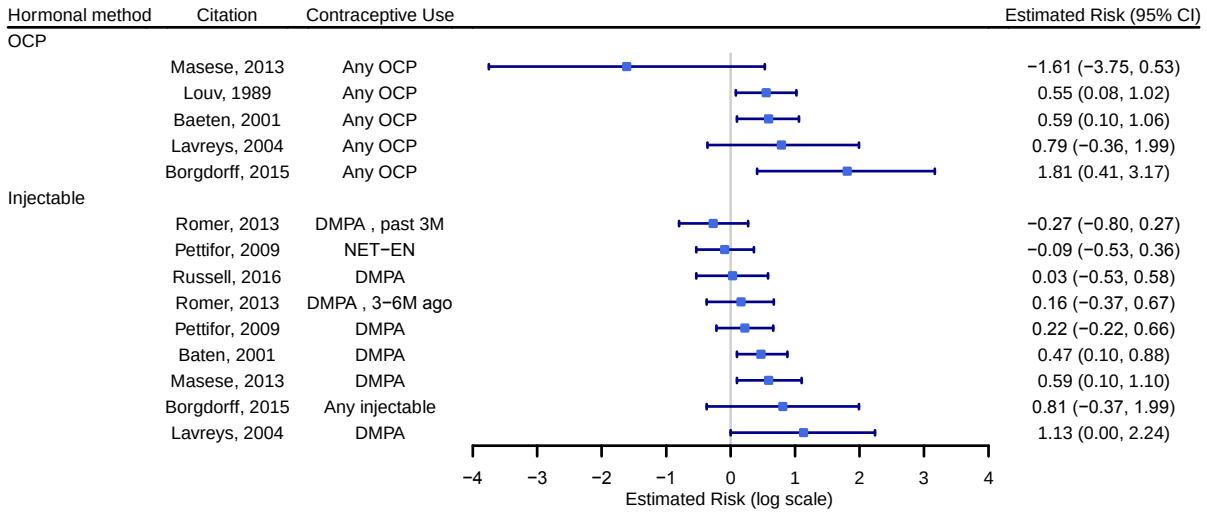
Figure 2. Use of hormonal contraception and human papillomavirus (HPV) infection.



Notes: Findings are presented from studies considered to be high and moderate quality.

NR (ns): estimate not reported due to non-significance. Estimated risk is log transformed adjusted odds ratio, adjusted hazard ratio or adjusted rate ratio; OCP: oral contraceptive pill; COC: combined oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate. Studies which report multiple outcomes are distinguished by subgroup.

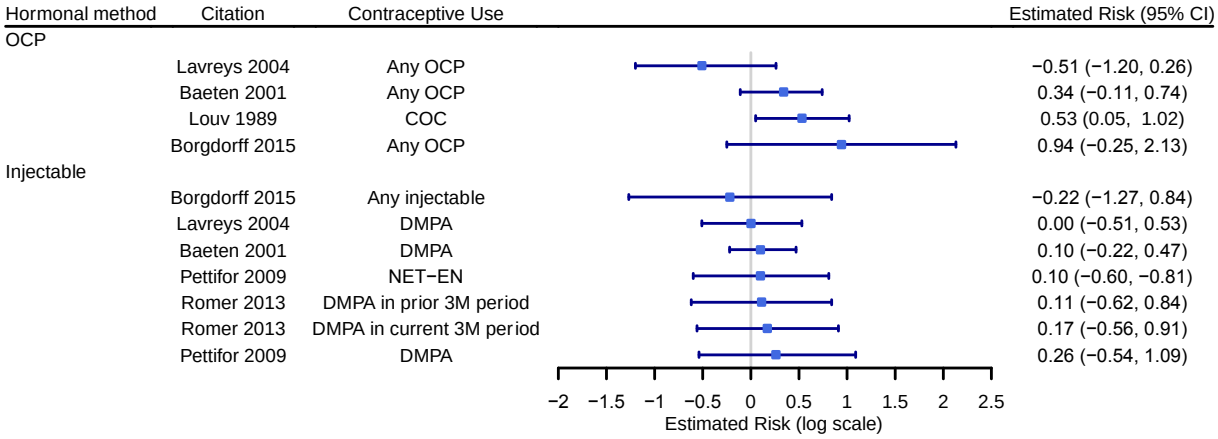
Figure 3. Use of hormonal contraception and *C. trachomatis* infection.



Notes: Findings are presented from studies considered to be high and moderate quality.

Estimated risk is log transformed adjusted odds ratio, adjusted hazard ratio or adjusted rate ratio; OCP: oral contraceptive pill; COC: combined oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate. Studies which report multiple outcomes are distinguished by subgroup.

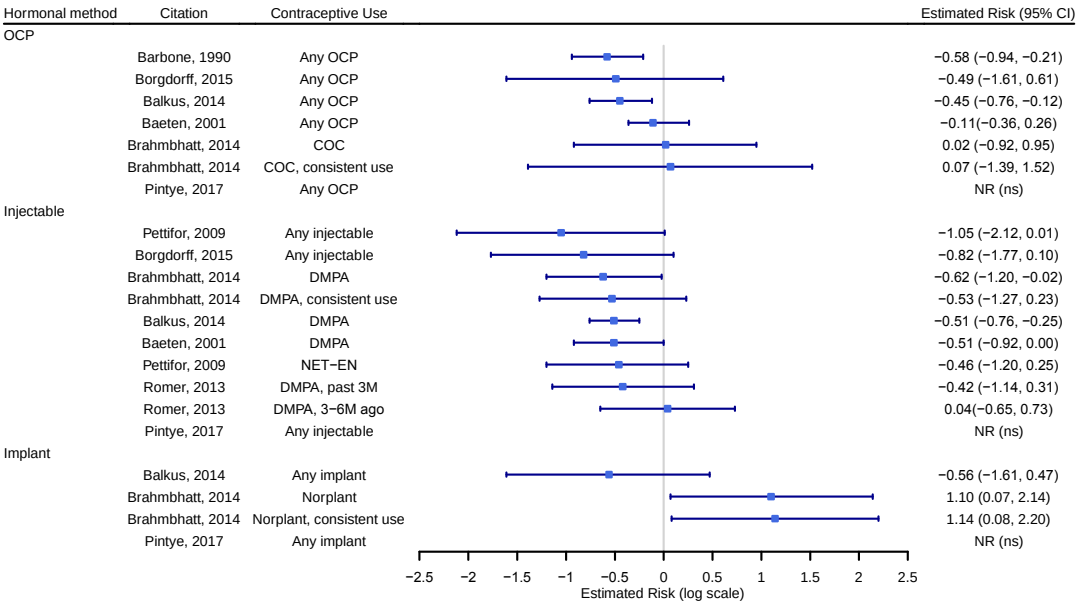
Figure 4. Use of hormonal contraception and *N. gonorrhoeae* infection.



Notes: Findings are presented from studies considered to be high and moderate quality.

Estimated risk is log transformed adjusted odds ratio, adjusted hazard ratio or adjusted rate ratio; OCP: oral contraceptive pill; COC: combined oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate. Studies which report multiple outcomes are distinguished by subgroup.

Figure 5. Use of hormonal contraception and *T. vaginalis* infection.



Notes: Findings are presented from studies considered to be high and moderate quality.

NR (ns): estimate not reported due to non-significance. Estimated risk is log transformed adjusted odds ratio, adjusted hazard ratio or adjusted rate ratio; OCP: oral contraceptive pill; COC: combined oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate. Studies which report multiple outcomes are distinguished by subgroup.

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SDC Table 4: References 31-59.

Supplemental Digital Content Figure 1

Pubmed search string:

((((((hormonal AND contracepti*) OR ("hormonal methods")) OR ((progestin* OR progestins[MeSH] OR Progesterone[MeSH]) AND contracept*) OR (oral contracept*) OR OC OR POP OR ((((depo OR depot) AND medroxyprogesterone) OR depo medroxyprogesterone OR depo OR depot OR dmpa OR "Sayana Press" OR "net en" OR "NET-EN" OR "norethisterone enanthate" OR norethisterone-enanthate OR Medroxyprogesterone 17-Acetate[MeSH]) AND (contracept* OR inject*)) OR "Depo Provera" OR "Depo-Provera" OR (((levonorgestrel OR etonogestrel) AND implant) OR (uniplant OR jadelle OR implanon OR nexplanon OR norplant OR norplant2 OR sino-implant)) OR (hormonal, transdermal[MeSH] OR (contracept* AND patch)) OR (contracept* AND pill) 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 lunell 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 ortho evra)) AND ("Sexually Transmitted Infection"[MeSH] OR "STI" OR ("sexually transmitted infect*") OR "STD" OR "Gonorrhea"[MeSH] OR " gonorrhoeae" OR "Chlamydia"[MeSH] OR "chlamydia trachomatis" OR "Chancre"[MeSH] OR chancroid OR "haemophilus ducreyi" OR "Trichomonas"[MeSH] OR "Trichomoniasis"[MeSH] OR "trichomonas vaginalis" OR "TV" OR "Treponema pallidum"[MeSH] OR herpes OR herpesvirus OR "herpes simplex" OR "herpes virus" OR HSV OR "Human papillomavirus"[MeSH] OR "HPV" OR "Syphilis"[MeSH] OR "genital warts" OR "condylomata")) OR (injectable contracepti* STI) OR (oral contracepti* STI) OR (CT OR GC OR NG AND "sexually transmitted infection") OR (CT OR GC OR NG AND STI))) AND ("2009/01/01"[EDAT] : "2017/06/15"[EDAT]))

EMBASE search string

hormonal AND contracepti* OR 'hormonal methods' OR (progestin* OR 'progestins' OR 'progesterone' AND contracept*) OR ('oral' AND contracept*) OR 'OC' OR 'POP' OR ((depo OR depot) AND 'medroxyprogesterone') OR depomedroxyprogesterone OR depo OR depot OR dmpa OR 'sayana press' OR 'net en' OR 'net-en' OR 'norethisterone enanthate' OR (('medroxyprogesterone' AND '17-acetate') AND (contracept* OR inject*)) OR (('levonorgestrel' OR 'etonogestrel') AND 'implant') OR 'uniplant' OR 'jadelle' OR 'implanon' OR 'nexplanon' OR 'norplant' OR norplant2 OR 'sino implant' OR (hormonal AND transdermal) OR (contracept* AND patch) OR ('levonorgestrel' AND 'intrauterine' AND 'devices') 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' AND 'devices') OR ('contraceptive' AND agents) AND ring) OR 'nuvaring' OR 'nuva ring' OR (('contraceptive' AND 'devices') OR ('contraceptive' AND agents) AND patch) OR 'ortho evra' OR orthoevra AND ('sexually transmitted infection' OR STI OR 'sexually transmitted infections' OR STD 'sexually transmitted disease' OR 'sexually transmitted diseases' OR gonorrhea OR 'neisseria gonorrhoeae' OR chlamydia OR 'chlamydia trachomatis' OR chancre OR chancroid OR 'haemophilus ducreyi' OR trichomonas OR trichomoniasis OR 'trichomonas vaginalis' OR TV OR 'treponema pallidum' OR herpes OR herpesvirus OR 'herpes simplex' OR 'herpes virus' OR hsv OR 'human papillomavirus' OR hpv OR syphilis OR 'genital warts' OR condylomata) OR (injectable contracepti* STI) OR (oral contracepti* STI) OR (CT OR GC OR NG AND 'sexually transmitted infection') OR (CT OR GC OR NG AND STI) AND [humans]/lim AND [1-1-2009]/sd NOT [15-6-2017]/sd AND ([article]/lim OR [article in press]/lim)

Supplemental Digital Content Table 2: Quality assessment of prospective or retrospective cohort studies.

Citation	Study design	Reference group drawn from same community as HC users (2)	Ascertainment of HC use (2)	Demonstration STI not present prior to incident/recurrent infection (1)	Comparability of HC users and reference group cohorts demonstrated or adjusted for (2)	Ascertainment of STI based on biomarker and blind to HC status (2)	Adequate follow-up of cohort (<20% lost or unlikely to introduce bias) (1)	Total score Quality rating: High (8-10) Medium (5-7) Low (<5)
Balkus 2014 [34]	Secondary RCT	2	2	1	2	1	1	**9** (High)
Baeten 2001 [21]	PC	2	2	0	2	1	0	**7** (Medium)
Barbone 1990 [24]	Secondary RCT	2	1	1	1	1	0	**6** (Medium)
Borgdorff 2015 [37]	PC	2	2	1	2	1	1	**9** (High)
Brahmbhatt 2014 [46]	PC	1	1	1	2	1	0	**6** (Medium)
Chohan 2009 [53]	PC	1	1	1	2	1	1	**7** (Medium)
Gosvig 2013 [38]	PC	2	2	1	2	2	0	**9** (High)
Grabowski 2015 [35]	Secondary RCT	2	1	1	2	1	0	**7** (Medium)
Kapiga 2009 [47]	PC	0	1	1	1	1	0	**4** (Low)
Lavreys 2004 [22]	PC	1	2	0	1	1	0	**5** (Medium)
Lekovich 2015 [39]	RC	2	1	1	1	1	0	**6** (Medium)
Louv 1989 [23]	Secondary RCT	1	2	1	1	1	0	**6** (Medium)
Louvanto 2011 [40]	PC	0	1	1	1	1	0	**4** (Low)
Low 2014 [55]	PC	1	2	1	1	0	0	**5** (Medium)
Marks 2011 [41]	PC	2	2	1	2	1	0	**8** (High)
Masese 2013 [51]	PC	1	2	1	2	1	0	**7** (Medium)
Morrison 2004 [25]	PC	2	1	1	2	0	1	**7** (Medium)
Moscicki 2001 [26]	PC	1	2	1	1	1	0	**6** (Medium)
Nielsen 2009 [42]	PC	1	1	1	2	2	0	**7** (Medium)
Pettifor 2009 [48]	PC	2	2	1	2	1	1	**9** (High)
Phelan 2009 [43]	PC	1	2	1	1	1	0	**6** (Medium)
Pintye 2017 [49]	PC	2	2	1	2	1	0	**8** (High)
Romer 2013 [50]	PC	1	2	1	2	1	1	**8** (High)

Russell 2016 [52]	PC	1	2	1	2	1	1	**8** (High)
Sellors 2003 [28]	PC	1	1	1	1	1	0	**5** (Medium)
Shew 2015 [44]	PC	1	2	1	2	1	0	**7** (Medium)
Socias 2017 [54]	PC	0	2	1	2	1	0	**6** (Medium)
Winer 2003 [27]	PC	0	2	1	2	1	0	**6** (Medium)
Winer 2016 [45]	PC	0	0	0	2	1	0	**3** (Low)

Notation: PC: prospective cohort, RC: retrospective cohort, Secondary RCT: secondary analysis of RCT. NR: not reported. NA: This criterion was not applicable: studies estimated recurrent infection.

Rating criteria: *Non-users drawn from same community as HC users*: a) respondents drawn from the same community as HC users (i.e., does not include pregnant women) (1 point) and b) comparison group does not include users of another HC method (unless intentional head-to-head comparison (1 point). *Ascertainment of HC use:* a) separate estimates for different types of HCs (1 point), b) HC use assessed more than once and at intervals <6 months (1 point). *Demonstration STI not present at start of study*: test for pathogen used to confirm respondents were STI negative at study start (1 point). *Comparability of cohorts demonstrated:* a) adjusted analyses performed (1 point); b) authors adjust for condom use or demonstrates negligible difference (1 point); *Ascertainment of STI*: a) independent blind assessment of STI performed (1 point); b) separate estimates for different types of STIs provided using test for pathogen (1 point); *Adequacy of follow-up of cohorts*: a) subjects lost to follow-up unlikely to introduce bias (either high retention >80% or description of those lost is provided and comparable to those who remain in the study) (1 point).

Supplemental Digital Content Table 3: Quality assessment of case-control studies.

Citation	STI case definition accurate (1)	Representativeness of cases (1)	Control selection (1) and definition (1)	Comparability of cases and controls in design or analysis (2)	Ascertainment of HC (3)	Same ascertainment method for cases and controls (1)	Comparable non-response rate for cases and controls (1)	Total score Quality rating: High (8-10) Medium (5-7) Low (<5)
Harris 2009 [36]	1	0	2	1	2	1	0	**7** (Medium)

Rating criteria: *STI definition accurate:* separate estimates for different types of STIs provided using test for pathogen (1 point); *Representation of cases*: consecutive or obviously representative series of cases; *Control selection & definition:* a) controls are sampled independent of HC use and from same source population of cases (1 point); b) if cases are first occurrence of outcome, then controls stated to have no history of outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest are not excluded (1 point); *Comparability of cases and controls in design or analysis*: a) adjusted analyses are performed (1 point); b) study controls for condom use or negligible differences reported in adjusted in unadjusted models (1 point); *Ascertainment of HC:* a) separated estimates for different types of HCs (1 point); b) HC use is assessed more than once at intervals <6 months (1 point); c) HC ascertainment is through structured interview blind to case-control status (1 point); *Same ascertainment method for cases and controls:* yes or no (1 point); *Comparable non-response rate:* equivalent rate demonstrated for both groups (1 point).

SDC Table 4: References 31-59.

31. Rousseau MC, Franco EL, Villa LL, Sobrinho JP, Termini L, Prado JM, et al. A cumulative case-control study of risk factor profiles for oncogenic and nononcogenic cervical human papillomavirus infections. Cancer Epidemiol Biomarkers Prev. 2000;9: 469–76.

32. Lavreys L, Chohan B, Ashley R, Richardson BA, Corey L, Mandaliya K, et al. Human Herpesvirus 8: Seroprevalence and correlates in prostitutes in Mombasa, Kenya. J Infect Dis. 2003;187: 359–363. doi:10.1086/367703

33. Overton ET, Shacham E, Singhatiraj E, Nurutdinova D. Incidence of sexually transmitted infections among HIV-infected women using depot medroxyprogesterone acetate contraception. Contraception. 2008;78: 125–130. doi:10.1016/j.contraception.2008.03.015

34. Balkus JE, Richardson BA, Rabe LK, Taha TE, Mgodi N, Kasaro MP, et al. Bacterial vaginosis and the risk of Trichomonas vaginalis acquisition among HIV-1–negative women. Sex Transm Dis. 2014;41: 123–128. doi:10.1097/OLQ.0000000000000075

35. Grabowski MK, Gray RH, Makumbi F, Kagaayi J, Redd AD, Kigozi G, et al. Use of injectable hormonal contraception and women's risk of herpes simplex virus type 2 acquisition: a prospective study of couples in Rakai, Uganda. Lancet Glob Heal. 2015;3: e478–e486. doi:10.1016/S2214-109X(15)00086-8

36. Harris TG, Miller L, Kulasingam SL, Feng Q, Kiviat NB, Schwartz SM, et al. Depot-medroxyprogesterone acetate and combined oral contraceptive use and cervical neoplasia among women with oncogenic human papillomavirus infection. Am J Obstet Gynecol. 2009;200: 489.e1-8. doi:10.1016/j.ajog.2009.01.030

37. Borgdorff H, Verwijs MC, Wit FWNM, Tsivtsivadze E, Ndayisaba GF, Verhelst R, et al. The impact of hormonal contraception and pregnancy on sexually transmitted infections and on cervicovaginal microbiota in African sex workers. Sex Transm Dis. 2015;42: 143–152.

doi:10.1097/OLQ.0000000000000245

38. Gosvig CF, Huusom LD, Andersen KK, Iftner A, Cederkvist L, Svare E, et al. Persistence and reappearance of high-risk human papillomavirus after conization. Gynecol Oncol. 2013;131: 661–666. doi:10.1016/j.ygyno.2013.09.002

39. Lekovich JP, Amrane S, Pangasa M, Pereira N, Frey MK, Varrey A, et al. Comparison of Human Papillomavirus infection and cervical cytology in women using copper-containing and levonorgestrel-containing intrauterine devices. Obstet Gynecol. 2015;125: 1101–1105. doi:10.1097/AOG.0000000000000760

40. Louvanto K, Rintala MA, Syrjänen KJ, Grénman SE, Syrjänen SM. Incident cervical infections with high- and low-risk human papillomavirus (HPV) infections among mothers in the prospective Finnish Family HPV Study. BMC Infect Dis. 2011;11: 179. doi:10.1186/1471-2334-11-179

41. Marks M, Gravitt PE, Gupta SB, Liaw K-L, Tadesse A, Kim E, et al. Combined oral contraceptive use increases HPV persistence but not new HPV detection in a cohort of women from Thailand. J Infect Dis. 2011;204: 1505–1513. doi:10.1093/infdis/jir560

42. Nielsen A, Iftner T, Munk C, Kjaer SK. Acquisition of high-risk human papillomavirus infection in a population-based cohort of Danish women. Sex Transm Dis. 2009;36: 609–615. doi:10.1097/OLQ.0b013e3181a96d0e

43. Phelan DF, Gange SJ, Ahdieh-Grant L, Mehta SH, Kirk GD, Shah K, et al. Determinants of newly detected human papillomavirus infection in HIV-infected and HIV-uninfected injection drug using women. Sex Transm Dis. 2009;36: 149–56. doi:10.1097/OLQ.0b013e31818d3df3

44. Shew ML, Ermel AC, Tong Y, Tu W, Qadadri B, Brown DR. Episodic detection of human papillomavirus within a longitudinal cohort of young women. J Med Virol. 2015;87: 2122–9. doi:10.1002/jmv.24284

45. Winer RL, Hughes JP, Feng Q, Stern JE, Xi LF, Koutsky LA. Incident detection of high-risk human

papillomavirus infections in a cohort of high-risk women aged 25–65 years. J Infect Dis. 2016;214: 665–675. doi:10.1093/infdis/jiw074

46. Brahmbhatt H, Musoke R, Makumbi F, Kigozi G, Serwadda D, Wawer M, et al. Trichomonas vaginalis incidence associated with hormonal contraceptive use and HIV infection among women in Rakai, Uganda. J Sex Transm Dis. 2014;2014: 916597. doi:10.1155/2014/916597

47. Kapiga S, Kelly C, Weiss S, Daley T, Peterson L, Leburg C, et al. Risk factors for incidence of sexually transmitted infections among women in South Africa, Tanzania, and Zambia: Results from HPTN 055 study. Sex Transm Dis. 2009;36: 199–206. doi:10.1097/OLQ.0b013e318191ba01

48. Pettifor A, Delany S, Kleinschmidt I, Miller WC, Atashili J, Rees H. Use of injectable progestin contraception and risk of STI among South African women. Contraception. 2009;80: 555–60. doi:10.1016/j.contraception.2009.06.007

49. Pintye J, Drake AL, Unger JA, Matemo D, Kinuthia J, McClelland RS, et al. Male partner circumcision associated with lower Trichomonas vaginalis incidence among pregnant and postpartum Kenyan women: a prospective cohort study. Sex Transm Infect. 2017;93: 137–143. doi:10.1136/sextrans-2016-052629

50. Romer A, Shew ML, Ofner S, Gilliam ML, Martins SL, Fortenberry JD. Depot medroxyprogesterone acetate use is not associated with risk of incident sexually transmitted infections among adolescent women. J Adolesc Heal. 2013;52: 83–88. doi:10.1016/j.jadohealth.2012.04.007

51. Masese L, Baeten JM, Richardson BA, Deya R, Kabare E, Bukusi E, et al. Incidence and correlates of Chlamydia trachomatis infection in a high-risk cohort of Kenyan women. Sex Transm Dis. 2013;40: 221–5. doi:10.1097/OLQ.0b013e318272fe45

52. Russell AN, Zheng X, O'Connell CM, Taylor BD, Wiesenfeld HC, Hillier SL, et al. Analysis of factors driving incident and ascending infection and the role of serum antibody in Chlamydia trachomatis genital tract infection. J Infect Dis. 2016;213: 523–31. doi:10.1093/infdis/jiv438

53. Chohan V, Baeten JM, Benki S, Graham SM, Lavreys L, Mandaliya K, et al. A prospective study of risk factors for herpes simplex virus type 2 acquisition among high-risk HIV-1 seronegative women in Kenya. Sex Transm Infect. 2009;85: 489–492. doi:10.1136/sti.2009.036103

54. Socías ME, Duff P, Shoveller J, Montaner JSG, Nguyen P, Ogilvie G, et al. Use of injectable hormonal contraception and HSV-2 acquisition in a cohort of female sex workers in Vancouver, Canada. Sex Transm Infect. 2017;93: 284–289. doi:10.1136/sextrans-2016-052838

55. Low AJ, Konate I, Nagot N, Weiss HA, Mabey D, Segondy M, et al. Neisseria gonorrhoeae and Chlamydia trachomatis infection in HIV-1-infected women taking antiretroviral therapy: a prospective cohort study from Burkina Faso. Sex Transm Infect. 2014;90: 100–103. doi:10.1136/sextrans-2013-051233

56. Kaushic C, Ashkar AA, Reid LA, Rosenthal KL. Progesterone increases susceptibility and decreases immune responses to genital herpes infection. J Virol. 2003;77: 4558–65.

57. Gillgrass AE, Ashkar AA, Rosenthal KL, Kaushic C. Prolonged exposure to progesterone prevents induction of protective mucosal responses following intravaginal immunization with attenuated herpes simplex virus type 2. J Virol. 2003;77: 9845–51.

58. Looker KJ, Elmes JAR, Gottlieb SL, Schiffer JT, Vickerman P, Turner KME, et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. Lancet Infect Dis. 2017;17: 1303–1316. doi:10.1016/S1473-3099(17)30405-X

59. United Nations Population Division Department of Economic and Social Affairs. Trends in contraceptive use worldwide 2015 [Internet]. 2015 [cited 21 May 2018]. Available: http://www.un.org/en/development/desa/population/publications/pdf/family/trendsContraceptiveUse2015Report.pdf

Hormonal contraceptives and the acquisition of sexually transmitted infections: an updated systematic review

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References = ~~48~~ 59 (31-~~48~~ 59 in supplemental table)

Tables = 6 / Figures = 5~~4~~

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Short summary: A systematic review of the association between hormonal contraception and incident STIs found that DMPA and oral contraceptive pills decrease risk of trichomoniasis, and DMPA may increase risk of HSV-2.

Key words: Hormonal contraception, sexually transmitted infections, systematic review

Abstract

Background: Evidence suggests that some forms of hormonal contraception (HC) increase women's risk of non-HIV sexually transmitted infections (STIs), yet evidence has not been reviewed since 2008. We conducted an updated systematic review to incorporate studies published between January 2009 and June 2017 to examine the relationship between HCs and incident and/or recurrent STIs.

Methods: We searched PubMed and EMBASE to identify prospective studies comparing risk of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, human papillomavirus (HPV), herpes simplex virus type 2 (HSV-2), *Treponema pallidum*, or *Trichomonas vaginalis*, between women using HC vs. non-hormonal methods or no methods. We summarize results by type of STI and HC and study quality using an adapted Newcastle-Ottawa Quality Assessment Scale.

Results: Thirty articles met the inclusion criteria. Depo-medroxyprogesterone acetate (DMPA) reduces the risk of trichomoniasis (consistent evidence) and may increase the risk of HSV-2 (strong effect, few studies); inconclusive evidence exists for HPV, chlamydia, gonorrhea and syphilis. Data on oral contraceptive pills (OCPs; generally not differentiated whether combined or progestin-only pills) suggest use is associated with a reduced risk of trichomoniasis with inconclusive findings for HSV-2, HPV, chlamydia, gonorrhea, and syphilis. Very few studies included norethisterone enanthate (Net-En) injectable, implants or the levonorgestrel IUD.

Conclusions: DMPA and OCPs reduce the risk of trichomoniasis and DMPA may increase the risk of HSV-2. However, the potential for confounding cannot be ruled out. Future studies should specify the type of injectable or OCP used to increase understanding of biological pathways; more research is needed on implants and hormonal IUDs.

Introduction

While access to hormonal contraception (HC) reduces unwanted pregnancy and maternal morbidity and mortality, a body of evidence from recent systematic reviews, meta-analyses and in vivo and in vitro studies suggest that the progestin injectable depo-medroxyprogesterone acetate (DMPA) increases risk of HIV acquisition [1–5]. Comparatively less emphasis, however, has focused on the potential association of DMPA and other HC and other sexually transmitted infections (STIs).

Several biological mechanisms by which HC use may facilitate STI acquisition have been proposed including through changes in the protective cervicovaginal epithelial barrier from hypo-estrogenism induced by progestin-only methods [6,7]. A second mechanism is through weakening of immune defense [8]. For example, DMPA is known to bind to glucocorticoid receptors, which generally results in immune modulation [5,9]. Third, hypo-estrogenism induced by progestin-only methods could lead to changes in the vaginal microbiota composition, leading to vaginal dysbiosis and inflammation [10], which in turn could lead to epithelial breaches and mucus degradation [11,12]. At a behavioral level, HC use may result in decreased condom use, thereby increasing risk of STI exposure [13,14].

Two prior systematic reviews have examined the association between HCs and STI acquisition; evidence has not been synthesized since 2008 [15,16]. Both reviews found that OCP and DMPA users had a possible increased risk of chlamydia but concluded there was inconclusive evidence for gonorrhea, herpes simplex virus type 2 (HSV-2), trichomoniasis, syphilis and human

papillomavirus (HPV). Given the magnitude of women using HC globally and the negative health repercussions of many STIs, we conducted an updated systematic review to incorporate literature from longitudinal studies published between 2009 and 2017 on the association between the HC use and non-HIV STI acquisition; systematic reviews on HIV acquisition have been updated regularly [1–4].

Materials and Methods

The protocol was registered *a priori* with PROSPERO [Record 42017069357] and follows PRISMA guidelines (Supplemental Table 1). Articles were identified using key term searches of two electronic databases: PubMed and EMBASE (Supplemental Figure 1).

Inclusion/exclusion criteria

Included articles were peer reviewed, published in English, Spanish or French between 01 January 2009 and 30 June 2017 and measured incident/recurrent cases of cervicovaginal HPV, HSV-2, chlamydia, gonorrhea, syphilis, and/or trichomoniasis, with laboratory diagnostic tests, among HC users compared with non-users or users of non-hormonal methods. All HC methods were included except for emergency contraception, since it is typically used in combination with other contraceptive methods [17]. We also reviewed articles identified from two earlier systematic reviews [15,16]; articles from these reviews which met our criteria are also included.

We excluded cross-sectional studies, review articles, studies which relied on clinical exam or self-reported STIs, and studies which did ~~.~~ not control for potential confounding variables. W~~W~~e

also excluded studies of HCs and HIV and bacterial vaginosis (BV), as both have been recently reviewed [18,19]. Two independent reviewers [KJM & HEJ or ELG] screened each abstract or article using Covidence software; a third reviewer who had not previously reviewed the study [HEJ or ELG] resolved discrepancies.

Data Extraction

One reviewer [KJM] extracted data, with independent review for accuracy [HEJ or ELG]. Extracted information included: participant characteristics, geographic location, sample size, sampling method, contraceptive method, duration of use, comparison group, STI, whether infection was incident or recurrent, STI diagnostic test, confounders in adjusted estimates, type of statistical analysis, treatment of missing data, length of time between exposure and outcome assessment, and the effect estimate, variance and significance level.

Study quality

Risk of bias was assessed using the Newcastle-Ottawa Quality Assessment Scale [20], adapted to reflect challenges identified previously for assessment of the relationship between HC use and STIs/HIV [3,15] (Supplemental Tables 2 and 3). Two reviewers [KJM & HEJ or ELG] independently rated study quality; discrepancies were resolved by discussion among all three reviewers.

Data synthesis

Our primary outcome is incident STI. We examined findings by HC method used (e.g., OCP, DMPA, levonorgestrel IUD, Net-En, Norplant) and type of STI. Forest plots were constructed using the forestplot package in R Studio (Version 1.1.383, Vienna, Austria).

Results

Our key term search resulted in 1,477 unique articles, 1,284 articles were excluded during abstract screening; 24 required full-text review of which two were excluded (Figure 1). An additional 13 prospective studies identified in the previous two systematic reviews were considered for inclusion. Of these eight met our study inclusion criteria and are included [21–28], five did not meet our criteria [29–33]. The 30 reviewed studies were all prospective and observational in design, most were longitudinal cohort studies (N=25), four were secondary analysis of a randomized control trial [23,24,34,35] and one used a nested case-control design [36].

The majority of articles assessed the incidence or recurrence of HPV (n=13) [26,27,43–45,28,36–42], followed by trichomoniasis (n=9) [21,24,34,37,46–50], chlamydia (n=9) [21–23,37,47,48,50–52], gonorrhea (n=7) [21–23,37,47,48,50], HSV-2 (n=4) [35,37,53,54], and syphilis (n=3) [24,37,47] (not mutually exclusive). Two studies combined incident chlamydia and/or gonorrhea [25,55]. Twelve studies included women ages 18-50 years [22–24,27,36,37,41,42,48,51,53,55], ten studies included adolescents (<age 18 years) [21,25,26,28,35,44,46,47,50,52], three included women older than age 49 years [34,45,47] and five did not report age range, but the majority of participants were of reproductive age [38–

40,43,49]. One-third of studies enrolled populations considered at increased STI risk: women reporting transactional sex (n=6) [21,22,37,51,53,54], injection drug use (n=1) [43], lower genital tract infection/partner with diagnosed STI (n=1) [52], or living with HIV (n=2) [22,55]. Three additional studies included women living with and without HIV [43,46,54].

Half of the studies (15 of 30) compared HC users to non-hormonal method users (e.g., condom), twelve studies compared two or more types of HCs [23,24,26–28,36,39,40,43,44,52,54], three compared HC use to women not using any method and/or women who were sterilized [21,22,46].

Study quality assessment and risk of bias

Most studies were considered high (n=8) or medium (n=19) quality (Supplemental Tables 2 and 3). Low quality studies (n=3) are presented in the data tables, but not included in forest plots or discussed [40,45,47].

Despite medium/high quality, a number of methodological challenges remained. Nearly all studies relied on self-reported HC exposure, despite known limitations [9]. Most studies (20 of 25) did not distinguish between combined or progestin only OCPs, and some did not distinguish between DMPA and Net-En injectable (3 of 19). The reference group of non-users of a given HC was not defined consistently and sometimes included users of other forms of contraception. Most studies employed empirically driven rather than theoretical adjustment for confounding.

Non-significant estimates were not always presented, prohibiting information on the direction of association. For some studies, incidence rates were low suggesting limited power.

HPV

Eleven studies evaluated the risk of HC on incident HPV infection and provide inconclusive evidence of association (Table 1, Figure 2). All diagnostic tests were DNA-based and five assessed one or more high-risk HPV (HR-HPV) types, one assessed one or more low-risk HPV (LR-HPV), while eight considered any HPV type; two disaggregated results more than one way. Four studies assessed the influence of injectables; two found that incidence of HR (one study) or any HPV (one study) was lower but not significantly lower compared to non-HC users [37,41]. A third study found recent DMPA users had increased incident HR-HPV (used in past six months aOR: 1.6; 95%CI: 0.7, 3.7) and long-term users (≥1 year of use aOR: 4.7; 95%CI: 1.4, 15.8) relative to non-users of DMPA [36]. Findings were in the same direction but not statistically significant among short term and former users. The fourth study found non-significant results in mixed directions, depending on HPV type [44]: DMPA use was associated with lower incidence of HR and increased risk of LR-HPV.

Ten studies evaluated OCP use. Three reported OCP use to be associated with increased HPV risk [27,42,44], two found non-significant increased risk, [37,41] one found significant decreased risk [26], two reported non-significant decreased risk [28,36], one found no effect [38] and one did not report the effect estimate for non-significant findings [43]. Only two studies specified combined OCP use (COC), both documented a non-significant association

[36,41]. Of the studies which documented evidence of increased risk, one was among OCP users vs. non-OCP users in the last three months among LR-HPV (aHR: 2.73; 95%CI: 1.52, 4.90) and all-HPV types (aHR: 2.0; 95%CI: 1.28, 3.15), but not HR-HPV types [44]. Another study which also assessed OCP users vs. non-OCP users on all-HPV types found a lower magnitude of increased risk (aHR: 1.40, 95%CI: 1.01, 1.80) [27]. The final significant finding of increased risk was documented in the longest exposure group only (7+ years) (aOR: 1.66; 95%CI: 1.17, 2.35), with attenuated evidence of marginal risk in lower exposure groups (5-6 year and 3-4 year groups) and null effects among users <2 years relative to nonusers of HC [42]. The one study that found significant decreased risk was among OCP using U.S. women attending a family planning clinic relative to non-current OCP users (aHR: 0.49, 0.28, 0.86) [26]. Overall, inconsistent exposure groups (current versus ever user), reference group (non-current versus never user) and differences in HPV-subtype may contribute to disparate findings.

Only one study assessed the risk of hormonal IUD use on incident HPV infection. This retrospective record review compared levonorgestrel IUD users to copper IUD users and documented a four-fold higher risk of HR-HPV among the former [39]. This effect was marginally significant and based on few incident cases.

HSV-2

Studies examining HSV-2 acquisition provide some evidence that injectable use increases risk [35,37,54] and inconclusive evidence regarding OCPs [35,37,53,54] (Table 2).

Three studies examined the risk of injectable use on HSV-2 incidence. Two studies reported evidence of a significantly increased risk following injectable use (one specifies DMPA, the other is unspecified) [35,54]. The remaining study reports evidence of non-significant increased risk (injectable type unspecified) [37]. The two studies that did not record the injectable type reported that DMPA was most common. Of the two studies that documented a significant effect, one study among HIV-negative women in Uganda reported increased risk (aOR: 2.26, 95%CI: 1.09, 4.69) among consistent DMPA users, but not those who discontinued use, relative to non-HC users [35]. The other study found DMPA use relative to non-DMPA use was strongly associated with HSV-2 acquisition among women both living with and without HIV (aHR: 4.43, 95%CI: 1.90, 10.35), and when restricted to women living without HIV (aHR: 3.97, 95%CI: 1.64, 9.60) [54]. The third study documented non-significant evidence of increased risk among HIV-negative women who engaged in sex work and used DMPA (aOR: 6.34, 95%CI: 0.25, 158.5) compared to non-HC users, [37] based on only five incident cases among DMPA users.

Three studies examined HSV-2 acquisition among OCP users: two documented a non-significant reduced risk of HSV-2 among OCP users relative to non-HC users [35,53]. The remaining study was in the harmful direction but was based on only two incident cases among OCP users [37].

Chlamydia

Seven studies provide inconclusive evidence of increased risk of chlamydia among injectable users [21,22,37,48,50–52] and three provide inconclusive evidence regarding OCP use [23,37,51] (Table 3, Figure 3).

Of the seven studies among injectable users, three documented a significant increased risk of acquisition among DMPA users [21,22,51]. The magnitude of increased risk ranged between 1.6 (95%CI: 1.1, 2.4) fold among DMPA users relative to women who were sterilized or using no contraception [21] to 3.1 (95%CI: 1.0, 9.4) among women living with HIV-1 who used DMPA compared to those who were sterilized or used IUD [22]. The latter effect was marginally significant (p=0.05). Four studies found a non-significant increased risk of acquisition among DMPA users relative to non-HC users [37,48,50]; the direction of effect varies by the reporting period in one study but remains non-significant [50]. An additional study documented a hazard ratio close to one among women who reported DMPA at any fourth month visit relative to non-DMPA users [52]. Only one study compared norethisterone enanthate (Net-En) users to non-HC users, and found a non-significant reduced risk of infection [48].

Six studies examined the incidence of chlamydia among OCP users [21–23,37,51,52], only one study specified combined or progestin-only pill use [23]. Three studies documented significant evidence of increased risk [21,23,37]. One study among HIV-negative women engaging in sex work in Rwanda compared OCP users to non-HC users (aOR: 6.13, 95%CI: 1.5, 23.8) [37]. Results from this study are based on few incident cases. The two other studies documented significant increased risk of similar magnitude. One study compared OCP users to women who were sterilized or using no contraceptive (aHR: 1.80, 95%CI: 1.10, 2.90) [21], the other compared OCP users to women who were sterilized or using IUD (aHR: 1.73, 95%CI: 1.08, 2.77) [23]. Three studies reported null findings. One study did not report the effect coefficient [52], and the

other found non-significant reduced risk (aHR: 0.2, 95%CI: 0.0, 1.7), among OCP users relative to non-HC users [51].

Gonorrhea

We found no significant prospective evidence that injectable use (five studies) [21,22,37,48,50], was associated with risk of gonorrhea. Only one of four studies of OCP use showed increased the risk of gonorrhea [21–23,37] (Table 4, Figure 4). Of the three studies which compared injectable users to non-HC users, two studies found non-significant evidence of increased risk among DMPA users [48,50], one found non-significant evidence of reduced risk among Net-En users [48], and one study found non-significant evidence of reduced risk (injectable type unspecified) [37]. Two additional studies which examined DMPA use relative to women who were sterilized or used no contraception found an association close to the null [21,22]. One of these was among women who were living with HIV-1 [22]. Information from the one study which found increased risk of gonorrhea following OCP use found nearly double risk (aHR 1.7, 95%CI: 1.05, 2.76) among COC users relative to women who used an IUD or were sterilized [23]. This was the only study to assess pill formulation and found that a higher ratio of progestin in COC had a nonsignificant, but positive correlation with the risk of gonorrhea acquisition. The other three studies evaluating OCP use found results in mixed directions and did not specify pill type.

Combined STI

Two studies evaluated a combined group of women who tested positive for either *C. trachomatis* or *N. gonorrhoeae* due to small sample sizes (Table 5) [25,55]. A study among American STI patients found significant increased risk among DMPA users (aHR: 3.6, 95%CI: 1.6, 8.5), and non-significant increased risk among COC users (aHR: 1.5, 95%CI: 0.6, 3.5) relative to non-HC users [25]. The second study was among HIV-1 positive women on antiretroviral therapy was unable to evaluate OCP use due to no incident infections among users. However, women who used DMPA had more than five times the incident risk of *N. gonorrhoeae* or *C. trachomatis* (combined) (aOR: 5.83, 95%CI: 0.90, 37.7), relative to non-HC users [55].

Syphilis

Two studies assessed HC use on syphilis incidence (Table 6), both which found non-significant results. One study found non-significant evidence of increased risk among Kenyan women who engaged in commercial sex work and used OCPs (aHR: 0.40, 95%CI: 0.10, 1.50) and DMPA (aHR: 0.50, 95%CI: 0.20, 1.40), relative to women who used no contraception or were sterilized [21]. The other study found non-significant evidence of increased risk among HIV-negative sex workers in Rwanda who used any injectable relative to non-HC users (aOR: 1.43, 95% CI: 0.11, 19.1) [37]. The finding, however, is based on only four incident cases.

Trichomoniasis

Studies of HC use on risk of trichomoniasis suggest injectables and OCPs are associated with reduced risk while findings are mixed regarding implant use (Table 7, Figure 5) [21,24,34,37,46,48–50].

All seven studies that measured incident trichomoniasis suggest that injectable use reduced incidence by a magnitude ranging from 0.35 (95%CI: 0.12, 1.01) to 0.70 (95%CI: 0.50, 1.0), though some results were not statistically significant. Three studies found significant reduced risk following injectable use (two specified DMPA and one was unspecified) [21,34,46] and two documented reduced risk that approached significance (one specified DMPA, one was unspecified but DMPA use was most common) [37,48]. Two of the studies which documented significant evidence of reduced risk compared HIV-1 negative injectable users (type unspecified) to non-HC users (aHR: 0.60, 95%CI: 0.47, 0.78), and DMPA users (aHR: 0.60, 95%CI: 0.4, 1.0, p=0.04) to women who were sterilized or did not use contraception [21,34]. The third study found women in Uganda who reported DMPA use in the past 12 months were at decreased risk compared to women who used neither HC nor condoms (aIRR: 0.54, 95%CI: 0.30, 0.98) [46]. Notably, the same study found non-significant findings of a similar magnitude among women who reported consistently using only DMPA at baseline and follow-up (aIRR: 0.59, 95%CI: 0.28, 1.26). Only one study reported results for Net-En relative to non-HC use and found non-significant reduced risk [48].

Six of seven studies that assessed OCP use and trichomoniasis documented reduced risk, although only two were significant. One significant finding was reported in a study among OCP users in five countries (Malawi, South Africa, the United States, Zambia and Zimbabwe) who were significantly less likely to acquire *T. vaginalis* relative to non-HC users (aHR: 0.64, 95%CI: 0.47, 0.89) [34]. The other was among OCP using women attending a STI clinic in the U.S.

relative to those who used IUD or were sterilized (aHR: 0.56, 95%CI: 0.39, 0.81) [24]. Only one study specified COC use [46]. This study documented null findings among women in Uganda who reported COC use in the past twelve months (aIRR: 1.02, 95%CI: 0.40, 2.59), or consistently using COCs in the past 12 months (aIRR: 1.07, 95%CI: 0.25, 4.56) relative to no method (neither hormonal nor condom).

One of three studies which assessed implant use on incident trichomoniasis found a three-fold increased risk of trichomoniasis (aIRR: 3.01, CI: 1.07, 8.49) among Norplant users relative to women who used no contraception method (hormonal or condoms) and slightly higher risk among consistent users of Norplant for 12 months (aIRR: 3.13, 95% CI: 1.08, 9.07) [46]. The two remaining studies found no relationship between implant use (type unspecified) and trichomoniasis [34,49].

Discussion

Among studies of sufficient quality, DMPA use is consistently associated with a reduced risk of *T. vaginalis* acquisition, with evidence of substantial (two times or higher) increased risk of HSV-2 incidence from a smaller number of studies. The results for HPV, chlamydia, gonorrhea and syphilis were inconclusive. Net-En was only assessed in one study [48]. Data on OCP use suggest reduced incidence of trichomoniasis, with inconclusive findings for HPV, HSV-2, chlamydia, gonorrhea and syphilis. Implant use was less studied (n=3), and only one specified type (Norplant). This study documented increased risk of trichomoniasis, but did not assess other

STIs [46]. Only one study assessed the levonorgestrel IUD and found a higher risk of HR-HPV incidence compared to the copper IUD; however, findings were marginally significant [39].

Findings from our study differ somewhat from two previous systematic reviews, which found inconclusive results for DMPA and OCPs on incident trichomoniasis, and increased risk of incident chlamydia [15,16]. However, one previous review primarily synthesized cross-sectional research [16]. In the second review, half of the studies (2 of 4 for trichomoniasis; 3 of 6 for chlamydia) did not include statistical adjustment for confounding [15]. Those studies that reported adjusted *T. vaginalis* analyses also found decreased risk [21,24]. Prior prospective evidence of incident HPV from four studies [26–28,31] also suggest mixed results regarding the influence of OCPs and DMPA [26],Figure without clear trends by HPV type or exposure time.

This review provides limited evidence that DMPA is associated with increased risk of HSV-2; we identified no prior review of HC use on incident HSV-2. Notably, our findings are based on a small number of studies. However, findings correspond with studies in mice which show heightened susceptibility to HSV-2 following prolonged (>2 weeks) treatment with DMPA [56,57]. These findings align with the one study that examined multiple exposure periods to DMPA and found a two-fold increased risk of HSV-2 in consistent DMPA users relative to non-HC users but not among those who initiated, or discontinued use [35]. A recent study in mice demonstrated that both DMPA and levonorgestrel, another progestin, increase mucosal epithelial permeability by acting on epithelial cell junction proteins (DSG1α), enhancing access of inflammatory and infectious viral molecules to the genital tissue, a possible biological

mechanism [7]. Given substantial evidence that HSV-2 increases risk of HIV infection, [58] if the finding that DMPA increases the risk of HSV-2 is substantiated, this could be a mechanism for the association between DMPA use and HIV acquisition.

Further prospective research is warranted in several areas. Very few studies have explored the prospective association between HC use and syphilis (n=3) or HSV-2 (n=4) incidence. Similarly, few prospective studies have explored the potential risk of Net-En (n=1), levonorgestrel IUD (n=1) or implants on STIs (n=3), while use of these methods is increasing [59]. No reviewed studies evaluated Sayana Press, the Nuva Ring, or patch. Current large-scale prospective studies of HIV risk among women should incorporate well measured contraceptive use and STI outcomes to help address these gaps. Further many of the studies of OCPs did not differentiate between combined or progestin-only OCPs and similarly some injectable studies did not differentiate between Net-En and DMPA. Given that biological responses to HC differ by class of drug as well as drug formulations,[5] future research needs to distinguish between HC formulations when estimating risk of STI/HIV acquisition.

This updated systematic review of prospective evidence published between 2009 and 2017 suggests that DMPA and OCP use are associated with a reduced risk of incident trichomoniasis, with evidence of increased substantial risk of HSV-2 acquisition with DMPA use from a small number of studies. Our review findings are tempered by notable methodological limitations. Prospective evidence regarding the STI risk of hormonal contraceptive methods are extremely limited or non-existent, highlighting an urgent research need.

References

1. Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies. Lancet Infect Dis. 2015;15: 181–189. doi:10.1016/S1473-3099(14)71052-7

2. Morrison CS, Chen P-L, Kwok C, Baeten JM, Brown J, Crook AM, et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. PLoS Med. Public Library of Science; 2015;12: e1001778. doi:10.1371/journal.pmed.1001778

3. Polis CB, Phillips SJ, Curtis KM, Westreich DJ, Steyn PS, Raymond E, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. Contraception. 2014;90: 360–390. doi:10.1016/j.contraception.2014.07.009

4. Polis CB, Curtis KM, Hannaford PC, Phillips SJ, Chipato T, Kiarie JN, et al. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. AIDS. 2016;30: 2665–2683. doi:10.1097/QAD.0000000000001228

5. Hapgood JP, Kaushic C, Hel Z. Hormonal contraception and HIV-1 acquisition: biological mechanisms. Endocr Rev. Oxford University Press; 2018;39: 36–78. doi:10.1210/er.2017-00103

6. 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: 431–9.

7. Quispe Calla NE, Vicetti Miguel RD, Boyaka PN, Hall-Stoodley L, Kaur B, Trout W, et al. Medroxyprogesterone acetate and levonorgestrel increase genital mucosal permeability and enhance susceptibility to genital herpes simplex virus type 2 infection. Mucosal Immunol. 2016;9: 1571–1583. doi:10.1038/mi.2016.22

8. Wira CR, Fahey J V., Ghosh M, Patel M V., Hickey DK, Ochiel DO. Sex hormone regulation of innate immunity in the female reproductive tract: The role of epithelial cells in balancing

reproductive potential with protection against sexually transmitted pathogens. Am J Reprod Immunol. 2010;63: 544–565. doi:10.1111/j.1600-0897.2010.00842.x

9. Achilles SL, Hillier SL. The complexity of contraceptives: understanding their impact on genital immune cells and vaginal microbiota. AIDS. 2013;27 Suppl 1: S5-15. doi:10.1097/QAD.0000000000000058

10. Jespers V, Kyongo J, Joseph S, Hardy L, Cools P, Crucitti T, et al. A longitudinal analysis of the vaginal microbiota and vaginal immune mediators in women from sub-Saharan Africa. Sci Rep. 2017;7: 11974. doi:10.1038/s41598-017-12198-6

11. Straub RH. The Complex Role of Estrogens in Inflammation. Endocr Rev. 2007;28: 521–574. doi:10.1210/er.2007-0001

12. Ghanem KG, Shah N, Klein RS, Mayer KH, Sobel JD, Warren DL, et al. Influence of sex hormones, HIV status, and concomitant sexually transmitted infection on cervicovaginal inflammation. J Infect Dis. 2005;191: 358–66. doi:10.1086/427190

13. Ott MA, Adler NE, Millstein SG, Tschann JM, Ellen JM. The trade-off between hormonal contraceptives and condoms among adolescents. Perspect Sex Reprod Health. 34: 6–14.

14. Mullinax M, Sanders S, Dennis B, Higgins J, Fortenberry JD, Reece M. How condom discontinuation occurs: interviews with emerging adult women. J Sex Res. 2017;54: 642–650. doi:10.1080/00224499.2016.1143440

15. Morrison CS, Turner AN, Jones LB. Highly effective contraception and acquisition of HIV and other sexually transmitted infections. Best Pract Res Clin Obstet Gynaecol. 2009;23: 263–284. doi:10.1016/j.bpobgyn.2008.11.004

16. Mohllajee AP, Curtis KM, Martins SL, Peterson HB. Hormonal contraceptive use and risk of sexually transmitted infections: a systematic review. Contraception. 2006;73: 154–65. doi:10.1016/j.contraception.2005.08.012

17. Jones R, Darroch J, Henshaw S. Contraceptive use among U.S. women having abortions in 2000–2001. Perspect Sex Reprod Health. 2002;34: 294–303.

18. van de Wijgert JHHM, Verwijs MC, Turner AN, Morrison CS. Hormonal contraception decreases bacterial vaginosis but oral contraception may increase candidiasis. AIDS. 2013;27: 2141–2153. doi:10.1097/QAD.0b013e32836290b6

19. Vodstrcil LA, Hocking JS, Law M, Walker S, Tabrizi SN, Fairley CK, et al. Hormonal contraception is associated with a reduced risk of Bacterial Vaginosis: a systematic review and meta-analysis. PLoS One. 2013;8: e73055. doi:10.1371/journal.pone.0073055

20. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. In: Ottawa Hospital Research Institute [Internet]. [cited 30 Nov 2017]. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

21. Baeten JM, Nyange PM, Richardson BA, Lavreys L, Chohan B, Martin HL, et al. Hormonal contraception and risk of sexually transmitted disease acquisition: Results from a prospective study. Am J Obstet Gynecol. 2001;185: 380–385. doi:10.1067/mob.2001.115862

22. Lavreys L, Chohan V, Overbaugh J, Hassan W, McClelland RS, Kreiss J, et al. Hormonal contraception and risk of cervical infections among HIV-1-seropositive Kenyan women. AIDS. 2004;18: 2179–84.

23. Louv WC, Austin H, Perlman J, Alexander WJ. Oral contraceptive use and the risk of chlamydial and gonococcal infections. Am J Obstet Gynecol. 1989;160: 396–402.

24. Barbone F, Austin H, Louv WC, Alexander WJ. A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. Am J Obstet Gynecol. 1990;163: 510–4.

25. 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 Transm Dis. 2004;31: 561–7.

26. Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. JAMA. 2001;285: 2995–3002.

27. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol. 2003;157: 218–26.

28. Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyn A, Chong S, et al. Incidence, clearance and predictors of human papillomavirus infection in women. CMAJ. 2003;168: 421–5.

29. Avonts D, Sercu M, Heyerick P, Vandermeeren I, Meheus A, Piot P. Incidence of uncomplicated genital infections in women using oral contraception or an intrauterine device: a prospective study. Sex Transm Dis. 17: 23–9.

30. Rahm VA, Odlind V, Pettersson R. Chlamydia trachomatis in sexually active teenage girls. Factors related to genital chlamydial infection: a prospective study. GenitourinMed. 1991;67: 317–321.

Table 1. Prospective associations between hormonal contraceptive use and Human Papillomavirus (HPV) (N=13).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
Borgdorff, 2015 [37]	166, HIV negative sex workers in Kigali Rwanda ages 18-49; *N=47 incident HPV (any type) cases*	24M; 0M, 6M, 24M	Linear Array HPV genotyping test (Roche)	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time between assessments	Non-pregnant non-hormonal user	OCP on HPV (any type) aOR: 1.08 (0.21, 5.44)	HPV (any type) Injectable (any type[b]) aOR: 0.79 (0.34, 1.83)	NA
Harris, 2009 [36]	257, HIV negative women with no history of cervical neoplasia in the United States seeking routine care at family planning clinics, ages 18-50; *N=152 cases, N=107 controls*[c]	Median follow-up: 60D; 0M, and colposcopy biopsy visit	PCR amplification, line blot assay (Roche) and histology assessment	Age at colposcopy-biopsy, lifetime number of male partners, and parity	Cases: women with positive oncogenic HPV type; Controls: HPV-negative women with negative histology and cytology at both visits: HC reference group: never user of specific method	Oncogenic HPV COC recent user: aOR: 0.6 (0.3, 1.5); COC ≥1Yr: aOR: 0.8 (0.3, 2.0); <1Yr: aOR: 0.5 (0.2, 1.2); COC former user aOR: 0.9 (0.3, 2.3)	Oncogenic HPV DMPA recent user[d] aOR: 1.6 (0.7, 3.7); ≥1Yr DMPA: aOR: 4.7 (1.4, 15.8)*; <1Yr DMPA user: aOR: 0.7 (0.3, 2.1); Former DMPA user[d] aOR: 1.3 (0.6, 3.1)	NA
Gosvig, 2013 [38]	604, women with CIN2 or worse at four hospitals in Denmark, age range NR; *N=18 cases of reappearance (2.2%)*	8-12M follow-up duration; 4-6M; 8-12M	Hybrid Capture 2; HPV genotype testing via line probe assay (INNO LiPAv2 Innogenetics)	Age, HPV viral load at baseline, condom use since last visit, # partners since last visit, time since last visit	Non-user of oral contraception in last 4-6M	OCP on re-appearance of any HPV: aOR 1.00 (0.21, 4.82)	NA	NA
Lekovich, 2015 [39]	302, HIV negative women with IUD placement between 2005 and 2012 and	Mean time b/w pre-IUD and post IUD HR-HPV test: 555 days (Copper	Hybrid Capture 2 test	Study groups matched on: age, high-risk HPV infection, rate of	Non-pregnant Copper IUD user	NA	NA	HR-HPV: Levonorgestrel vs. Copper IUD

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
	pre/post insertion HPV testing at participating U.S. institution, Mean age 33; *N=8 /152 cases Levonorgestrel IUD, 2/150 cases Copper IUD*	IUD), 534 days (Levonorgestrel IUD); IUD placement and repeat HR-HPV test: 356 (Copper IUD), 349 (Levonorgestrel IUD)		abnormal cytology and proportion of smokers				OR: 4.11, p=0.056
Louvanto, 2011 [40]	255, postpartum women in Finland, Mean age 26 (SD 3.1); *N=203 incident cases, 133 for HPV- species α7 and α9 included in analyses*	6Y; 0M, 2M, 12M, 24M, 36M, 6Y	Multiplex-HPV genotyping kit (Progen Biotechnik GmbH)	Age, HR-HPV seropositive at baseline, seroconverted to HR-HPV, # sexual partners until age 20, lifetime # sex partners, age initiation of OC use, marital status, employment status, age of onset of sexual activity, baseline PAP smear results, baseline oral HR-HPV DNA status, frequency of sex, # of births, oral sex, ever had STD, history of genital warts, history of oral warts, age initiation of smoking, pregnancy during follow-up, change in marital status during follow-up Final model (empirical strategy): age, seroconverted to HR-	Never used OC pills	OCP (ever use) on Species α7 and α9 HR- HPV: aIRR: (ns) NR (respectively)	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
				HPV, # sexual partners until age 20, lifetime # sexual partners, age initiated OC use, smoking, pregnancy during follow-up, change in marital status during follow-up				
Marks, 2011 [41]	1135, HIV-negative women ages 20-37 in Thailand, reporting no commercial sex work in past 6M and willing to adhere to self-selected contraceptive method for at least 1Y; *N=269 (8%) incident cases for any HPV, 157 (4.7%) incident HR-HPV cases*	18M; 0M, 6M, 12M, 18M	QIAamp DNA Blood Kit (Qiagen), HPV Linear Array, PCR assay (Roche Diagnostics)	Age, study site, # live births, male condom use P6M, age sexual debut, # lifetime partners, # partners P6M, smoking P6M, cervical cytology at enrollment and follow-up, BV at enrollment, prior STI infection, cervical ectopy Final model (empirical strategy): age, study site, # of lifetime and recent sexual partners, new sexual partner, concurrent BV, duration of HC use	Non-hormonal user during same interval of assessment	COC on HPV (any type) aOR: 1.27 (0.93, 1.74); HR-HPV aOR: 1.22 (0.81, 1.83)	DMPA on HPV (any type) aOR: 0.90 (0.63, 1.31), HR-HPV aOR: 0.87 (0.55, 1.35)	NA
Moscicki 2001 [26]	105, women aged 13 to 21 attending 2 family planning clinics in San Francisco, USA; *N=54 incident cases*	Median follow-up: 50M [IQR: 23-79M]; ~4-6M (9 median visits, IQR: 4-15)	PCR assay; B-globin control; dot blot and Roche reverse blot method (Roche Molecular Systems)	Rate of new partners per month since last visit, history of HSV, history of vulvar warts, lifetime sexual partners, marijuana use	Non-current OCP user	OCP on HPV (any type) aHR 0.49 (0.28, 0.86)*	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
				Final model: rate of new partners per month since last visit, history of HSV, history of vulvar warts.				
Nielsen, 2009 [42]	6246, women aged 20-29 in Copenhagen, Denmark, randomly sampled from general population; *N*= 798 *(12.8%) HR-HPV incident cases*	2Y; 0M and 2Y[e]	Hybrid Capture 2 and LiPA V2 PCR assay (Innogenetics); B-globin control	Age, # sexual partners, marital status, self-reported history of chlamydia, self-reported history of genital warts, parity, current condom use, amount of smoking Final model (empirical strategy): age, # of sexual partners during follow-up, marital status, interaction between marital status and number of sexual partners during follow-up	Current non-hormonal user	OCP on HR-HPV: ≤2Yr aOR: 1.01 (0.68, 1.50), 3-4Yr aOR: 1.39 (0.98, 1.99); 5-6Yr aOR: 1.44 (1.00, 2.07); 7+Yr aOR: 1.66 (1.17, 2.35)*, Per Yr): 1.04 (0.98, 1.10)	NA	NA
Phelan, 2009 [43]	220, HIV+ and HIV women ages 18+ who reported injection drug use in past 10 years in Baltimore, USA; Mean age 37 (SD 6.6); *Detection of new type-specific HPV cases 22% of 775 visits*	5Y; 0M and every 6M	PCR assay; B-globin controls, oligonucleotide dot blot hybridization	Age, HIV status and CD4 category, smoking in P6M, injection drug use P6M, marijuana use P6M, any STD P6M, # male sex partners P6M, # male sex partners P10Y, # live lifetime births Final model (empirical and theoretical approach): age, HIV	Never user of OC (lifetime)	OCP (ever): Not significant at univariate level (among HIV+ or HIV- women) so multivariate not reported	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
				status and CD4 level, crack use in P6M, # of male sex partners in P10Y				
Sellors, 2003 [28]	253, Canadian women ages 15 to 49 in selected physician practices; *28 incident HPV cases (11.1%)*	1Y; 0M and 12M	PCR assay with HPV-genotyping; HCII assay for HR-HPV detection	Age, median number of sex partners in the last year, median number of lifetime sex partners, marital status, smoking status	Non-OCP user	OCP on HR-HPV aOR: 0.70 (0.20, 2.0)	NA	NA
Shew, 2015 [44]	150, adolescents ages 14-17 in Indianapolis, U.S. visiting one of 3 primary care clinics	Mean follow-up: 5.8Y (3.9-9.2); Every 3M	Linear array HPV genotyping test (Roche Diagnostics) and PCR assay with B-globin control	STIs (clinic test): CT, NG and TV; contraceptive use, condom use, coital frequency, number of partners	Non-user of OCP in last 3M, Non-user of DMPA in last 3M, respectively	OCP on HPV (all types) aHR: 2.0 (1.28, 3.15)*; HR-HPV aHR: 1.31 (0.73, 2.35); LR-HPV aHR: 2.73 (1.52, 4.90)*	DMPA on HPV (all types) aHR: 0.96 (0.67, 1.38); HR-HPV aHR: 0.80 (0.54, 1.19); LR-HPV aHR: 1.57 (0.90, 2.75)	NA
Winer, 2003 [27]	553, university women in Seattle, USA ages 18-20; *incident cases (all HPV type) among OCP users: 92 per 503 PY vs. 56/553 PY among non-OCP users*	5Y; 4M intervals	PCR assay and dot-blot hybridization with B-globin control	Time interval, current smoking, history of non-genital warts, history of tampon use, being delivered by cesarean section, length of time having known a partner, partner's ethnicity, partner's age, partner's educational level, partner's lifetime number of partners, partner's circumcision status, condom use with a new partner.	Non-OCP user	OCP on HPV (all types) aHR: 1.40 (1.01, 1.80)*	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference Group	OCP[a]	Injectable	IUD or Combined HC
				Whether partner had ever had a STI, subject/partner alcohol use during sex. Final model: no. sex partners, condom use with new partners, sex partner's no. of other partners, new partner in past 12 M, time knowing partner before sex, current smoker				
Winer, 2016 [45]	420, women aged 25-65 in the USA sampled from internet dating group; *cumulative incidence of HR-HPV: 25.4%*	Mean follow-up: 12.5M +/- 5M; Mean interval b/w assessment: 5.1M +/- 1.4M	PCR assay with B-globin controls, Roche Linear Array genotyping test	Age at first sex, (time dependent variables): age, marital status, smoking history, abnormal PAP history, current HC use, menopausal status, sex with ≥1 male partner in past 6M, lifetime # sex partners Final model (empirical strategy): lifetime # of male sex partners, and male sex partners in the P6M (women with ≥1 partner in P6M)	Current non-hormonal user	NA	NA	Any HC use on HR-HPV, all women aHR: 1.82 (1.17, 2.83)*; Women with no sex partners in P6M aHR: 4.16 (1.27, 13.63)*; Women with ≥ 1 partner in P6M aHR: 1.65 (1.05, 2.59)*

Notes: PY: person-years at risk; aOR: adjusted odds ratio; aHR: adjusted hazard ratio. HR-HPV: high-risk HPV, LR-HPV: low-risk HPV. *p<0.05; #p=0.056;

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate (NE-ENT) use.

[c] Case control study.

[d] Former user defined as having stopped using method at least one year before colposcopy-biopsy. Recent use defined as having used that method within 6 months of biopsy.

[e] Contraceptive use exposure period retrospectively recalled, exceeds study follow-up duration.

Table 2. Prospective associations between hormonal contraceptive use and herpes simplex virus type 2 (HSV-2) (N=4).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Length of follow-up; frequency STI assessment	Covariates	Reference group	OCP[a]	Injectable	Combined HC
Borgdorff, 2015 [37]	163, HIV-negative sex workers in Kigali, Rwanda ages 18 to 49, *N=21 HSV-2 incident cases*[c]	24M; 0M, 3M, 6M, 12M, 24M	HerpeSelect 2 ELISA (index ≥3.5 defined as positive)	24M; 0M, 3M, 6M, 12M, 24M	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	OCP aOR: 4.28 (0.07, 262.1)	Injectable (type not specified[d]) aOR: 6.34 (0.25, 158.5)	NA
Chohan, 2009 [53]	297, HIV-negative sex workers in Mombasa, Kenya ages 18 to 46, N=*115 HSV-2 incident cases (23 cases per 100 PY)*[b]	13Y; every 1M (median time b/w visits: 33d [IQR 28-48]	HSV-2- type-specific HSV-2 gG based ELISA (index value of >1.1 defined as positive)	13Y; every 1M (median time b/w visits: 33d [IQR 28-48]	Education, parity, alcohol and tobacco use, vaginal washing practices, bar vs. night club work. Time-dependent variables: age, duration of sex work, presence of other genital tract infections, # sex partners per week, condom use during past working week Final model: duration of sex work, bar (vs. night club) work, # sex partners per week, percentage condom use past week, presence of BV	Non-hormonal user	OCP aHR: 0.50 (0.23, 1.08)[#]	NA	aHR Norplant/ DMPA (combined): 0.92 (0.53, 1.61)

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Length of follow-up; frequency STI assessment	Covariates	Reference group	OCP[a]	Injectable	Combined HC
Grabowski, 2015 [35]	682, HIV-negative women in Rakai, Uganda ages 15 to 49 who had a HIV-negative male partner, N=*52 HSV-2 incident cases*[e]	3Y; 0M, 12M & 24M	HSV-2 ELISA test	3Y; 0M, 12M & 24M	Age, education of woman and male partner, # of lifetime sexual partners. Time-varying variables: male circumcision, coital frequency, and female and male self-report of any condom use and non-marital partners in the past year. Final model: did not include coital frequency or male circumcision based on model fit	Non-pregnant non-hormonal user	OCP aHR: 0.49 (0.08, 3.01)	Consistent DMPA users aHR: 2.26 (1.09, 4.69)*; Initiated DMPA aHR: 0.75 (0.29, 1.92); Discontinued DMPA use aHR: 0.58 (0.13,2.51)	NA
Socias, 2017 [54]	149, HIV-positive (N=13) and HIV-negative (N=136) sex workers in Vancouver, Canada ages 14+, *N=39 HSV-2 incident cases;* 17.1 cases per 100 PY (12.4, 23.6)	4Y; every 4M	Serum samples via non-specific EIA HSV IgG. If reactive, anti-HSV-2 using TSS Focus HerpeSelect-2 IgG EIA (Focus Diagnostics)	4Y; every 4M	Time invariant: Age, indigenous ancestry, education. Time-varying: HIV status, incident STIs (*T. pallidum*, NG and CT), average # of clients per week, # male non-commercial partners, inconsistent use of condoms by clients and non-clients, respectively, type of sex work venue Final model (stepwise selection): type of sex work venue	Non-DMPA user in prior 6M	NA	HIV positive and negative DMPA users aHR: 4.43 (1.90, 10.35)*; HIV negative DMPA users aHR: 3.97 (1.64, 9.60)*	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05. # Marginally significant at p=0.08;

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] *10 women seroconverted to HSV-2 & HIV-1 at same visit; PY: person-years; NA: not assessed by study.*

[c] Women censored after first incident infection.

[d] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate use.

[e] Excluding incident cases among pregnant women.

Table 3. Prospective associations between hormonal contraceptive use and *Chlamydia trachomatis* (CT) (N=9).

Study	N, study sample, *N of incident cases or incident rate*	Length of follow-up; frequency STI assessment	STI Diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Borgdorff, 2015 [37]	397, HIV-negative sex workers in Kigali, Rwanda ages 18-49; *N=30 incident cases*[b,e]	12M; 0M, 6M, 12M	Endocervical swabs via Amplicor CT/NG PCR test (Roche Diagnostics)	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	OCP aOR: 6.13 (1.5, 23.8)*	Injectable (type not specified[d]) aOR: 2.24 (0.69, 7.29)	NA
Baeten, 2001 [21]	948, HIV-1 negative sex workers in Mombasa, Kenya ages 16-48; N=175 incident cases (11.1/100 PY)	Range 15 to 2366 days (median: 421 days); median time b/w visits: 35 days	Enzyme-linked immunoabsorbent assay (ELISA) (Microtrak)	Age, years of education, years of prostitution, parity, number of sexual partners, place of work (ie, bar vs. nightclub), number of sexual contacts, and condom usage	No contraceptives or tubal ligation	OCP aHR: 1.8 (1.1, 2.9)*	DMPA aHR: 1.6 (1.1, 2.4)*	NA
Kapiga, 2009 [47]	958, HIV negative women ages 16 to 62 in Lusaka, Zambia (ZA), Moshi Tanzania (TZ) and Durban/Hlabisa, South Africa (SA); *Incidence rate*[b]*: 19.5/100 PYAR (SA); 4.9/100 PYAR (TZ, ZA)*	12M, every 3M	TZ/ZA site: endocervical swabs via enzyme-linked immunosorbent assay (ELISA), (Murex Biotech); SA site: urine samples via BD Probe Tec ET assay[c]	Age, site, partner earns income, # sex partners, frequency vaginal sex in past 1W, anal sex in past 3M, other STIs, bacterial vaginosis, candida, abnormal vaginal discharge on exam, abnormal cervical discharge on exam, incident HIV Final model (empirical approach): site, age, # sex partners, incident HIV infection and *N. gonorrhoeae* infection (SA model); site, presence of candida and abnormal vaginal discharge on exam (TZ/ZA model)	Not specified	OCP Durban/Hlabis ,SA aOR: NR (ns); Moshi TZ/Lusaka ZA site aOR: NR (ns)	DMPA Durban/Hlabis, SA aOR: 1.8 (1.0, 3.3)*; DMPA Moshi TZ/Lusaka ZA site aOR: NR (ns)	Norplant Durban/Hlabis,SA aOR: NR (ns); Norplant Moshi TZ/Lusaka ZA site aOR: NR (ns)
Louv, 1989 [23]	818, U.S. women ages 19 to 29 attending a STI clinic in Birmingham Alabama; *N=214 incident cases*[b]	6M; Monthly	Fluorescein-tagged antibody; Microtrak Culture confirmation (Syva CO)	Age, mean number of sex acts per month, mean number of partners during follow-up period, parity, gravidity	Tubal ligation or IUD user	COC: aHR: 1.73 (1.08, 2.77)*	NA	NA

Study	N, study sample, *N of incident cases or incident rate*	Length of follow-up; frequency STI assessment	STI Diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Lavreys, 2004 [22]	242, HIV-1 positive commercial sex workers attending STI clinic in Mombasa, Kenya; *N=26 incident cases, incidence rate: 7.7/100 PY*	Median follow-up 35M (IQR: 11-62M); Every 1M	Antigen test by ELISA (Microtrak, Syva)	Age, years of education, years of sex work, parity, workplace, number of sexual partners per week, condom use	No contraception or tubal ligation	OCP: aHR 2.20 (0.70, 7.30)	DMPA: aHR 3.10 (1.0, 9.4)#	NA
Masese, 2013 [51]	865, HIV positive and HIV-negative women who report engaging in transactional sex, ages 18 to 50 in Mombasa, Kenya; *N=101 incident cases[b], incidence rate = 5.0/100 PY*	4Y, every 1-3M	Endocervical swab via Gen-Probe Aptima GC/CT Detection System	Age, vaginal microbiota, place of work (bar vs. nightclub or home based/ other), educational level, marital status, unprotected intercourse in past wk, # of sex partners in past wk, vaginal washing, presence of other genital tract infections (*T. vaginalis*, *C. albicans*, *N. gonorrhoeae*), HIV-1 serostatus, and cervical ectopy Final model (empirical approach): Age, unprotected sex with >1 sex partner in past week, HIV status, *N. gonorrhoeae* infection	Non-hormonal user	OCP aHR: 0.2 (0.0, 1.7)	DMPA aHR: 1.8 (1.1, 3.0)*	NA
Pettifor, 2009 [48]	567, HIV-negative women ages 18 to 40 recruited from family planning clinics in Orange Farm, South Africa; *N=119 incident cases[b], incident rate: 28.2 per 100 PY*	1Y; every 3M	Urine sample via ligase chain reaction (LCx®; Abbot Laboratories)	Age, relationship status, education, frequency of sex in the past 3M, # partners in the past 3M, condom use in the past 3M, vaginal douching past 3M, age of first sex Final model (empirical and theoretical approach): Age, education, condom use consistency in past 3M	Non- pregnant, non-hormonal user	NA	DMPA aIRR: 1.24 (0.80, 1.94); NET-EN aIRR: 0.91 (0.59, 1.43)	NA

Study	N, study sample, *N of incident cases or incident rate*	Length of follow-up; frequency STI assessment	STI Diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Romer, 2013 [50]	342, adolescent girls ages 14-17 attending clinics in inner-city areas of Indianapolis, USA; *N=165 incident cases*[b]	Originally 27M, extended to 5Y for some participants; every 3M	Clinician obtained cervical samples or self-obtained vaginal swabs via nucleic acid amplification tests (NAATs) (Amplicor PCR, Roche Diagnostics)	Age, positive STI test at start of period, # of partners in past 3M, # of lifetime partners, # of sexual events in last 3M (diary period), # of unprotected sexual events in last 3M (diary period)	Non-hormonal user	NA	DMPA, use in past 3M aOR: 0.76 (0.45, 1.31); DMPA used 3-6M ago aOR: 1.17 (0.69, 1.96)	NA
Russell, 2016 [52]	225, HIV-negative women recruited from outpatient clinics ages 15-35 who had lower genital tract infection or were biologically at risk of STI infection from Pittsburgh PA, USA; *Incidence rate: 48 women tested positive, 28 per 100 PY*[c] *incident rate*	Median 12M FU; 0M, 1M, 4M, 8M, 12M	Endocervical swab via nucleic acid amplification tests (NAATs)	Age, education, site of *C. trachomatis* (CT) infection at enrollment (cervix vs. cervix/endometrium, or uninfected), GN infection during follow-up, STI diagnosis among partner during follow-up, # of male partners since last visit, new male partners since last visit, sex with uncircumcised male in last 3M, condoms (reported at any visit) Final model (empirical approach): age, *N. gonorrhoeae* during follow-up, site of CT infection, CT infection by partner during follow-up, new male partner since last visit, sex with uncircumcised male last 3M	Non-user of OCP or DMPA, respectively	OCP aHR: NR (ns)	DMPA aHR: 1.03 (0.59, 1.78)	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05. # p=0.05

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only) is noted.

[b] Multiple incident cases per woman were allowed, i.e., incident cases defined as a positive test following a negative test.

[c] Incident infection defined as any positive test during follow-up.

[d] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate (NE-ENT) use.

[e] Excluding cases among pregnant women.

Table 4. Prospective associations between hormonal contraceptive use and *Neisseria gonorrhoeae* (NG) (N=7).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Borgdorff, 2015 [37]	381, HIV-negative sex workers in Kigali, Rwanda ages 18 to 49, *N=42 incident cases* [b,d]	12M; 0M, 6M, 12M	Endocervical swab via Amplicor CT/NG PCR test (Roche Diagnostics)	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	OCP aOR: 2.57 (0.78, 8.45)	Injectable (type not specified[c]) aOR: 0.80 (0.28, 2.31)	NA
Baeten, 2001 [21]	948, HIV-1 negative sex workers in Mombasa, Kenya ages 16-48; N=272 incident cases (16.5/100 PY)	Range 15 to 2366 days (median: 421 days); median time b/w visits: 35 days	Culture on Thayer-Martin media	Age, years of education, years of prostitution, parity, number of sexual partners, place of work (ie, bar vs. nightclub), number of sexual contacts per week, and condom usage	No contraception or tubal ligation	OCP aHR: 1.4 (0.9, 2.1)	DMPA aHR: 1.1 (0.8, 1.6)	NA
Louv 1989 [23]	818, U.S. women ages 19 to 29 attending a STI clinic in Birmingham Alabama; *N=155 incident cases* [b]	6M; Monthly	Gram stain or oxidase reagent (Marion Scientific), confirmation by Rapid NH system (Innovative Diagnostic Systems)	Age, mean number of sex acts per month, mean number of partners during follow-up period, parity, gravidity	Tubal ligation or IUD user	COC: aHR: 1.70 (1.05, 2.76)*	NA	NA
Lavreys 2004 [22]	242, HIV-1 positive commercial sex workers attending STI clinic in Mombasa, Kenya; *N=119 incident cases, incidence rate: 14.9/100 PY*	Median follow-up 35M (IQR: 11-62M); Every 1M	Antigen test by ELISA (Microtrak, Syva)	Age, years of education, years of sex work, parity, workplace, number of sexual partners per week, condom use	No contraception or tubal ligation	OCP: aHR 0.6 (0.3, 1.3)	DMPA: 1.0 (0.6, 1.7)	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Kapiga, 2009 [47]	958, HIV negative women ages 16 to 62 in Lusaka, Zambia (ZA), Moshi Tanzania (TZ) and Durban/Hlabisa, South Africa (SA), *Incidence rate[a]: 16.5/100 PYAR (SA); 5.3/100 PYAR (TZ, ZA)*	12M; every 3M	TZ and ZA: culture methods used. SA: urine sample via BD Probe Tec ET assay	Age, site, partner earns income, # sex partners, frequency vaginal sex past 1W, anal sex past 3M, other STIs, BV, candida, abnormal vaginal discharge on exam, abnormal cervical discharge on exam, incident HIV Final model (empirical approach): site and incident HIV infection (SA model); age (TZ/ZA model)	Not specified	OCP Durban/Hlabisa SA site: aOR: NR (ns); Moshi TZ/Lusaka ZA site aOR: NR (ns)	DMPA Durban/Hlabisa SA site: aOR: NR (ns); Moshi TZ/Lusaka ZA site aOR: NR (ns)	Norplant Durban/Hlabisa SA site: aOR: NR (ns); Moshi TZ/Lusaka ZA site aOR: 4.7 (1.3, 16.5)*
Pettifor, 2009 [48]	567, HIV-negative women ages 18 to 40 recruited from family planning clinics in Orange Farm, South Africa; *N=45 incident cases [b] incident rate: 9.9 per 100 PY*	1Y; 0M, 2M, 6M, 8M and 12M (NET-EN users) or 0M, 3M, 6M, 9M and 12M (DMPA users and controls)	Urine sample via ligase chain reaction (LCx®; Abbot Laboratories)	Age, relationship status, education, frequency of sex past 3M, # sex partners past 3M, condom use past 3M, vagina douching past 3M, age of first sex Final model (empirical and theoretical approach): Age, education and condom use consistency in past 3M	Non-pregnant non-hormonal user	NA	DMPA aIRR: 1.30 (0.58, 2.98); NET-EN aIRR: 1.11 (0.55, 2.25)	NA
Romer, 2013 [50]	342, adolescent girls ages 14-17 attending clinics in inner-city areas of Indianapolis, USA; *N=65 incident cases [b]*	Originally 27M, extended to 5Y for some participants; every 3M	Nucleic acid amplification tests (Amplicor CT/NG PCR; Roche Diagnostics). Positive results confirmed by Gen-Probe	Age, positive STI test at start of period, # of sexual partners in past 3M, # of lifetime sexual partners, # of sexual events in last 3M (diary period), # of unprotected sexual events in last 3M (diary period)	Non-hormonal user	NA	DMPA use in current 3M period aOR: 1.19 (0.57, 2.48); DMPA use in prior 3M aOR: 1.12 (0.54, 2.32)	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05.

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] Multiple incident cases per woman were allowed, i.e., incident cases defined as a positive test following a negative test.

[c] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate use.

[d] Excludes cases among pregnant women.

Table 5. Prospective associations between hormonal contraceptive use and *Chlamydia trachomatis* (CT) or *Neisseria gonorrhoeae* (NG) (combined) (N=2).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Low 2014 [55]	172, HIV-1 positive women on antiretrovirals who engage in transactional sex in Bobo-Dioulasso Burkina Faso, ages 18 to 50, *N=11 incident cases GN; rate of 2.76 cases per 100 PY; 3 incident cases CT, rate of 0.75 per 100 PY* [b]	4Y; 0M, ~3-6M	Cervical swab via PCR (Amplicor CT/NG PCR assay, Roche) using pooling approach	Age, education, tobacco use, # sex acts past wk, alcohol use, sex work, condom use, vaginal washing, antibiotic use past 1M, abnormal vaginal discharge on exam, genital ulcers on exam, abnormal cervical exam, genital warts, concurrent BV, *T. vaginalis*, *Candida albicans*, or HSV-2 DNA, presence of Y-PCR, HIV-1 plasma viral load, HIV-1 eCVL RNA detected, CD4 count, time since sample collection, antiretroviral status Final model (empirical and theoretical approach): # sex acts past wk, CD4 count, education	Non-hormonal user	OCP aOR: ns (NR)	DMPA on NG/CT aOR: 5.83 (0.90, 37.70)	NA
Morrison 2004 [25]	819, women attending 2 reproductive health clinics in Baltimore, USA ages 15 to 45. N=45 incident cases of CT or GN; 6.2 per 100 PY.	3, 6 and 12M	CT by ligase chain reaction (LCx; Abbott Laboratories). GN by Gram stain, oxidase reaction, lactamase and production. Confirmation by Gonocheck II (E-Y Laboratories).	Age, race, and site and measures of contraceptive exposure.	Non-hormonal user	COC aHR: 1.5 (0.6, 3.5)	DMPA: aHR: 3.6 (1.6, 8.5)	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05.

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] Incidence is new cases of NG or CT during study period, divided by number of women at risk; cases at baseline excluded.

Table 6. Prospective associations between hormonal contraceptive use and *Treponema pallidum* (syphilis) (N=3).

Study	(N), study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant
Borgdorff, 2015 [37]	354, HIV-negative sex workers in Kigali, Rwanda ages 18 to 49, *N=4 incident cases* [b]	12M; 0M, 6M, 12M	Spinreact Raplid Plasma Reagin test, confirmation by Spinreact T. pallidum Haemagglutination test	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	NA	Injectable (type not specified[b]) aOR: 1.43 (0.11, 19.1)	NA
Baeten, 2001 [21]	948, HIV-1 negative sex workers in Mombasa, Kenya ages 16-48; N=48 incident cases (2.9/100 PY)	Range 15 to 2366 days (median: 421 days); median time b/w visits: 35 days	Hemagglutination assay (Biotech Laboratories)	Age, years of education, years of prostitution, parity, number of sexual partners, place of work (ie, bar vs. nightclub), number of sexual contacts per week, and condom usage	Non-hormonal user or tubal ligation	OCP aHR: 0.40 (0.10, 1.50)	DMPA aHR: 0.50 (0.20 1.4)	NA
Kapiga, 2009 [47]	958, HIV negative women from general population ages 16 to 62 in Lusaka, Zambia (ZA), Moshi Tanzania (TZ) and Durban/Hlabisa, South Africa (SA), Incidence rate[b]: 7.5/100 PY (all sites)	12M; every 3M	Positive serum reaction after both a rapid plasma reagin card test and treponema pallidum haemagglutination assay (TPHA) or microhaemagglutination assay-treponema pallidum (MHA-TP)	Age, site, partner earns income, # sex partners, frequency vaginal sex in past wk, anal sex in past 3M, other STIs, bacterial vaginosis, candida, abnormal vaginal discharge on exam, abnormal cervical discharge on exam, incident HIV infection Final model (empirical selection): site, age, husband/partner earns income, frequency of vaginal sex past wk, T. vaginalis	Not specified	OCP All sites aOR: NR (ns)	All sites, DMPA: aOR: NR (ns)	All sites, Norplant aOR: NR (ns)

Notes: PY: person-years at risk. * Statistically significant at p<0.05.

[a] OCP type was unspecified unless COC (combined oral contraception) or POP (progestin-only pill) is noted.

[b] Multiple incident cases per woman were allowed; included positive serology results from baseline, incident cases defined as a positive test following a negative test.

Table 7. Prospective associations between hormonal contraceptive use and *T. vaginalis* (TV) (N=9).

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant or combined HC
Balkus, 2014 [34]	2920, HIV-negative women ages 18+ with no-drug use in past 12M in Blantyre, Lilongwe Malawi; Durban, Hlabisa, South Africa; Philadelphia USA; Lusaka Zambia; Harare, Chitungwiza, Zimbabwe, Detection at *N=400 of 16,259 visits*[d]	12 to 30 M; 0M, 12M, 30M (or study exit)	Vaginal wet mount via saline microscopy	Age, marital status, unprotected sex in the last week, T. vaginalis at baseline, intermediate Nugent score, BV at prior visit	Non-pregnant non-hormonal user	OCP aHR: 0.64 (0.47, 0.89)*	Injectable (type not specified) aHR: 0.60 (0.47, 0.78)*	Implant (type not specified) aHR: 0.57 (0.20, 1.60)
Baeten, 2001 [21]	948, HIV-1 negative sex workers in Mombasa, Kenya ages 16-48; N=435 incident cases (26.4/100 PY)	Range 15 to 2366 days (median: 421 days); median time b/w visits: 35 days	Vaginal wet mount	Age, years of education, years of prostitution, parity, number of sexual partners, place of work (ie, bar vs. nightclub), number of sexual contacts per week, and condom usage	Non-hormonal user or tubal ligation	OCP aHR: 0.90 (0.70, 1.30)	DMPA aHR: 0.60 (0.40 1.0)*	NA
Barbone [24]	818, U.S. women ages 19 to 29 attending a STI clinic in Birmingham Alabama; *N=171 incident cases*[e]	6M; Monthly	Vaginal wet mount	Spermicide use, sexual activity, age, race	Tubal ligation or IUD user	OCP: aHR 0.56 (0.39, 0.81)*	NA	NA

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant or combined HC
Borgdorff, 2015 [37]	381, HIV-negative sex workers in Kigali, Rwanda ages 18 to 49, *N=89 incident cases*[b]	24M; 0M, 6M, 12M, 24M	Vaginal swab via culture kit (InPouch, BioMed Diagnostics) and Gram stain (presence of >20% clue cells and Nugent criteria). Considered positive if tested positive on either test.	Age, education, years worked as sex worker, breast-feeding, consistent condom use, antibiotic use past 14 d, ever used antibiotics, time duration between assessments	Non-pregnant non-hormonal user	OCP aOR: 0.61 (0.20, 1.84)	Injectable (type not specified[f]) aOR: 0.44 (0.17, 1.10)	NA
Brahmbhatt, 2014 [46]	2374, HIV+ (304) and HIV- (2070) women ages 15 to 49 in rural Rakai, Uganda[c]; N=96/2374 cases; 2.4/100 PY	12M; 0M, 12M	Self-collected vaginal swab via culture kit (InPouch, TV, BioMed Diagnostics)	10-year age group, marital status, education, # sex partners past 12M, SES (home building materials), Nugent score for BV, condom use, syphilis result, HIV status Final model (empirical and theory informed): age, marital status, education, SES, condom use and other STIs, interaction b/w HC use and HIV status	No method (neither hormonal or condom)	COC past 12M aIRR: 1.02 (0.40, 2.59); Consistently used COC (at baseline and follow-up) aIRR: 1.07 (0.25, 4.56)	DMPA past 12M aIRR: 0.54 (0.30, 0.98)*; Consistently used DMPA only (at baseline and follow-up) aIRR: 0.59 (0.28, 1.26)	Norplant past 12M aIRR: 3.01 (1.07, 8.49)*; Consistently used Norplant only (at baseline and follow-up) aIRR: 3.13 (1.08, 9.07)*

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant or combined HC
Kapiga, 2009 [47]	958, HIV negative women ages 16 to 62 in Lusaka, Zambia (ZA), Moshi Tanzania (TZ) and Durban/Hlabisa, South Africa (SA), Incidence rate: 31.9/100 PY (all sites)	12M; every 3M	Vaginal swab via Gram stain using Nugent criteria	Age, site, partner earns income, # sex partners, frequency vaginal sex in past 1W, anal sex in past 3M, other STIs, bacterial vaginosis, candida, abnormal vaginal discharge on exam, abnormal cervical discharge on exam, incident HIV infection Final model (empirical selection): site and incident HIV infection included in SA model and only age in TZ/ZA model	Not specified	OCP All sites aOR: 0.6 (0.3, 1.0)	All sites DMPA aOR: 0.7 (0.5, 1.0)	All sites Norplant aOR: NR (ns)
Pettifor, 2009 [48]	567, HIV-negative women ages 18 to 40 recruited from family planning clinics in Orange Farm, South Africa; *N=47 incident infections[b], incident rate: 10.2 per 100 PY*	1Y; 0M, 2M, 6M, 8M and 12M (NET-EN users) or 0M, 3M, 6M, 9M and 12M (DMPA users and controls)	Vaginal swabs via culture in Diamond's media	Age, relationship status, education, frequency of sex past 3M, # partners in past 3M, condom use in past 3M, vagina douching past 3M, age of first sex Final model (empirical and theoretical selection): Age, education, condom consistency in past 3M	Non-pregnant non-hormonal user	NA	DMPA aIRR: 0.35 (0.12, 1.01); NET-EN aIRR: 0.63 (0.30, 1.29)	NA
Pintye, 2017 [49]	1271, HIV-negative women enrolled during pregnancy and followed until 9M postpartum in western Kenya, median age 22 (IQR: 19-27),	~14M; 20, 24, 32 and 36 weeks gestation and post partum (2, 6, 10 and 14 weeks; 6 and 9 months)	Self-collected vaginal swabs treated with metronidazole, detection via wet mount microscopy	Final model (empirical selection): employment, male partner circumcision status, pregnancy status and other non-TV curable STIs (CT, NG, *T. pallidum*, BV or candidas) detected at enrolment.	Non-hormonal user	OCP aHR: NR (ns)	Injectable (type not specified) aHR: NR (ns)	Implant (type not specified) aHR: NR (ns)

Study	N, study sample	Length of follow-up; frequency STI assessment	STI diagnostic test	Covariates	Reference group	OCP[a]	Injectable	Implant or combined HC
	N=112 incident infections[b]; 10.4 per 100 PY							
Romer, 2013 [50]	342, adolescent girls ages 14-17 attending clinics in inner-city areas of Indianapolis, USA; *N=80 incident cases*[b]	Originally 27M, extended to 5Y for some participants; every 3M	Detection of T vaginalis DNA was performed using a modification of the Amplicor CT/NG PCR assay that included primers and probes specific for T vaginalis.	Age, positive STI test at start of period, # of partners in past 3M, # of lifetime partners, # of sexual events in last 3M (diary period), # of unprotected sexual events in last 3M (diary period)	Non-hormonal user	NA	DMPA use in current 3M period aOR: OR: 0.66 (0.32, 1.36); DMPA use in prior 3M aOR: 1.04 (0.52, 2.08)	NA

Notes: PY: person-years at risk. * Statistically significant at p<0.05.

[a] OCP type was unspecified unless COC (combined oral contraception)) or POP (progestin-only pill) is noted.

[b] Multiple incident cases per woman were allowed, i.e., incident cases defined as a positive test following a negative test.

[c] All women tested negative for T. vaginalis at baseline. Incident cases were number of T. vaginalis positive women at follow-up (only 1 follow-up).

[d] Women censored after first T. vaginalis incident, or if became pregnant, acquired HIV or tested positive for CT or NG. N=211 women who tested positive for T. vaginalis at baseline were included and prescribed treatment; N=39 [18%] of these women were also infected at the subsequent visit.

[e] Women censored after first T. vaginalis incident.

[f] Injectable type not reported but authors note most commonly DMPA in setting with occasional norethisterone enanthate use.

Figure 1. PRISMA Flow Chart

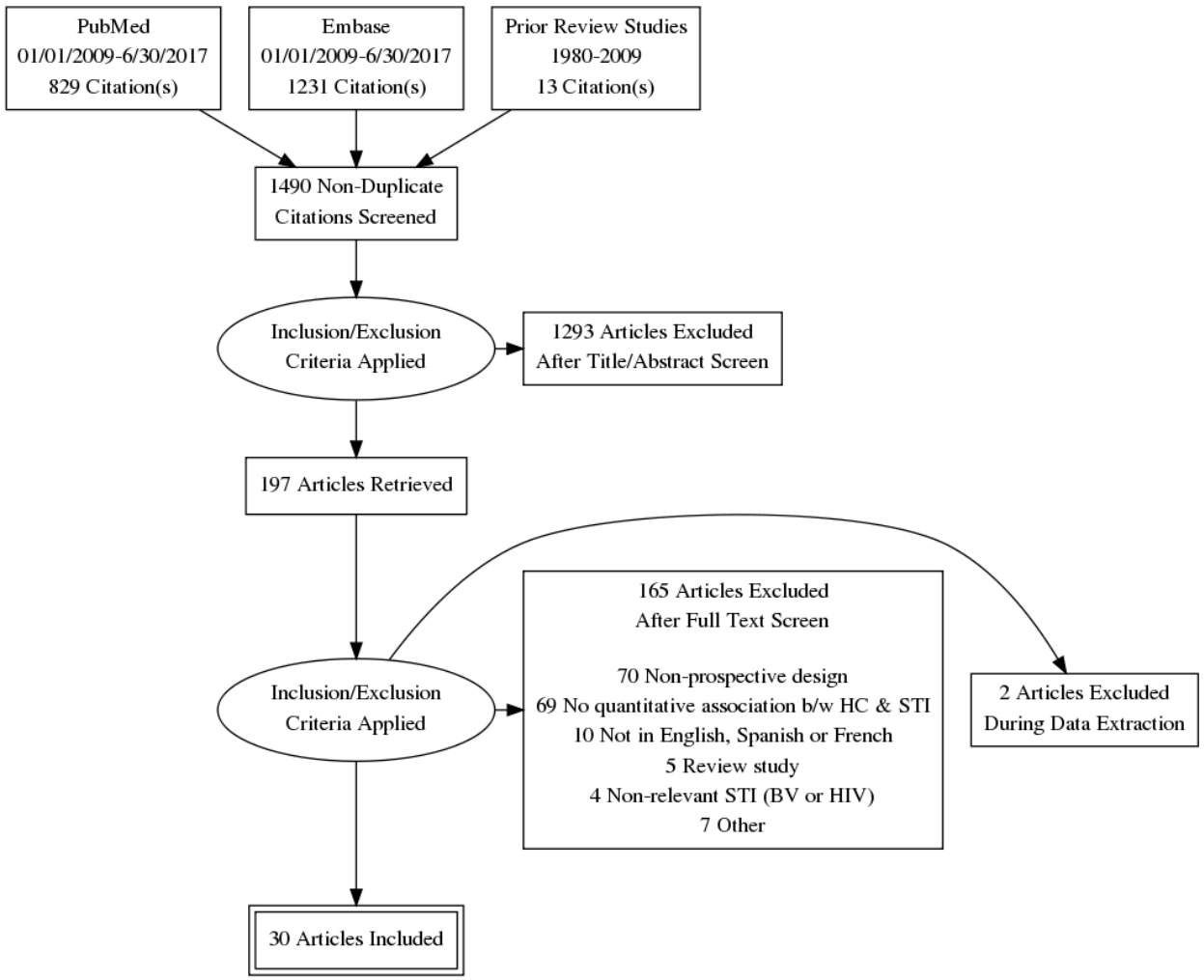
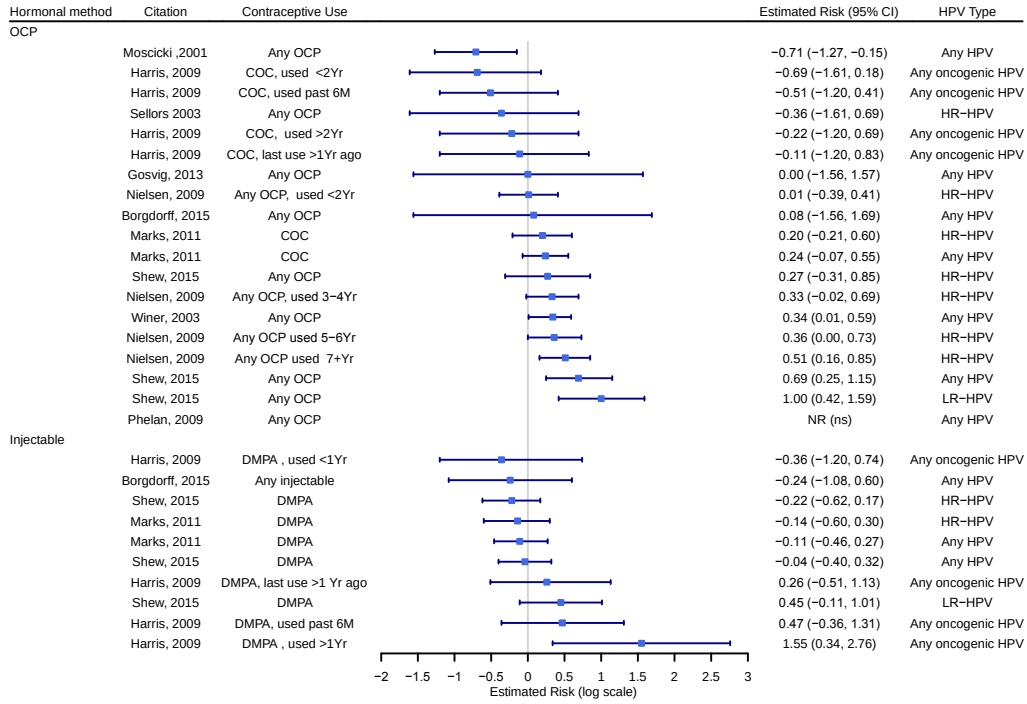


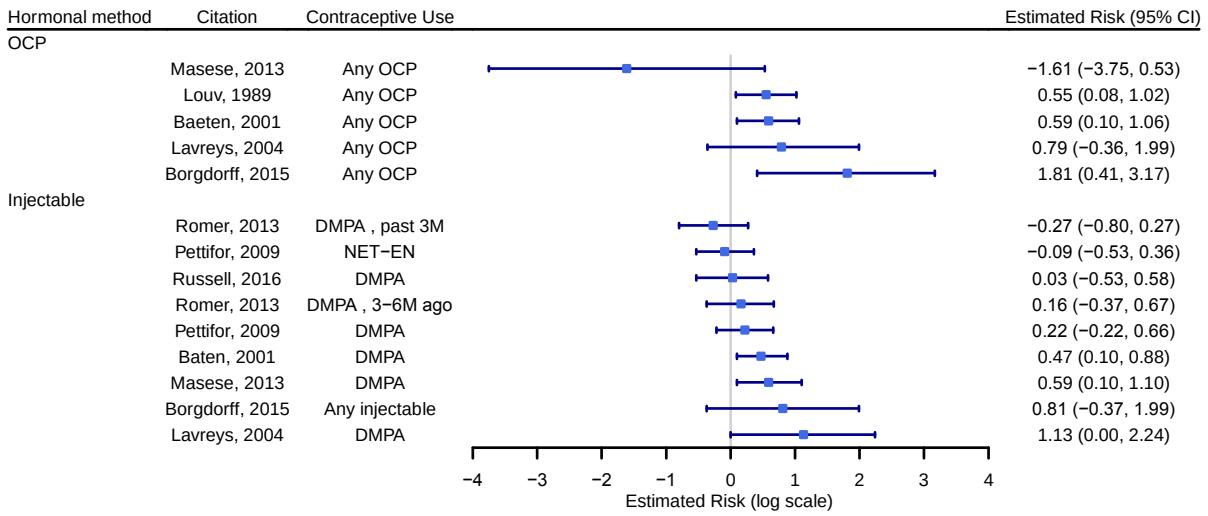
Figure 2. Use of hormonal contraception and human papillomavirus (HPV) infection.



Notes: Findings are presented from studies considered to be high and moderate quality.

NR (ns): estimate not reported due to non-significance. Estimated risk is log transformed adjusted odds ratio, adjusted hazard ratio or adjusted rate ratio; OCP: oral contraceptive pill; COC: combined oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate. Studies which report multiple outcomes are distinguished by subgroup.

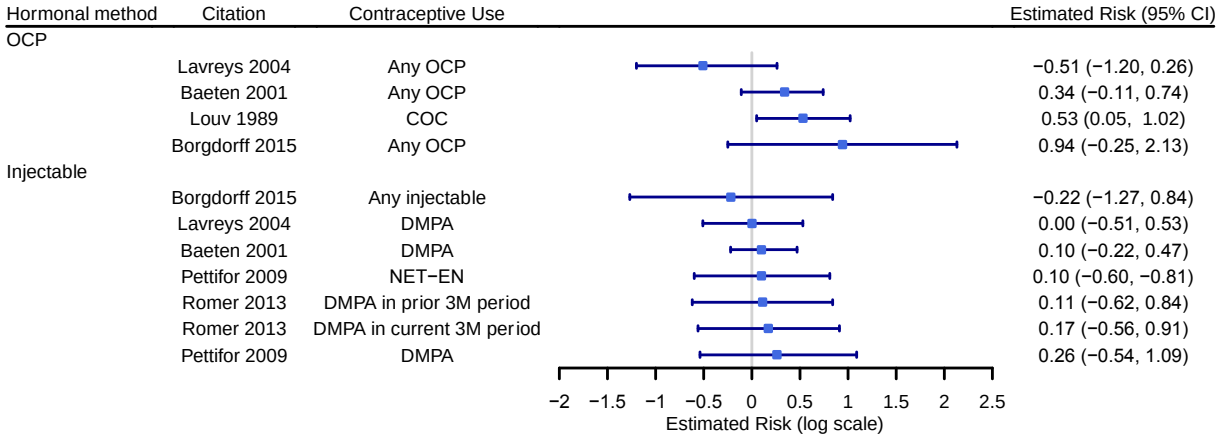
Figure 3. Use of hormonal contraception and *C. trachomatis* infection.



Notes: Findings are presented from studies considered to be high and moderate quality.

Estimated risk is log transformed adjusted odds ratio, adjusted hazard ratio or adjusted rate ratio; OCP: oral contraceptive pill; COC: combined oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate. Studies which report multiple outcomes are distinguished by subgroup.

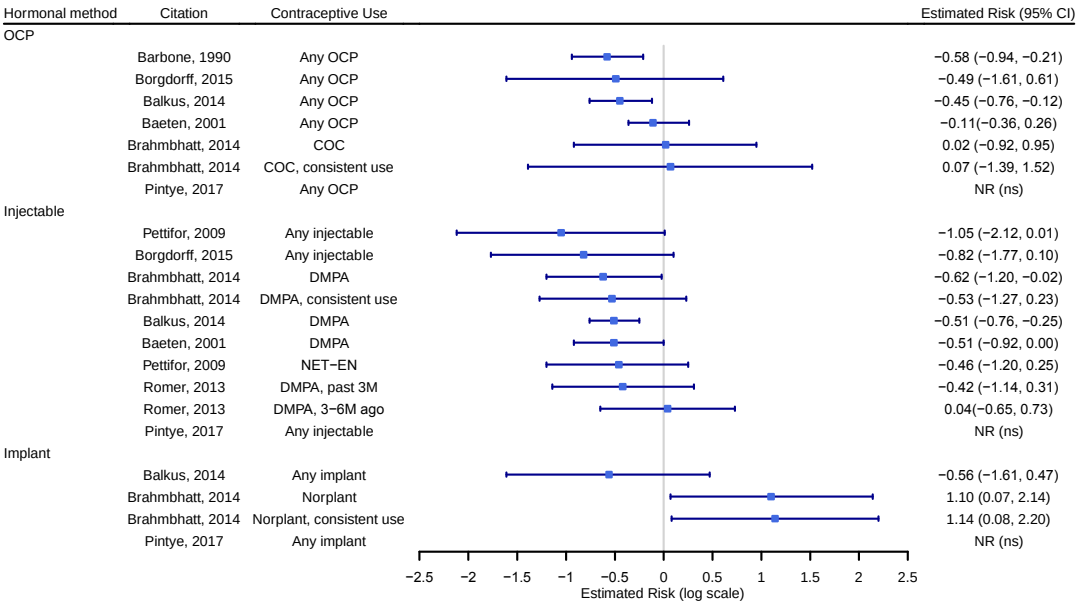
Figure 4. Use of hormonal contraception and *N. gonorrhoeae* infection.



Notes: Findings are presented from studies considered to be high and moderate quality.

Estimated risk is log transformed adjusted odds ratio, adjusted hazard ratio or adjusted rate ratio; OCP: oral contraceptive pill; COC: combined oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate. Studies which report multiple outcomes are distinguished by subgroup.

Figure 5. Use of hormonal contraception and *T. vaginalis* infection.



Notes: Findings are presented from studies considered to be high and moderate quality.

NR (ns): estimate not reported due to non-significance. Estimated risk is log transformed adjusted odds ratio, adjusted hazard ratio or adjusted rate ratio; OCP: oral contraceptive pill; COC: combined oral contraceptive pill; DMPA: Depot Medroxyprogesterone Acetate. Studies which report multiple outcomes are distinguished by subgroup.

List of Supplemental Digital Content

SDC Table 1: PRISMA checklist.

SDC Figure 1: Example search string: Pubmed and Embase.

SDC Table 2: Quality assessment of cohort studies.

SDC Table 3: Quality assessment of case control studies.

SDC Table 4: References 31-59.

Supplemental Digital Content Figure 1

Pubmed search string:

((((((hormonal AND contracepti*) OR ("hormonal methods")) OR ((progestin* OR progestins[MeSH] OR Progesterone[MeSH]) AND contracept*) OR (oral contracept*) OR OC OR POP OR ((((depo OR depot) AND medroxyprogesterone) OR depo medroxyprogesterone OR depo OR depot OR dmpa OR "Sayana Press" OR "net en" OR "NET-EN" OR "norethisterone enanthate" OR norethisterone-enanthate OR Medroxyprogesterone 17-Acetate[MeSH]) AND (contracept* OR inject*)) OR "Depo Provera" OR "Depo-Provera" OR (((levonorgestrel OR etonogestrel) AND implant) OR (uniplant OR jadelle OR implanon OR nexplanon OR norplant OR norplant2 OR sino-implant)) OR (hormonal, transdermal[MeSH] OR (contracept* AND patch)) OR (contracept* AND pill) 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 lunell 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 ortho evra)) AND ("Sexually Transmitted Infection"[MeSH] OR "STI" OR ("sexually transmitted infect*") OR "STD" OR "Gonorrhea"[MeSH] OR " gonorrhoeae" OR "Chlamydia"[MeSH] OR "chlamydia trachomatis" OR "Chancre"[MeSH] OR chancroid OR "haemophilus ducreyi" OR "Trichomonas"[MeSH] OR "Trichomoniasis"[MeSH] OR "trichomonas vaginalis" OR "TV" OR "Treponema pallidum"[MeSH] OR herpes OR herpesvirus OR "herpes simplex" OR "herpes virus" OR HSV OR "Human papillomavirus"[MeSH] OR "HPV" OR "Syphilis"[MeSH] OR "genital warts" OR "condylomata")) OR (injectable contracepti* STI) OR (oral contracepti* STI) OR (CT OR GC OR NG AND "sexually transmitted infection") OR (CT OR GC OR NG AND STI))) AND ("2009/01/01"[EDAT] : "2017/06/15"[EDAT]))

EMBASE search string

hormonal AND contracepti* OR 'hormonal methods' OR (progestin* OR 'progestins' OR 'progesterone' AND contracept*) OR ('oral' AND contracept*) OR 'OC' OR 'POP' OR ((depo OR depot) AND 'medroxyprogesterone') OR depomedroxyprogesterone OR depo OR depot OR dmpa OR 'sayana press' OR 'net en' OR 'net-en' OR 'norethisterone enanthate' OR (('medroxyprogesterone' AND '17-acetate') AND (contracept* OR inject*)) OR (('levonorgestrel' OR 'etonogestrel') AND 'implant') OR 'uniplant' OR 'jadelle' OR 'implanon' OR 'nexplanon' OR 'norplant' OR norplant2 OR 'sino implant' OR (hormonal AND transdermal) OR (contracept* AND patch) OR ('levonorgestrel' AND 'intrauterine' AND 'devices') 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' AND 'devices') OR ('contraceptive' AND agents) AND ring) OR 'nuvaring' OR 'nuva ring' OR (('contraceptive' AND 'devices') OR ('contraceptive' AND agents) AND patch) OR 'ortho evra' OR orthoevra AND ('sexually transmitted infection' OR STI OR 'sexually transmitted infections' OR STD 'sexually transmitted disease' OR 'sexually transmitted diseases' OR gonorrhea OR 'neisseria gonorrhoeae' OR chlamydia OR 'chlamydia trachomatis' OR chancre OR chancroid OR 'haemophilus ducreyi' OR trichomonas OR trichomoniasis OR 'trichomonas vaginalis' OR TV OR 'treponema pallidum' OR herpes OR herpesvirus OR 'herpes simplex' OR 'herpes virus' OR hsv OR 'human papillomavirus' OR hpv OR syphilis OR 'genital warts' OR condylomata) OR (injectable contracepti* STI) OR (oral contracepti* STI) OR (CT OR GC OR NG AND 'sexually transmitted infection') OR (CT OR GC OR NG AND STI) AND [humans]/lim AND [1-1-2009]/sd NOT [15-6-2017]/sd AND ([article]/lim OR [article in press]/lim)

Supplemental Digital Content Table 2: Quality assessment of prospective or retrospective cohort studies.

Citation	Study design	Reference group drawn from same community as HC users (2)	Ascertainment of HC use (2)	Demonstration STI not present prior to incident/recurrent infection (1)	Comparability of HC users and reference group cohorts demonstrated or adjusted for (2)	Ascertainment of STI based on biomarker and blind to HC status (2)	Adequate follow-up of cohort (<20% lost or unlikely to introduce bias) (1)	Total score Quality rating: High (8-10) Medium (5-7) Low (<5)
Balkus 2014 [34]	Secondary RCT	2	2	1	2	1	1	**9** (High)
Baeten 2001 [21]	PC	2	2	0	2	1	0	**7** (Medium)
Barbone 1990 [24]	Secondary RCT	2	1	1	1	1	0	**6** (Medium)
Borgdorff 2015 [37]	PC	2	2	1	2	1	1	**9** (High)
Brahmbhatt 2014 [46]	PC	1	1	1	2	1	0	**6** (Medium)
Chohan 2009 [53]	PC	1	1	1	2	1	1	**7** (Medium)
Gosvig 2013 [38]	PC	2	2	1	2	2	0	**9** (High)
Grabowski 2015 [35]	Secondary RCT	2	1	1	2	1	0	**7** (Medium)
Kapiga 2009 [47]	PC	0	1	1	1	1	0	**4** (Low)
Lavreys 2004 [22]	PC	1	2	0	1	1	0	**5** (Medium)
Lekovich 2015 [39]	RC	2	1	1	1	1	0	**6** (Medium)
Louv 1989 [23]	Secondary RCT	1	2	1	1	1	0	**6** (Medium)
Louvanto 2011 [40]	PC	0	1	1	1	1	0	**4** (Low)
Low 2014 [55]	PC	1	2	1	1	0	0	**5** (Medium)
Marks 2011 [41]	PC	2	2	1	2	1	0	**8** (High)
Masese 2013 [51]	PC	1	2	1	2	1	0	**7** (Medium)
Morrison 2004 [25]	PC	2	1	1	2	0	1	**7** (Medium)
Moscicki 2001 [26]	PC	1	2	1	1	1	0	**6** (Medium)
Nielsen 2009 [42]	PC	1	1	1	2	2	0	**7** (Medium)
Pettifor 2009 [48]	PC	2	2	1	2	1	1	**9** (High)
Phelan 2009 [43]	PC	1	2	1	1	1	0	**6** (Medium)
Pintye 2017 [49]	PC	2	2	1	2	1	0	**8** (High)
Romer 2013 [50]	PC	1	2	1	2	1	1	**8** (High)

Russell 2016 [52]	PC	1	2	1	2	1	1	**8** (High)
Sellors 2003 [28]	PC	1	1	1	1	1	0	**5** (Medium)
Shew 2015 [44]	PC	1	2	1	2	1	0	**7** (Medium)
Socias 2017 [54]	PC	0	2	1	2	1	0	**6** (Medium)
Winer 2003 [27]	PC	0	2	1	2	1	0	**6** (Medium)
Winer 2016 [45]	PC	0	0	0	2	1	0	**3** (Low)

Notation: PC: prospective cohort, RC: retrospective cohort, Secondary RCT: secondary analysis of RCT. NR: not reported. NA: This criterion was not applicable: studies estimated recurrent infection.

Rating criteria: *Non-users drawn from same community as HC users*: a) respondents drawn from the same community as HC users (i.e., does not include pregnant women) (1 point) and b) comparison group does not include users of another HC method (unless intentional head-to-head comparison (1 point). *Ascertainment of HC use:* a) separate estimates for different types of HCs (1 point), b) HC use assessed more than once and at intervals <6 months (1 point). *Demonstration STI not present at start of study*: test for pathogen used to confirm respondents were STI negative at study start (1 point). *Comparability of cohorts demonstrated:* a) adjusted analyses performed (1 point); b) authors adjust for condom use or demonstrates negligible difference (1 point); *Ascertainment of STI*: a) independent blind assessment of STI performed (1 point); b) separate estimates for different types of STIs provided using test for pathogen (1 point); *Adequacy of follow-up of cohorts*: a) subjects lost to follow-up unlikely to introduce bias (either high retention >80% or description of those lost is provided and comparable to those who remain in the study) (1 point).

Supplemental Digital Content Table 3: Quality assessment of case-control studies.

Citation	STI case definition accurate (1)	Representativeness of cases (1)	Control selection (1) and definition (1)	Comparability of cases and controls in design or analysis (2)	Ascertainment of HC (3)	Same ascertainment method for cases and controls (1)	Comparable non-response rate for cases and controls (1)	Total score Quality rating: High (8-10) Medium (5-7) Low (<5)
Harris 2009 [36]	1	0	2	1	2	1	0	**7** (Medium)

Rating criteria: *STI definition accurate:* separate estimates for different types of STIs provided using test for pathogen (1 point); *Representation of cases*: consecutive or obviously representative series of cases; *Control selection & definition:* a) controls are sampled independent of HC use and from same source population of cases (1 point); b) if cases are first occurrence of outcome, then controls stated to have no history of outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest are not excluded (1 point); *Comparability of cases and controls in design or analysis*: a) adjusted analyses are performed (1 point); b) study controls for condom use or negligible differences reported in adjusted in unadjusted models (1 point); *Ascertainment of HC:* a) separated estimates for different types of HCs (1 point); b) HC use is assessed more than once at intervals <6 months (1 point); c) HC ascertainment is through structured interview blind to case-control status (1 point); *Same ascertainment method for cases and controls:* yes or no (1 point); *Comparable non-response rate:* equivalent rate demonstrated for both groups (1 point).

SDC Table 4: References 31-59.

31. Rousseau MC, Franco EL, Villa LL, Sobrinho JP, Termini L, Prado JM, et al. A cumulative case-control study of risk factor profiles for oncogenic and nononcogenic cervical human papillomavirus infections. Cancer Epidemiol Biomarkers Prev. 2000;9: 469–76.

32. Lavreys L, Chohan B, Ashley R, Richardson BA, Corey L, Mandaliya K, et al. Human Herpesvirus 8: Seroprevalence and correlates in prostitutes in Mombasa, Kenya. J Infect Dis. 2003;187: 359–363. doi:10.1086/367703

33. Overton ET, Shacham E, Singhatiraj E, Nurutdinova D. Incidence of sexually transmitted infections among HIV-infected women using depot medroxyprogesterone acetate contraception. Contraception. 2008;78: 125–130. doi:10.1016/j.contraception.2008.03.015

34. Balkus JE, Richardson BA, Rabe LK, Taha TE, Mgodi N, Kasaro MP, et al. Bacterial vaginosis and the risk of Trichomonas vaginalis acquisition among HIV-1–negative women. Sex Transm Dis. 2014;41: 123–128. doi:10.1097/OLQ.0000000000000075

35. Grabowski MK, Gray RH, Makumbi F, Kagaayi J, Redd AD, Kigozi G, et al. Use of injectable hormonal contraception and women's risk of herpes simplex virus type 2 acquisition: a prospective study of couples in Rakai, Uganda. Lancet Glob Heal. 2015;3: e478–e486. doi:10.1016/S2214-109X(15)00086-8

36. Harris TG, Miller L, Kulasingam SL, Feng Q, Kiviat NB, Schwartz SM, et al. Depot-medroxyprogesterone acetate and combined oral contraceptive use and cervical neoplasia among women with oncogenic human papillomavirus infection. Am J Obstet Gynecol. 2009;200: 489.e1-8. doi:10.1016/j.ajog.2009.01.030

37. Borgdorff H, Verwijs MC, Wit FWNM, Tsivtsivadze E, Ndayisaba GF, Verhelst R, et al. The impact of hormonal contraception and pregnancy on sexually transmitted infections and on cervicovaginal microbiota in African sex workers. Sex Transm Dis. 2015;42: 143–152.

doi:10.1097/OLQ.0000000000000245

38. Gosvig CF, Huusom LD, Andersen KK, Iftner A, Cederkvist L, Svare E, et al. Persistence and reappearance of high-risk human papillomavirus after conization. Gynecol Oncol. 2013;131: 661–666. doi:10.1016/j.ygyno.2013.09.002

39. Lekovich JP, Amrane S, Pangasa M, Pereira N, Frey MK, Varrey A, et al. Comparison of Human Papillomavirus infection and cervical cytology in women using copper-containing and levonorgestrel-containing intrauterine devices. Obstet Gynecol. 2015;125: 1101–1105. doi:10.1097/AOG.0000000000000760

40. Louvanto K, Rintala MA, Syrjänen KJ, Grénman SE, Syrjänen SM. Incident cervical infections with high- and low-risk human papillomavirus (HPV) infections among mothers in the prospective Finnish Family HPV Study. BMC Infect Dis. 2011;11: 179. doi:10.1186/1471-2334-11-179

41. Marks M, Gravitt PE, Gupta SB, Liaw K-L, Tadesse A, Kim E, et al. Combined oral contraceptive use increases HPV persistence but not new HPV detection in a cohort of women from Thailand. J Infect Dis. 2011;204: 1505–1513. doi:10.1093/infdis/jir560

42. Nielsen A, Iftner T, Munk C, Kjaer SK. Acquisition of high-risk human papillomavirus infection in a population-based cohort of Danish women. Sex Transm Dis. 2009;36: 609–615. doi:10.1097/OLQ.0b013e3181a96d0e

43. Phelan DF, Gange SJ, Ahdieh-Grant L, Mehta SH, Kirk GD, Shah K, et al. Determinants of newly detected human papillomavirus infection in HIV-infected and HIV-uninfected injection drug using women. Sex Transm Dis. 2009;36: 149–56. doi:10.1097/OLQ.0b013e31818d3df3

44. Shew ML, Ermel AC, Tong Y, Tu W, Qadadri B, Brown DR. Episodic detection of human papillomavirus within a longitudinal cohort of young women. J Med Virol. 2015;87: 2122–9. doi:10.1002/jmv.24284

45. Winer RL, Hughes JP, Feng Q, Stern JE, Xi LF, Koutsky LA. Incident detection of high-risk human

papillomavirus infections in a cohort of high-risk women aged 25–65 years. J Infect Dis. 2016;214: 665–675. doi:10.1093/infdis/jiw074

46. Brahmbhatt H, Musoke R, Makumbi F, Kigozi G, Serwadda D, Wawer M, et al. Trichomonas vaginalis incidence associated with hormonal contraceptive use and HIV infection among women in Rakai, Uganda. J Sex Transm Dis. 2014;2014: 916597. doi:10.1155/2014/916597

47. Kapiga S, Kelly C, Weiss S, Daley T, Peterson L, Leburg C, et al. Risk factors for incidence of sexually transmitted infections among women in South Africa, Tanzania, and Zambia: Results from HPTN 055 study. Sex Transm Dis. 2009;36: 199–206. doi:10.1097/OLQ.0b013e318191ba01

48. Pettifor A, Delany S, Kleinschmidt I, Miller WC, Atashili J, Rees H. Use of injectable progestin contraception and risk of STI among South African women. Contraception. 2009;80: 555–60. doi:10.1016/j.contraception.2009.06.007

49. Pintye J, Drake AL, Unger JA, Matemo D, Kinuthia J, McClelland RS, et al. Male partner circumcision associated with lower Trichomonas vaginalis incidence among pregnant and postpartum Kenyan women: a prospective cohort study. Sex Transm Infect. 2017;93: 137–143. doi:10.1136/sextrans-2016-052629

50. Romer A, Shew ML, Ofner S, Gilliam ML, Martins SL, Fortenberry JD. Depot medroxyprogesterone acetate use is not associated with risk of incident sexually transmitted infections among adolescent women. J Adolesc Heal. 2013;52: 83–88. doi:10.1016/j.jadohealth.2012.04.007

51. Masese L, Baeten JM, Richardson BA, Deya R, Kabare E, Bukusi E, et al. Incidence and correlates of Chlamydia trachomatis infection in a high-risk cohort of Kenyan women. Sex Transm Dis. 2013;40: 221–5. doi:10.1097/OLQ.0b013e318272fe45

52. Russell AN, Zheng X, O'Connell CM, Taylor BD, Wiesenfeld HC, Hillier SL, et al. Analysis of factors driving incident and ascending infection and the role of serum antibody in Chlamydia trachomatis genital tract infection. J Infect Dis. 2016;213: 523–31. doi:10.1093/infdis/jiv438

53. Chohan V, Baeten JM, Benki S, Graham SM, Lavreys L, Mandaliya K, et al. A prospective study of risk factors for herpes simplex virus type 2 acquisition among high-risk HIV-1 seronegative women in Kenya. Sex Transm Infect. 2009;85: 489–492. doi:10.1136/sti.2009.036103

54. Socías ME, Duff P, Shoveller J, Montaner JSG, Nguyen P, Ogilvie G, et al. Use of injectable hormonal contraception and HSV-2 acquisition in a cohort of female sex workers in Vancouver, Canada. Sex Transm Infect. 2017;93: 284–289. doi:10.1136/sextrans-2016-052838

55. Low AJ, Konate I, Nagot N, Weiss HA, Mabey D, Segondy M, et al. Neisseria gonorrhoeae and Chlamydia trachomatis infection in HIV-1-infected women taking antiretroviral therapy: a prospective cohort study from Burkina Faso. Sex Transm Infect. 2014;90: 100–103. doi:10.1136/sextrans-2013-051233

56. Kaushic C, Ashkar AA, Reid LA, Rosenthal KL. Progesterone increases susceptibility and decreases immune responses to genital herpes infection. J Virol. 2003;77: 4558–65.

57. Gillgrass AE, Ashkar AA, Rosenthal KL, Kaushic C. Prolonged exposure to progesterone prevents induction of protective mucosal responses following intravaginal immunization with attenuated herpes simplex virus type 2. J Virol. 2003;77: 9845–51.

58. Looker KJ, Elmes JAR, Gottlieb SL, Schiffer JT, Vickerman P, Turner KME, et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. Lancet Infect Dis. 2017;17: 1303–1316. doi:10.1016/S1473-3099(17)30405-X

59. United Nations Population Division Department of Economic and Social Affairs. Trends in contraceptive use worldwide 2015 [Internet]. 2015 [cited 21 May 2018]. Available: http://www.un.org/en/development/desa/population/publications/pdf/family/trendsContraceptiveUse2015Report.pdf

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