Title

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Does hormonal contraceptive use increase women's risk of HIV acquisition? A meta-analysis of observational studies

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Abstract

Background—Epidemiologic research has yielded inconsistent evidence on whether use of hormonal contraception (HC) increases women's risk of HIV acquisition. A robust meta-analysis of existing data can yield a valid summary estimate to inform guidelines, models and future studies.

Methods—We updated a recent systematic review to identify studies examining the relationship between various HC methods and women's risk of HIV. We assessed statistical heterogeneity, and, when appropriate, combined point estimates using random effects models. We explored heterogeneity through subgroup and stratified analyses according to study populations and design features.

Findings—We identified 26 studies, 12 of which met inclusion criteria. There was evidence of a modest increase in HIV risk in the ten studies examining depot-medroxyprogesterone acetate (DMPA) [pooled relative risk (RR) =1.40, 95% CI: 1.16, 1.69]. This risk was lower in the eight studies conducted with women in the general population [pooled RR=1.31, 95% CI: 1.10, 1.57]. There was substantial between study heterogeneity in secondary analyses of trials (n=7, I^2=51.1%). Although individual study estimates suggested an elevated risk, substantial heterogeneity between the two studies conducted with high risk women (I^2=54%) precluded pooling estimates. There was no evidence of an elevated HIV risk in the ten studies examining oral contraceptive pills (OCPs) [pooled RR = 1.00, 95% CI: 0.86, 1.16] or the five studies examining norethisterone enanthate (Net-En) ([pooled RR=1.10; 95% CI: 0.88, 1.37].

Interpretation—The risks of HIV found here would not merit complete withdrawal of DMPA, OCPs, or Net-En from the contraceptive method mix in most settings for women in the general population.

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Contributors

LJR, SIM, and NSP conceptualized the study and developed the research protocol. LJR and KS identified articles for full-text review, and LJR, SIM, and KS extracted data from all eligible studies. LJR conducted all statistical analyses with input from SIM and NSP. All authors contributed to manuscript preparation.

Conflicts of interest

All authors have no financial or personal conflicts to disclose.

INTRODUCTION

Despite over two decades of scientific inquiry, uncertainty remains regarding whether use of hormonal contraception (HC) increases women's risk of HIV acquisition(1). The potential implications of an elevated risk are significant. Globally, 140 million women use HC, including 41 million injectable users and 100 million oral contraceptive pill (OCP) users(2). Use of these methods prevents unintended pregnancies, reduces maternal and infant morbidity and mortality, and enables women to achieve other life goals(3). Given high fertility levels and rates of maternal mortality, particularly in settings of high HIV prevalence, women must be able to avoid pregnancy without increasing their risk of HIV.

After reviewing available epidemiologic evidence, an expert panel convened by the World Health Organization (WHO) in 2012 recommended leaving HC a "Category 1" method with no restrictions for use. However, the panel also recommended that women using progestin-only injectables like DMPA be "strongly advised to *also always use condoms*"(4). Despite this guidance, some countries in sub-Saharan Africa (SSA) are considering withdrawing DMPA from their family planning programs, while modeling studies suggest that the effects of such a decision on unintended births and maternal and infant morbidity and mortality would be substantial in most settings (5–7). Thus, the decision to remove HC will depend not only on whether there is an actual association, but importantly its magnitude to determine whether the increased HIV risk outweighs the tremendous benefits of highly effective contraception.

Given the public health urgency of this question, it is critical to maximally leverage existing observational evidence. Several recent systematic reviews concluded that existing evidence suggests an increased risk of HIV associated with use of progestin-only injectables, potentially isolated to high risk women, but stopped short of quantitatively summarizing results due to perceived heterogeneity in study designs and populations (8–10). However, up to now, heterogeneity has never been quantitatively assessed, and even a moderate amount should not preclude moving forward with meta-analyses of observational data, especially when randomized control trial data are not available to address an urgent public health issue requiring policy decisions(11, 12). Furthermore, as research on this topic has intensified in recent years, the methodological approaches to answering this question have increased in rigor and similarity, making it an opportune time for meta-analysis.

Here, we build on one recent review(8) to quantitatively summarize observational evidence, offering a series of pooled estimates of the effect of HC use on HIV risk by method type. We focus our analyses on studies of sufficient quality and comparability, and explore heterogeneity through a series of a priori secondary analyses.

METHODS

This meta-analysis was conducted in accordance with the PRISMA guidance(13). All statistical analyses were guided by Egger, Davey-Smith, and Altman(14).

Study identification and selection

We used the WHO technical review (4) to identify studies.* We searched PubMed using the terms “hormonal contraception”, “HIV/acquisition”, “injectables” “progestin”, and “oral contraceptive pills”. In addition, we identified relevant abstracts presented at the 2011 through 2014 International AIDS Society and Conference on Retroviruses and Opportunistic Infections meetings and followed up with authors to determine if their analyses had been published. Finally, we reviewed lists of studies with experts in the field.

Two investigators (LR, KS) reviewed the full text of articles identified to determine if they met the following inclusion criteria: Assessed hormonal contraceptive use as an exposure, including at least one of the following categories: depot-medroxyprogesterone acetate (DMPA), norethisterone enanthate (Net-En), combined oral contraceptives (COCs), or progestin only pills (POPs); Employed a prospective design and excluded HIV positive women at baseline, ensuring exposure assessment preceded detection of an incident HIV infection; Analytic approach minimized confounding and selection bias by: Adjusting for confounders in multivariate models, including at a minimum age and condom use; Having minimal loss to follow up (defined as ≤ 30%); Published in a peer-reviewed journal by May 2014; Data collection took place in a low or middle income country as defined by the World Bank.

Data extraction and coding

Two reviewers independently extracted data using a custom, piloted spreadsheet. One investigator compared extractions to ensure inter-coder reliability; when discrepancies arose, a third investigator was brought in to arbitrate.

Given the array of hormonal contraceptive methods available, studies often differed in their classification of contraceptive types and many presented multiple effect estimates. We focused extraction on estimates disaggregated by hormone formulation (e.g, DMPA, Net-En, COCs, or POPs). When only method type (e.g., “injectable” or “pill”) was specified, we reviewed the article to identify whether a specific formulation (e.g., DMPA vs. NetEn) predominated. We coded how comparison groups were constructed, noting whether women using condoms (either alone or in addition to HC), other types of HC, or no contraception were included.

We extracted effect estimates and 95% confidence intervals (CIs) for each model. We made note of the confounders adjusted for in multivariate models and the analytic strategy used [e.g., Cox, inverse probability of treatment weighted marginal structural model (IPTW-MSM)]. In one instance, we also extracted a DMPA specific estimate and its 95% CI from a letter (15) submitted in response to an original manuscript (16).

We extracted information on features that might influence internal or external validity (and overall study quality) or explain heterogeneity, including: study retention rates, inter-survey intervals, the risk profile of study participants, and the study design underlying the estimate.

*The WHO used an unpublished version of the systematic review later published by Polis and Curtis (8), which was subsequently updated and published in October 2014 (10).

For the risk profile of participants, we distinguished high-risk women or key populations (e.g., commercial sex workers, injection drug users, or women in serodiscordant [SD] partnerships) from women in the general population. Finally, we extracted details on the demographic characteristics of participants, recruitment sites, study durations, and exclusion criteria.

Statistical analysis

Effect estimates and their 95% CIs were log transformed and the standard error of each estimate was calculated. Funnel plots were generated to assess publication bias.

We selected one effect estimate per HC formulation per study[†] to include in primary pooled analyses.[‡] When multiple effect estimates were available, we selected the estimate from the most fully adjusted multivariate model. Although four studies(16–19) presented estimates derived using IPTW-MSMs, we did not include these estimates in our primary pooled analyses as they estimate different parameters than traditional regression approaches and the two should not be compared or combined. Specifically, traditional Cox models estimate the average effect of treatment on an individual, whereas MSMs provide the average effect of treatment on the population(20). However, we performed separate analyses that combined only those estimates generated using IPTW-MSMs.

Evidence for statistical heterogeneity between studies was assessed for each HC formulation (DMPA, OCPs/COCs, NetEn) using the I^2 statistic and its 95% CI; an $I^2 \geq 50\%$ was considered evidence of sufficient heterogeneity to contraindicate a pooled estimate. (21). When the I^2 was less than 50%, pooled effect estimates were calculated using DerSimonian and Laird random effects models(22).

We assessed the robustness of findings and explored heterogeneity through a series of a priori secondary analyses. First, we conducted an influence analysis to identify whether any one study disproportionately affected the results. Second, we stratified meta-analyses according to: 1) the risk profile of the study population (high risk vs. general population), and 2) the original study design (prospective cohort *vs.* randomized trial). Third, given concerns that having a reference group that is composed largely of condom users may artificially inflate the risk of HIV acquisition for HC users(23), we explored whether our results were sensitive to the exclusion of condom users from the comparison group. Finally, we explored whether results were qualitatively different when studies with inter-survey intervals longer than the duration of the contraceptive methods under study (1 to 3 months) were excluded. All analyses were conducted in Stata 12.0.

[†]When analyses on the same study population were published in multiple articles and all articles met inclusion criteria, we selected only the most comprehensive or recent paper to include in pooled analyses. See Appendix Table 1 for details.

[‡]Although some authors did not explicitly describe the OCP under study as either combined or progestin-only method, use of POPs is less common in sub-Saharan Africa, and typically restricted to postpartum, breastfeeding women. Thus, we assumed that OCP categories would be comprised predominantly of COC users, and combine those studies that offer estimates for COCs specifically or OCPs generally in our analysis, to produce pooled effect estimates that represent the COC-HIV relationship. Four studies [18, 19, 38, 40] did present separate COC and POP estimates, and we use the COC estimate in pooled analyses.

We refer to effect estimates as hazard ratios (HRs) since all of the studies in our pooled analyses used this measure, with one exception (24). That study estimated an incidence rate ratio (IRR), which is comparable in practical interpretation to the HR (25, 26).

RESULTS

We identified 26 articles (16–19, 24, 27–47), 12 of which met our inclusion criteria (16–19, 24, 37–40, 44, 45, 47) [Figure 1 and Appendix Table 1]. Two represented analyses on the same population; however, since they employed different analytic approaches (Cox regression (40) vs. IPTW-MSM (17)), both were included but in separate pooled analyses to prevent double counting.

All studies in the final sample were conducted in SSA. Three, all prospective cohort studies, were designed specifically to assess the HC-HIV relationship (37, 39, 40). The rest were secondary analyses on cohorts enrolled in randomized trials of various HIV (16, 18, 19, 24, 44, 45, 47) and one cervical cancer (38) prevention interventions. Two study populations consisted of high risk women, either CSWs (37) or women in SD partnerships (16). The remainder were composed of women in the general population, typically recruited at family planning or other health centers. The median age of participants ranged from 25 to 40. With the exception of two studies that surveyed women every six (38) or ten (24) months, the remainder surveyed women at least every three months. With the exception of one study which followed a subset of women for six months (38), all studies planned to follow women for at least one year. The median follow up ranged from 12 to 31.2 months. Given heterogeneity in how study authors presented estimates of loss to follow up, we did not quantitatively summarize this metric. However, in general, study retention was high, with a minimum of six of 12 studies having retention rates over 85% (Tables 1 and 2).

Funnel plots for studies assessing injectables and OCPs were symmetrical, suggesting no major evidence of publication bias (Appendix, Figure 1A and 1B).

DMPA-HIV

Ten articles examined the DMPA-HIV association. In pooled analyses, DMPA use was associated with an elevated risk of HIV acquisition as compared to use of non-hormonal or no methods [pooled relative risk (RR) =1.40, 95% CI: 1.16, 1.69] (Figure 2). An influence analysis revealed that no single study was driving results. The pooled effect estimate across the two studies that used IPTW-MSMs was comparable to the overall estimate [pooled relative risk (RR)=1.41, 95% CI: 1.15, 1.72] (Table 3).

In subgroup analyses, the pooled relative risk among the three prospective cohort studies was 1.44 (95% CI: 1.04, 2.01). A high level of between-study heterogeneity (I^2=51.1%, 95% CI: 0%, 79.3%) among the seven secondary analyses of cohorts from RCTs precluded calculating a pooled estimate among this subgroup (Table 3).

The eight studies conducted among women in the general population had a lower amount of heterogeneity (I^2=27.3%, 95% CI: 0%, 67.3%) than the primary analysis (42.5%, 95% CI: 0%, 72.5%). The pooled estimate suggested a moderate increase in risk of HIV acquisition

[pooled relative risk=1.31, 95% CI: 1.10, 1.57]. Individual study-level estimates were higher in the two studies with high-risk women (HR=1.73 [95%CI:1.28, 2.34] among CSWs (37) and 3.93 [95% CI: 1.37, 11.2] among women in SD partnerships(16)) (Table 3). However, a high level of heterogeneity (I^2= 54%, 95% CI: 0%, 88.7%) between these two studies contraindicated pooling estimates.

In an analysis restricted to the nine studies in which the reference group included women using condoms (in addition to other methods or no method), the pooled effect estimate did not change substantively from the primary analysis (pooled RR = 1.44, 95% CI: 1.20, 1.73). An analysis restricted to the eight studies in which the inter-survey interval did not exceed three months revealed a pooled effect estimate that was slightly larger than our primary analysis (pooled RR=1.48, 95% CI: 1.24, 1.76) (Table 3).

COC/OCP-HIV

Ten studies presented estimates of the COC/OCP-HIV relationship. There was no elevated risk of HIV acquisition among COC/OCP users as compared to those using non-hormonal or no methods (pooled relative risk = 1.00, 95% CI: 0.86, 1.16) (Table 4) and our influence analysis revealed that no one study was driving these results. There was minimal evidence of between study heterogeneity (I^2=0%, 95% CI: 0%, 48.6%). The pooled estimate among five studies using IPTW-MSMs was similar to the primary pooled result (pooled RR= 1.03, 95%CI: 0.81, 1.32) (Table 4). A subgroup analysis of the two studies conducted among high risk women revealed an elevated risk of HIV acquisition among COC/OCP users (pooled RR= 1.49, 95%CI: 1.04, 2.13) (Table 4).

NetEn-HIV

Analysis of the five studies that presented estimates on the Net-En-HIV relationship revealed no elevated risk of HIV acquisition (pooled RR=1.10; 95% CI: 0.88, 1.37) (Table 4) and minimal heterogeneity (I^2=0%, 95% CI: 0%, 74.6%). Similar results were observed for the two studies estimated using IPTW-MSMs (pooled RR=1.08, 95% CI: 0.78, 1.52) (Table 4). An influence analysis was non-significant and subgroup analyses were not possible given the small number of studies.

DISCUSSION

Our meta-analysis found that among observational studies with similarly and precisely defined exposures, adjustment for key confounders, minimal selection bias, and sound analytic approaches, there is evidence of a small but increased risk of HIV acquisition associated with DMPA use. Consistent with an earlier meta-analysis on OCPs (48), no elevated risk was observed for OCP/COC users in the general population. Further, there was no elevated risk among Net-En users; however, the few studies contributing to this analysis precludes making any definitive statements on its association with HIV.

The results from this analysis, particularly for DMPA, should be used as an input parameter in ongoing modeling studies quantifying the tradeoffs associated with removing injectables from the contraceptive method mix. For example, Butler et al. (6) used both a hypothetical (RR=1.2) and a single study (OR=2.19)(16) estimate to predict changes in the numbers of

HIV and maternal deaths following reductions in injectable HC use. Their findings suggest that, except in southern Africa where both HIV incidence and injectable use are high, the effect of removing HC on the number of maternal and HIV related deaths is sensitive to the effect estimate chosen. Given these results, it is possible that an increased risk of the magnitude found in our study (RR=1.4), particularly for women in the general population, would not merit complete withdrawal of DMPA as maternal mortality would still exceed HIV related deaths in most settings, particularly if women did not immediately have access to and uptake alternate, effective contraceptive options in the absence of DMPA, one of the assumption in Butler et al.'s models. Moving forward, we encourage Butler et al. (6) and others (5, 7) to apply our estimates and more fully explore regional/geographic and subpopulation differences so that context-specific contraceptive policy can be developed.

Our analysis also offers insight into potential sources of heterogeneity in results. Studies among women in the general population, which constitute the majority in our analysis, provide estimates of the average population level effect of HC on women's risk of HIV acquisition. In contrast, those conducted among high risk women, of which there were two in our analysis, provide estimates of the effect of HC conditioned on a high likelihood of HIV exposure. For the millions of HC users worldwide, most of whom are *not* in serodiscordant or other high risk partnerships, this distinction is critical. While the elevated risks for DMPA and COC/OCP users reported in the two studies with CSWs (37) and women in SD partnerships(16) may warrant consideration of changing contraceptive guidelines for these populations, it would be premature to do so based on two studies. Further, it is critical that their results not be inadvertently generalized to women in the general population, which our study found had a more modest increase in risk that may only warrant a policy change in specific local contexts.

A priori, we established a strict set of inclusion criteria for our meta-analysis. Although this left us with fewer studies, and less power in our planned secondary analyses or to explore heterogeneity through meta-regression, it ensured that only comparable estimates were combined. Contrary to the perception that this literature is too diverse for meta-analysis, we did not uncover levels of heterogeneity that would preclude pooling estimates in most analyses. One notable exception is that although they contribute to the primary pooled analyses, we were unable to present a separate pooled estimate among the subset of studies conducted as secondary analyses of randomized controlled trials. The heterogeneity statistic for this group (I^2=51.1%, 95% CI: 0%, 79.3%) rests on the border between "moderate" and "substantial" according to current Cochrane guidance(49). Whereas the prospective cohort studies were all designed specifically to answer this research question, the trials had divergent research objectives that may be reflected in the higher level of heterogeneity. Given this, a very conservative application of our findings would be to use the pooled RR and CI from only the prospective cohort studies. However, the strengths of the randomized trials, notably their large sample sizes, frequent assessment of contraceptive method use and switching, and efforts to ensure high retention, are compelling. Regardless, in the absence of another prospective cohort study or data from the proposed RCT on HC-HIV(50), the results of which would not be available for several years, other HIV prevention trials represent the primary source of data with which to explore this important question in the near future(51).

Our study findings should be interpreted in the context of several limitations. First, meta-analyses of observational studies, like observational studies themselves, are inherently more prone to concerns about bias and are not able to address whether the association between HC and HIV is causal (14). There has been extensive discussion about whether studies to date have sufficiently addressed the potential confounding effects of misreported condom use (23, 52), particularly since many study populations were drawn from HIV prevention trials where condom use is strongly encouraged and women may feel pressure to report socially desirable behaviors(53, 54). However, recent modeling studies suggest that the practical effects of condom misreporting may be overstated. For example, Smith et al. (55) demonstrate that only a substantial amount of condom use underreporting by non-hormonal contraceptive users, an unlikely scenario, could explain the elevated effect estimate observed in the recent Heffron et al. study (HR=2.19 for all injectables and HR=3.93 for DMPA specifically). Further, our own work with biomarkers of unprotected sex has demonstrated that misreporting of condom use is not statistically different between women using HC and those using other methods, and therefore may not bias effect estimates to the extent suggested(56). Note that even a randomized controlled trial will likely not be able to overcome many of the measurement challenges inherent to studying this question (5, 57). Likewise, the limitations of the original studies remain limitations of our analysis. For example, none of the studies prospectively assessed acute HIV infection, which would strengthen our confidence in the timing of exposure to HC and women's subsequent acquisition of HIV.

A second limitation is that, despite our efforts to ensure systematic inclusion of all studies that assessed the HC-HIV relationship and explore publication bias using funnel plots, as with all meta-analyses, our results may be biased if only studies with significant results have been published. However, here, publication bias is less likely because over the past two decades, a null finding was equally compelling in terms of advancing the debate. Regardless, if studies that found positive and significant effects of HC on women's risk of HIV acquisition were more likely to be published, that would imply that our findings represent an overestimate of the true association between HC and HIV.

Although our study findings echo what was previously presented qualitatively in two systematic reviews(8–10) (ie, there is evidence of a moderate increase in risk of HIV for injectable users, potentially isolated to high risk women), this study is the first to quantitatively summarize existing evidence, particularly for DMPA, and offer a series of weighted, pooled estimates of effect and their variances, by precise HC method type, for all studies published through May 2014. Since we approached data extraction and definitions of study quality independently from the other reviews, our study also contributes another perspective on the methodological rigor of the existing body of evidence.

Given concerns about the observational evidence collected to date, efforts are currently underway to fund a randomized trial on the HC-HIV relationship. Some might argue that the moderate increase in risk found in our study for DMPA users, who would comprise one of the intervention arms, might violate the principal of equipoise required for a trial (58). Importantly, also of concern is whether, given the methodological challenges inherent to studying this question (57), the randomized trial will offer evidence superior to that which

currently exists, especially when also considering the personal and financial investments required for a trial(1). Our pooled estimates can immediately inform contraceptive policy, without waiting several years for trial data. In addition, our findings highlight an immediate need to refocus secondary analyses on CSWs and women in serodiscordant partnerships, because evidence for these high risk women is limited but suggests an elevated risk. Meanwhile, basic science research must continue to definitely document the biological mechanisms underlying the observed association documented here(59). Finally, it is the public health imperative to continue to promote a wider array of existing methods and develop and promote long-term reversible contraceptive options for women worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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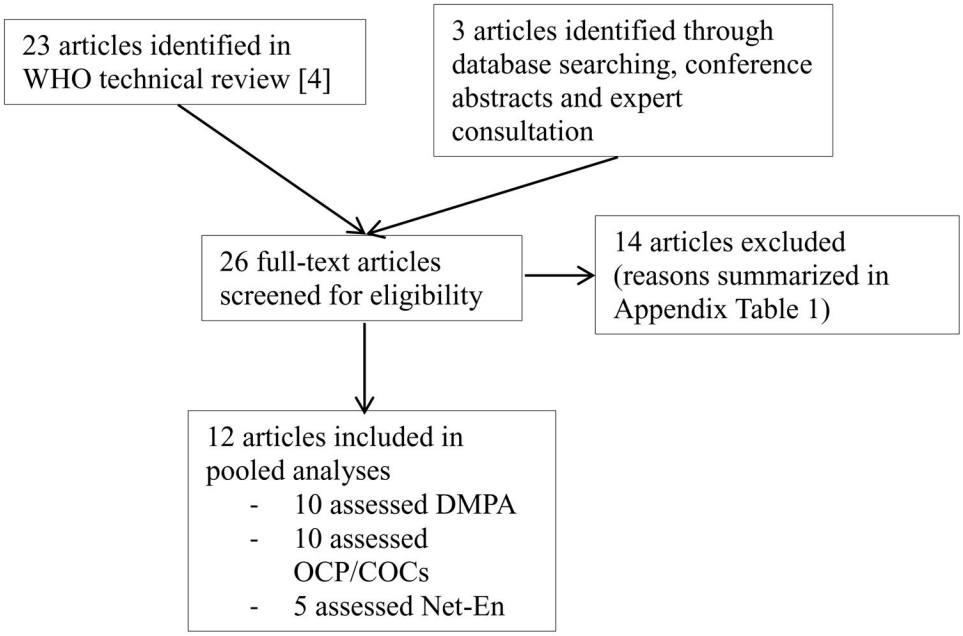

FIGURE 1.
Flowchart of study selection

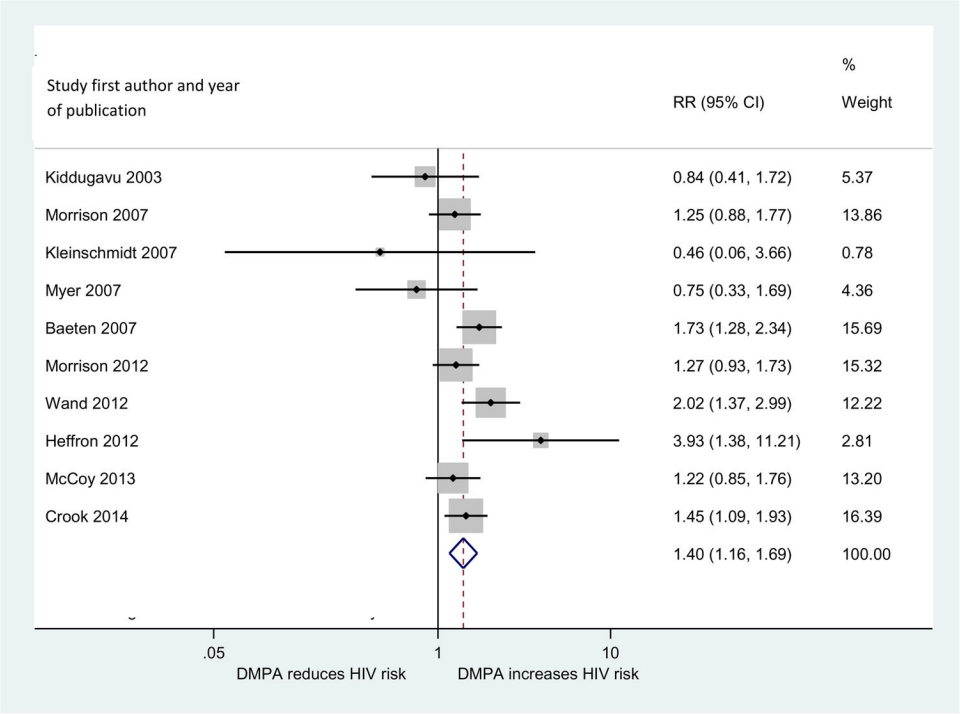

FIGURE 2.
Forest plot of primary analysis of DMPA-HIV relationship

TABLE 1

Descriptive characteristics of studies included in primary DMPA-HIV, COC-HIV, and NetEn-HIV pooled analyses

First autho and citation	Year	Study location(s)	Study Participants (SDP=serodiscordant partnerships; CSW=commercial sex workers)	Mean age of study popln.	Exposures assessed*	# of HIV sero-conversions	Effect Estimate (adjusted hazard ratio, unless otherwise noted)	Reference group	Inter-survey interval (months)	Duration of follow up (months)	Present IPTW-MSM^ estimates
Crook [47]	2013	S. Africa, Uganda, Tanzania, Zambia	N=8663 women in microbicide trial; 786 in SDPs	27	DMPA	146	1.45 (1.09, 1.93)	Non-hormonal or no method	1	12 (planned)	X
					Net-En	69	1.20 (0.84, 1.69)				
					OCPs	50	0.90 (0.63, 1.26)				
					Ref	117	--				
McCoy [19]	2012	Zimbabwe, S. Africa	N=4913 women in MIRA trial	27.5	DMPA	63	1.22 (0.84, 1.74)	Non-hormonal or no method	3	17.9 (median)	X
					Net-En	17	1.15 (0.58, 1.95)				
					OCPs	61	0.84 (0.57, 1.22)				
					Ref	108	--				
Morrison [18]	2012	S. Africa	N=5567 women in Carraguard trial	28	DMPA	270 (total)	1.27 (0.93, 1.73)	Non-hormonal or no method	3	24 (planned)	X
					Net-En		0.87 (0.60, 1.25)				
					COCs		0.88 (0.49, 1.30)				
					Ref		--				
Heffron [16]	2012	Bostwana, Kenya, Rwanda, S. Africa, Tanzania, Uganda, Zambia	N=1314 women in SDP in Partners in Prevention Trial	30.2	Inj	10	1.80 (0.92, 3.52)	Non-hormonal or no method	3	18 (median)	X
					DMPA#	Not reported	3.93 (1.38,11.22)				
					OCPs	3	1.80 (0.55, 5.82)				
Wand [15]	2012	S. Africa	N=2236 women in microbicide trial	27	Inj-DMPA&	Not reported	2.02 (1.37, 3.00)	Non-hormonal method^^	3	Not reported	
					OCPs	Not reported	0.95 (0.62, 1.46)				
Morrison [40][18]	2007 2010	Uganda, Zimbabwe	N=4435 women recruited at health clinics	25	DMPA	213 (total)	1.25 (0.89, 1.78)	Non-hormonal method^^	3	21.5 (mean)	X
					COCs		0.99 (0.69, 1.42)				
Reid [44]	2010	S. Africa, Zambia, Zimbabwe	N=1358 women in acyclovir trial (HPTN 039)	31	Inj	Not reported	0.94 (0.46, 1.92)	No method&&	3	18 (planned)	
					OCs	Not reported	0.91 (0.45, 1.83)				
Baeten [37]	2007	Kenya	N=1206 CSWs recruited at communicable disease clinics	26	DMPA	79	1.73 (1.28, 2.34)	No method or tubal ligation@@	1	14.9 (median)	
					OCPs	38	1.46 (1.00, 2.13)				
					Ref	118	--				

First autho and citation	Year	Study location(s)	Study Participants (SDP=serodiscordant partnerships; CSW=commercial sex workers)	Mean age of study popln.	Exposures assessed*	# of HIV sero-conversions	Effect Estimate (adjusted hazard ratio, unless otherwise noted)	Reference group	Inter-survey interval (months)	Duration of follow up (months)	Present IPTW-MSM^ estimate
Kleinschmidt [39]	2007	S. Africa	N=551 women recruited at family planning clinics	27.7	DMPA	1	0.46 (0.06, 3.79)	Non-hormonal or no method	3	12 (planned)	
					Net-En	10	1.76 (0.64, 4.84)				
					Ref	12	--				
Myer** [38]	2007	S. Africa	N=4200 women in cervical cancer prevention trial	40	DMPA	Not reported	0.75 (0.33, 1.68)	Non-hormonal or no method	6–12**	14.3** (median)	
					Net-En	Not reported	1.60 (0.63, 4.09)				
					COC	Not reported	0.66 (0.09, 4.78)				
					Ref	Not reported	--				
Kiddugavu [24]	2003	Uganda	N=5117 women in Rakai community-based HIV prevention trial	25	Inj-DMPA%%	16	0.84 (0.41, 1.72)$$	Non-hormonal or no method, excluding condoms	10	31.2 (median)	
					OCs	12	1.12 (0.48, 2.56) $$				

* OCP = oral contraceptive pills, type not specified; COC = combined oral contraceptive pills; DMPA = injectable depo medroxyprogesterone acetate; Net-En = injectable norethisterone enanthate

^ Inverse probability of treatment weighted marginal structural model

Original analysis [16] presented pooled estimate for all injectables; subsequent reply presented results separately for DMPA users [15];

& Authors note that injectable category includes only DMPA or generic alternative;

%% Authors note that the injectable group includes “mainly Depo-Provera users”;

^^ Women using no method were excluded from all analyses;

&& Women using condoms or non-hormonal methods were considered as separate exposure categories and therefore were not included in the reference group;

** Authors present effect estimates for women in both a 6 and 24 month cohort. Given high loss to follow up in the 24 month cohort (32%), we include only the estimate from the 6 month cohort in pooled analyses. However, since the authors do not present the number of sero-conversions or mean duration of follow up for the 6 month cohort, we include these indicators here;

$$ Incidence Rate Ratio;

@@ Authors note that condom use was analyzed as a separate covariate and was not used to determine the reference group. As a result, women using only condoms would likely be classified in the reference group as a “no method” user.

TABLE 2

Exposures assessed in studies included in primary pooled analyses of the association of hormonal contraception and HIV

First author and citation	Exposures	Number of HIV seroconversions	Effect estimate (adjusted hazard ratio, unless otherwise noted)	IPTW-MSM estimate
Crook [47]	Injectable depot medroxyprogesterone acetate	146+	1.45 (1.09–1.93)	1.49 (1.06–2.09)
	Injectable norethisterone enanthate	69	1.20(0.84–1.69)	1.31 (0.86–1.99)
	Oral contraceptive pills, type not specified	50	0.90 (0.63–1.26)	1.00 (0.62–1.61)
	Reference	117	--	--
McCoy [18]	Injectable depot medroxyprogesterone acetate	63	1.22 (0.84–1.74)	Not reported
	Injectable norethisterone enanthate	17	1.15 (0.58-0.58–1.95)	Not reported
	Oral contraceptive pills, type not specified	61	0.84 (0.57–1.22)	0.86 (0.32–1.78)
	Combined oral contraceptive pills	44	0.80 (0.53–1.19)	Not reported
	Reference	108	--	--
Morrison [17]	Injectable depot medroxyprogesterone acetate	270 (total)	1.27 (0.93–1.73)	1.28 (0.92–1.78)
	Injectable norethisterone enanthate	270 (total)	0.87 (0.60–1.25)	0.92 (0.64–1.32)
	Combined oral contraceptive pills	270 (total)	0.88 (0.49–1.30)	0.84 (0.51–1.39)
	Reference	270 (total)	--	--
Heffron [16]	Injectable form, type not specified	10	2.05 (1.04–4.04)	2.19 (1.01–4.74)*
	Injectable depot medroxyprogesterone acetate^	Not reported	3.93 (1.38–11.22)	Not reported
	Oral contraceptive pills, type not specified	3	1.80 (0.55–5.82)	1.63 (0.57–5.66)
	Reference	60	--	--
Wand [45]	Injectable depot medroxyprogesterone acetate**	Not reported	2.02 (1.37–3.00)	--
	Oral contraceptive pills, type not specified	Not reported	0.95 (0.62–1.46)	--
	Reference	Not reported	--	--
Morrison [17, 20]	Injectable depot medroxyprogesterone acetate	87	1.25 (0.89–1.78)	1.48 (1.02–2.15)
	Combined oral contraceptive pills	71	0.99 (0.69–1.42)	1.19 (0.80–1.76)
	Reference	58	--	--
Reid [44]	Injectable form, type not specified	Not reported	0.94 (0.46–1.92)	--
	Oral contraceptive pills, type not specified	Not reported	0.91 (0.45–1.83)	--
	Reference	Not reported	--	--

First author and citation	Exposures	Number of HIV seroconversions	Effect estimate (adjusted hazard ratio, unless otherwise noted)	IPTW-MSM estimate
Baeten [39]	Injectable depot medroxyprogesterone acetate	79	1.73 (1.28–2.34)	--
	Oral contraceptive pills, type not specified	38	1.46 (1.00–2.13)	--
	Reference	118	--	--
Kleinschmidt [40]	Injectable depot medroxyprogesterone acetate	1	0.46 (0.06–3.79)	--
	Injectable norethisterone enanthate	10	1.76 (0.64–4.84)	--
	Reference	12	--	--
Myer [19] #	Injectable depot medroxyprogesterone acetate	Not reported	0.75 (0.33–1.68)	--
	Injectable norethisterone enanthate	Not reported	1.60 (0.63–4.09)	--
	Combined oral contraceptive pills	Not reported	0.66 (0.09–4.78)	--
	Reference	Not reported	--	--
Kiddugavu [26]	Injectable depot medroxyprogesterone acetate^^	16	0.84 (0.41–1.72) ||	--
	Oral contraceptive pills, type not specified	12	1.12 (0.48–2.56) ||	--
	Reference	Not reported	--	--

IPTW-MSM – inverse probability of treatment-weighted marginal structural model.

* This estimate was not used in pooled analysis since it was not specific to depot medroxyprogesterone.

^ Original analysis [16] presented pooled estimates for all injectable hormonal contraception; subsequently, results were presented separately for users of injectable depot medroxyprogesterone acetate. [15]

** Wand and colleagues [45] noted that the injectable category includes only depot medroxyprogesterone acetate or a generic alternative.

Investigators presented effect estimates for women in both 6-month and 24-month cohorts; with the high loss to follow-up in the 24month cohort (32%), we included only the estimate from the 6-month cohort in pooled analyses; however, since the investigators did not present the number of seroconversions or mean duration of follow-up for the 6-month cohort, we include these indicators here.

^^ Kiddugavu and colleagues [26] noted that the injectable group includes mainly users of depot medroxyprogesterone acetate.

|| Incidence rate ratio.

TABLE 3

Comparison of results for primary, subgroup, and sensitivity analyses of the DMPA-HIV relationship using random effects models[*]

	Number of studies	I^2 statistic (95% Confidence Interval)	Pooled HR (95% Confidence Interval)	Studies included
Primary analysis	10	42.5% (0%, 72.5%)	1.40 (1.16, 1.69)	16, 18, 19, 24, 37, 38, 39, 40, 45, 47
IPTW-MSM analysis[#]	3	0% (0%, 58.2%)	1.41 (1.15, 1.72)	17, 18, 47
Subgroup analysis				
Higher risk women	2	54.0% (0%, 88.7%)	--	16, 37
Women in the general population	8	27.3% (0%, 67.3%)	1.31 (1.10, 1.57)	18, 19, 24, 38, 39, 40, 45, 47
Prospective cohort	3	36.7% (0%, 79.9%)	1.44 (1.04, 2.01)	37, 39, 40
Sample from RCT	7	51.1% (0%, 79.3%)	--	16, 18, 19, 24, 38, 45, 47
Sensitivity analysis				
Reference group includes women using non-hormonal or no methods[^]	9	40.8% (0%, 72.7%)	1.44 (1.20, 1.73)	16, 18, 19, 37, 38, 39, 40, 45, 47
Inter-survey interval ≤ 3 months[%]	8	36.1% (0%, 71.7%)	1.48 (1.24, 1.77)	16, 18, 19, 37, 39, 40, 45, 47

[*] All pooled analyses were limited to published, prospective studies that assessed incident HIV infection where the exposure category was predominantly (or exclusively) DMPA, the comparison group was comprised of women using non-hormonal or no contraceptive method (including condom users, unless noted), the model was adjusted for potential confounders of the HC-HIV relationship, including condom use and age, and no more than 30% of the study population was lost to follow up.

[#] Two additional studies [16, 19] present estimates derived using IPTW-MSMs; however they were for injectables and not specific to DMPA and are therefore not included here.

[^] One study in which condom users were explicitly excluded from the reference group [24] was excluded.

[%] Two studies with inter-survey intervals of 6 [38] and 10 months [24] were excluded.

TABLE 4

Comparison of results for primary and subgroup analyses of the COC-HIV and NetEn-HIV relationship using random effects models*

	Number of studies	I^2 statistic (95% Confidence Interval)	Pooled HR (95% Confidence Interval)	Studies included
Primary analysis – COCs	10	0% (0%, 48.6%)	1.00 (0.86, 1.16)	16, 18, 19, 24, 37, 38, 40, 44, 45, 47
MSM-IPTW analysis – COCs	5	0% (0%, 55.2%)	1.03 (0.81, 1.32)	16, 17, 18, 19, 47
Subgroup analysis – COCs				
Higher risk women	2	0% (0%, 0%)	1.49 (1.04, 2.13)	16, 37
Women in the general population	8	0% (0%, 0%)	0.92 (0.78, 1.18)	18, 19, 24, 38, 40, 44, 45, 47
Prospective cohort	2	52% (0%, 88.3%)	--	37, 40
Sample from RCT	8	0% (0%, 0%)	0.91 (0.75, 1.10)	16, 18, 19, 24, 38, 44, 45, 47
Sensitivity analysis – COCs				
Reference group includes women using non-hormonal or no methods#	8	0% (0%, 64.8%)	1.00 (0.85, 1.17)	16, 18, 19, 37, 38, 40, 45, 47
Inter-survey interval ≤ 3 months%	8	0% (0%, 64.3%)	1.00 (0.86, 1.16)	16, 18, 19, 37, 40, 44, 45, 47
Primary analysis – NetEN	5	0% (0%, 74.6%)	1.10 (0.88, 1.37)	18, 19, 38, 39, 47
IPTW-MSM analysis – NetEn	2	36% (0%, 78.1%)	1.08 (0.77, 1.52)	18, 47

*All pooled analyses were limited to published, prospective studies that assessed incident HIV infection where the exposure category was predominantly (or exclusively) COCs/NetEn, the comparison group was comprised of women using non-hormonal or no contraceptive method (including condom users, unless noted), the model was adjusted for potential confounders of the HC-HIV relationship, including condom use and age, and no more than 30% of the study population was lost to follow up.

#Two studies in which condom users were explicitly excluded from the reference group [24, 44] were excluded.

%Two studies with inter-survey intervals for 6 [38] and 10 months [24] were excluded.