Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies

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Summary

Background The evidence from epidemiological research into whether use of hormonal contraception increases women's risk of HIV acquisition is inconsistent. We did a robust meta-analysis of existing data to provide summary estimates by hormonal contraceptive method which can be used to inform contraceptive guidelines, models, and future studies.

Methods We updated a recent systematic review to identify and describe studies that met inclusion criteria. To ensure inclusion of more recent research, we searched PubMed for articles published after December, 2011, using the terms "hormonal contraception", "HIV/acquisition", "injectables", "progestin", and "oral contraceptive pills". We assessed statistical heterogeneity for these studies, and, when appropriate, combined point estimates by hormonal contraception formulation using random-effects models. We assessed publication bias and investigated heterogeneity through subgroup and stratified analyses according to study population and design features.

Findings We identified 26 studies, 12 of which met inclusion criteria. There was evidence of an increase in HIV risk in the ten studies of depot medroxyprogesterone acetate (pooled hazard ratio [HR] 1·40, 95% CI 1·16–1·69). This risk was lower in the eight studies done in women in the general population (pooled HR 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%, 95% CI 0–79·3). Although individual study estimates suggested an increased risk, substantial heterogeneity between two studies done in women at high risk of HIV infection (I^2 54%, 0–88·7) precluded pooling estimates. There was no evidence of an increased HIV risk in ten studies of oral contraceptive pills (pooled HR 1·00, 0·86–1·16) or five studies of norethisterone enanthate (pooled HR 1·10, 0·88–1·37).

Interpretation Our findings show a moderate increased risk of HIV acquisition for all women using depot medroxyprogesterone acetate, with a smaller increase in risk for women in the general population. Whether the risks of HIV observed in our study would merit complete withdrawal of depot medroxyprogesterone acetate needs to be balanced against the known benefits of a highly effective contraceptive.

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Introduction

Despite more than two decades of scientific investigation, uncertainty remains about whether the use of hormonal contraception increases women's risk of HIV infection.[1] Worldwide, 144 million women use hormonal contraception, including 41 million users of injectables and 103 million who take oral contraceptive pills.[2] Use of these hormonal contraceptives prevents unintended pregnancies, reduces the rate of maternal and infant morbidity and mortality, and enables women to achieve other life goals.[3] With high fertility and maternal mortality rates, particularly in settings of high HIV prevalence, women need to be able to avoid pregnancy without increasing their risk of HIV infection. An increased risk of HIV associated with hormonal contraceptive use might have important contraceptive counselling and other policy implications.

After reviewing available epidemiological evidence, an expert panel convened by WHO in 2012 recommended keeping hormonal contraception as a category 1 method with no restrictions for use. However, the panel also recommended that women using progestin-only injectable contraception, including depot medroxyprogesterone acetate, be "strongly advised to also always use condoms".[4] Despite this guidance, some countries in sub-Saharan Africa are considering withdrawing depot medroxyprogesterone acetate from their family planning programmes, even though the results of modelling studies suggest that the effects of such a decision on unintended births and maternal and infant morbidity and mortality rates would be substantial in most settings.[5–7] Thus, the decision to withdraw hormonal contraception will depend not only on whether there is an actual association, but importantly also on whether the increased HIV risk outweighs the tremendous benefits of highly effective contraception.

Because of the public health urgency about whether use of hormonal contraception is associated with increased risk of HIV infection, it is crucial to take full advantage of existing observational evidence. The authors of systematic reviews concluded that existing evidence suggests an increased risk of HIV associated with use of progestin-only injectable contraception, possibly only in women at high risk, but did not quantitatively summarise results

because of 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 data from randomised control trials are not available to address an urgent public health issue requiring policy decisions.[11,12] Furthermore, as research in this topic has intensified in recent years, the methodological approaches to addressing this issue have increased in rigour and similarity, making it an opportune time to do a meta-analysis.

Here, we build on the findings of one recent review[8] to quantitatively summarise observational evidence, providing a series of pooled estimates of the effect of the use of hormonal contraception on HIV risk by type of method. We focus our analyses on studies of sufficient quality and comparability, and assess the heterogeneity through a series of a-priori secondary analyses.

Methods

Search strategy and selection criteria

We did this meta-analysis in accordance with PRISMA guidelines.[13] All our statistical analyses were guided by Egger and colleagues.[14]

We used the 2012 WHO technical review[4] to initially identify studies. WHO used an unpublished version of the systematic review that was later published by Polis and Curtis,[8] which was subsequently updated and published in October, 2014.[10] To ensure inclusion of recent research, we searched PubMed for articles published in English after Dec 1, 2011, using the terms "hormonal contraception", "HIV/acquisition", "injectables", "progestin", and "oral contraceptive pills". Additionally, we identified relevant abstracts presented at the 2011–14 International AIDS Society and Conference on Retroviruses and Opportunistic Infections and followed up with authors to ascertain if their analyses had been published. We also reviewed lists of studies with experts in the specialty.

Two investigators (LJR and KS) reviewed the full text of articles identified to ascertain if the studies met the following inclusion criteria: assessed hormonal contraceptive use as an exposure, including at least one of the following categories: depot medroxyprogesterone acetate, norethisterone enanthate, combined oral contraceptives, or progestin-only pills; used a prospective design and excluded HIV-positive women at baseline, ensuring exposure assessment preceded detection of an incident HIV infection; used an analytic approach that minimised confounding and selection bias by adjustment for, at least, age and condom use, and having minimum loss to follow-up (defined as <30%); published in a peer-reviewed journal by May, 2014; and data gathering took place in a low-income or middle-income country as defined by the World Bank.

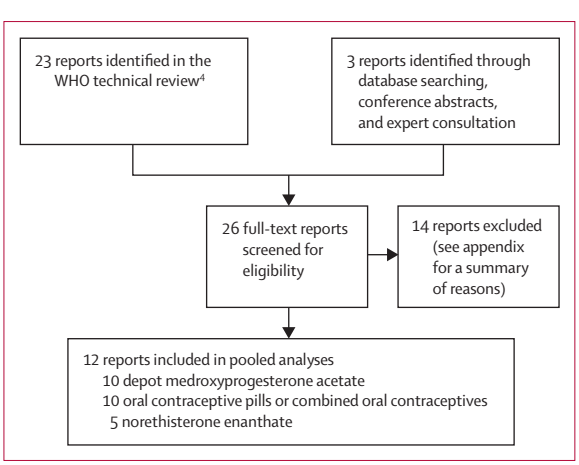

Figure 1: **Flowchart of study selection**

Data extraction and coding

Two reviewers (LR, KS, or SM) independently extracted data from studies using a custom, piloted spreadsheet. One investigator (LR) compared extractions to ensure intercoder reliability, and when discrepancies arose a third investigator who was not involved in the original extraction arbitrated.

With the array of hormonal contraceptive methods available, studies often differed in their classification of the types of contraception and many presented several effect estimates. We focused our data extraction on estimates disaggregated by hormone formulation (eg, depot medroxyprogesterone acetate, norethisterone enanthate, combined oral contraceptives, or progestin-only pills). When only the type of method (eg, injectable or pill) was specified, we reviewed the article to identify whether a specific formulation (eg, depot medroxyprogesterone acetate *vs* norethisterone enanthate) predominated. We coded how comparison groups were constructed, noting whether women using condoms (alone or in addition to hormonal contraception), other types of hormonal contraception, or no contraception were included.

We extracted effect estimates and 95% CIs for each model presented in the paper. We noted the confounders adjusted for in multivariate models and the analytic strategy used (eg, Cox or inverse probability of treatment weighted marginal structural model). In one instance, we also extracted a depot medroxyprogesterone acetate specific estimate and its 95% CI from a letter[15] submitted in response to an original manuscript.[16]

We extracted information about features that might affect internal or external validity (and overall study quality) or explain heterogeneity, including study retention rates, intersurvey intervals, the risk profile of study participants, and the study design. For participants' risk profile, we distinguished women at high risk or key populations (eg, commercial sex workers, injection drug users, or women in serodiscordant partnerships) from women in the general population. Also, we extracted details about 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 SE of each estimate was calculated. Funnel plots were generated to assess publication bias.

We selected one effect estimate per hormonal contraception formulation for each study to include in the primary pooled analyses. When analyses of the same study population were published in different articles and all articles met inclusion criteria, we selected only the most comprehensive or recent paper to include in pooled analyses (for details, see appendix). Although some investigators of the studies did not explicitly describe the oral contraceptive pill as combined or progestin only, use of progestin-only pills is less common in sub-Saharan Africa than in the rest of the world and is typically restricted to post-partum, breastfeeding women. Thus, we assumed that categories of the oral contraceptive pill would be comprised predominantly of users of the combined oral contraception and combined studies that presented estimates for combined oral contraception specifically or oral contraceptive pills generally in our analysis to produce pooled-effect estimates that represent the relation between combined oral contraception and HIV. Four studies[17–20] presented separate estimates for combined oral contraception and progestin-only pills and we used the estimate for combined oral contraception in pooled analyses. When several effect estimates were available, we selected the estimate from the most fully adjusted multivariate model. Although in four studies[16–18,21] estimates were derived with inverse probability of treatment-weighted marginal structural models, we did not include these estimates in our primary pooled analyses because they were different from traditional regression approaches and the two should not be compared or combined. Specifically, traditional Cox models are used to estimate the average effect of treatment on an individual, whereas marginal structural models provide the average effect of treatment on the population.[22] However, we did separate analyses that combined only those estimates generated using inverse probability of treatment-weighted marginal structural model.

See Online for appendix

Evidence for statistical heterogeneity between studies was assessed for each hormonal contraception formulation (depot medroxyprogesterone acetate, norethisterone enanthate, combined oral contraceptives, or progestin-only

	Year	Study location(s)	Number of participants in study	Mean age of study population	Reference group	Intersurvey interval	Duration of follow-up
Crook, et al[47]	2013	South Africa, Uganda, Tanzania, Zambia	8663 women in microbicide trial; 786 in serodiscordant partnerships	27 years	Non-hormonal or no method	1 month	12 months (planned)
McCoy, et al[18]	2012	Zimbabwe, South Africa	4913 women in the MIRA trial	27·5 years	Non-hormonal or no method	3 months	17·9 months (median)
Morrison, et al[17]	2012	South Africa	5567 women in the Carraguard trial	28 years	Non-hormonal or no method	3 months	24 months (planned)
Heffron, et al[16]	2012	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	1314 women in serodiscordant partnerships in the Partners in Prevention Trial	30·2 years	Non-hormonal or no method	3 months	18 months (median)
Wand, et al[45]	2012	South Africa	2236 women in microbicide trial	27 years	Non-hormonal method*	3 months	Not reported
Morrison, et al[20,21]	2007, 2010	Uganda, Zimbabwe	4435 women recruited at health clinics	25 years	Non-hormonal method*	3 months	21·5 months (mean)
Reid, et al[44]	2010	South Africa, Zambia, Zimbabwe	1358 women in acyclovir trial (HPTN 039)	31 years	No method†	3 months	18 months (planned)
Baeten, et al[39]	2007	Kenya	1206 commercial sex workers recruited at communicable disease clinics	26 years	No method or tubal ligation‡	1 month	14·9 months (median)
Kleinschmidt, et al[40]	2007	South Africa	551 women recruited at family planning clinics	27·7 years	Non-hormonal or no method	3 months	12 months (planned)
Myer, et al[19]	2007	South Africa	4200 women in cervical cancer prevention trial	40 years	Non-hormonal or no method	6–12 months	14·3 months (median)
Kiddugavu, et al[26]	2003	Uganda	5117 women in the Rakai-community-based HIV prevention trial	25 years	Non-hormonal or no method, excluding condoms	10 months	31·2 months (median)

*Women using no method were excluded from all analyses. †Women using condoms or non-hormone methods were separate exposure categories and therefore were not included in the reference group. ‡Baeten and colleagues[39] noted that condom use was analysed 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. §Incidence rate ratio.

Table 1: **Descriptive characteristics of studies included in primary pooled analyses of the association of hormonal contraception and HIV**

pill) using the I^2 statistic and its 95% CI; an I^2 of greater than 50% indicated sufficient heterogeneity to contraindicate a pooled estimate.[23] When the I^2 was less than 50%, pooled-effect estimates were calculated with DerSimonian and Laird random-effects models.[24]

We assessed the robustness of findings and investigated heterogeneity through a series of a-priori secondary analyses. First, we did an influence analysis to identify whether any study alone disproportionately affected the results. Second, we stratified meta-analyses according to the risk profile of the study population (high risk *vs* general population), and the original study design (prospective cohort *vs* randomised trial). Third, because of concerns that having a reference group that is composed largely of condom users might artificially inflate the risk of HIV acquisition for users of hormonal contraception,[25] we investigated whether our results were sensitive to the exclusion of condom users from the comparison group. Last, we investigated whether the results were qualitatively different when studies with intersurvey intervals longer than the duration of the contraceptive methods under study (1–3 months) were excluded. All analyses were done in Stata (version 12.0).

We reported effect estimates as hazard ratios (HRs) because these were reported in all but one[26] of the studies in our pooled analyses. The investigators of that study reported incidence rate ratios, which are comparable to the HR.[27,28]

	Number of HIV seroconversions	Effect estimate (adjusted hazard ratio, unless otherwise noted)	IPTW-MSM estimate
Crook, et al[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, et al[18]			
Injectable depot medroxyprogesterone acetate	63	1·22 (0·84–1·74)	Not reported
Injectable norethisterone enanthate	17	1·15 (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, et al[37]			
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, et al[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, et al[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, et al[37,20]			
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, et al[44]			
Injectables, type not specified	Not reported	0·94 (0·46–1·92)	..
Oral contraceptive pill, type not specified	Not reported	0·91 (0·45–1·83)	..
Reference	Not reported	..	..
Baeten, et al[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	..	..

(Table 2 continued on next page)

Role of the funding source

There was no funder for this analysis. The corresponding author had full access to all the data in the study (previous publications) and had final responsibility for the decision to submit for publication.

Results

We identified 26 articles,[16–21,26,29–47] 12 of which met our inclusion criteria (figure 1; appendix).[16–21,26,39,40,44,45,47] Two articles were analyses of the same population; however, because different analytic approaches were used (Cox regression[20] *vs* inverse probability of treatment weighted marginal structural model[21]), both were included but in separate pooled analyses to prevent double counting.

All studies in the final sample were done in sub-Saharan Africa. Three, all prospective cohort studies, were designed specifically to assess the hormonal contraception–HIV relation.[20,39,40] Seven studies were secondary analyses on cohorts enrolled in randomised trials of various HIV[16–18,44,45,47] and one cervical cancer[19] prevention interventions. Two study populations consisted of women at high risk of HIV, commercial sex workers[39] or women in serodiscordant partnerships.[16] The remainder were composed of women in the general population, typically recruited at family planning or other health centres. The median age of participants ranged from 25 years to 40 years. With the exception of two studies in which women were surveyed every 6 months[19] or 10 months,[26] women in the other studies were surveyed at least every 3 months. With the exception of one study in which a subset of women were followed up for 6 months,[19] women were followed up for at least 1 year in the other studies. The median follow-up ranged from 12 months to 31·2 months. Because of

the heterogeneity in the presentation of estimates of loss to follow-up, we did not quantitatively summarise this metric. However, generally, study retention was high, with a minimum of six of 12 studies having retention rates of more than 85% (tables 1 and 2).

Funnel plots to assess injectable contraception and oral contraceptive pills were symmetrical, suggesting no publication bias for studies (appendix).

Ten reports were investigations of the association between depot medroxyprogesterone acetate and HIV. In pooled analyses, use of depot medroxyprogesterone acetate was associated with an increased risk of HIV acquisition compared with use of non-hormonal or no methods (pooled hazard ratio [HR] 1·40, 95% CI 1·16–1·69; figure 2). An influence analysis showed that no single study was altering the results (data not shown). The pooled-effect estimate for the three studies in which the inverse probability of treatment weighted marginal structural model was used (pooled HR 1·41, 1·15–1·72; table 3) was similar to the overall estimate.

In subgroup analyses, the pooled HR for the three prospective cohort studies was 1·44 (95% CI 1·04–2·01; table 3). A high level of between-study heterogeneity (I^2 51·1%, 95% CI 0–79·3) in the seven secondary analyses of cohorts from randomised controlled trials precluded the calculation of a pooled estimate for this subgroup (table 3).

The eight studies of women in the general population had a lower heterogeneity (I^2 27·3%, 95% CI 0–67·3) than did the primary analysis (42·5%, 0–72·5; table 3). The pooled estimate suggested a moderate increase in the risk of HIV acquisition (pooled HR 1·31, 95% CI 1·10–1·57; table 3). Estimates were higher in each of the two studies with women at high risk (1·73, 1·28–2·34, in commercial sex workers[39] and 3·93, 1·37–11·2, in women in serodiscordant partnerships).[16] However, the high heterogeneity (I^2 54·0%, 95% CI 0–88·7%; table 3) between these two studies contraindicated the pooled estimates.

In an analysis of the nine studies in which the reference group comprised women whose partners were using condoms (in addition to other methods or no method), the pooled effect estimate did not change much from the primary analysis (pooled HR 1·44, 95% CI 1·20–1·73; table 3). An analysis restricted to the eight studies in which the intersurvey interval did not exceed 3 months showed a pooled-effect estimate that was slightly larger than our primary analysis (1·48, 1·24–1·77; table 3).

The estimates of the relation between combined oral contraceptives or oral contraceptive pills with HIV were reported in ten studies. Risk of HIV acquisition was not increased in users of combined oral contraception or oral contraceptive pills compared with those using non-hormonal or no methods (pooled HR 1·00, 95% CI 0·86–1·16; table 4) and the results of our influence analysis showed that no study was affecting these results (data not shown). There was minimum evidence of between-study heterogeneity (I^2 0%, 95% CI 0–48·6; table 4). The pooled estimate for the five studies in which inverse probability of treatment weighted marginal structural model was used was similar to the primary pooled result (pooled HR 1·03, 95% CI 0·81–1·32; table 4). A subgroup analysis of the two studies in high risk women

	Number of HIV seroconversions	Effect estimate (adjusted hazard ratio, unless otherwise noted)	IPTW-MSM estimate
(Table continued from previous page)			
Kleinschmidt, et al[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, et al[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, et al[26]			
Injectable depot medroxyprogesterone acetate¶	16	0·84 (0·41–1·72)‖	..
Oral contraceptive pill, 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.[35] ‡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 24-month 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 2: **Exposures assessed in studies included in primary pooled analyses of the association of hormonal contraception and HIV**

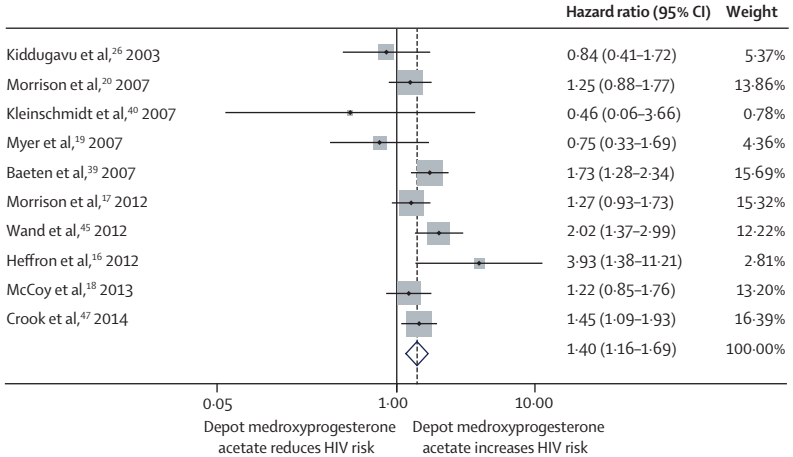

Figure 2: **Forest plot of the primary analysis of the relation between depot medroxyprogesterone acetate and HIV**

	Number of studies	I^2 (95% CI)	Pooled hazard ratio (95% CI)
Primary analysis[16–20,26,39,40,45,47]	10	42·5% (0–72·5)	1·40 (1·16–1·69)
IPTW-MSM analysis[17,21,47]†	3	0% (0–58·2)	1·41 (1·15–1·72)
Subgroup analysis			
Higher risk women[16,39]	2	54·0% (0–88·7)	··
Women in the general population[17–20,26,40,45,47]	8	27·3% (0–67·3)	1·31 (1·10–1·57)
Prospective cohort[20,39,40]	3	36·7% (0–79·9)	1·44 (1·04–2·01)
Sample from randomised control trials[16–19,26,45,47]	7	51·1% (0–79·3)	··
Sensitivity analysis			
Reference group includes women using non-hormonal or no methods[16–20,39,40,45,47]‡	9	40·8% (0–72·7)	1·44 (1·20–1·73)
Intersurvey interval of up to 3 months[16–18,20,39,40,45,47]§	8	36·1% (0–71·7)	1·48 (1·24–1·77)

IPTW-MSM=inverse probability of treatment weighted marginal structural model. *All pooled analyses were restricted to published, prospective studies of incident HIV infection in which depot medroxyprogesterone acetate was the predominant (or exclusive) exposure category, the comparison group was women using non-hormone or no contraceptive method (including condoms, unless otherwise noted), the model was adjusted for potential confounders of the hormonal-contraception-HIV relation, including condom use and age, and no more than 30% of the study population was lost to follow up. †In two additional studies,[16,18] estimates were derived with IPTW-MSMs; however, they were for injectable hormonal contraception and not specific to depot medroxyprogesterone acetate and are therefore not included here. ‡One study in which condom users were excluded from the reference group[26] was excluded from the meta-analysis. §Two studies with intersurvey intervals of 6 months[19] and 10 months[26] were excluded.

Table 3: **Comparison of results for primary, subgroup, and sensitivity analyses of the relation between depot medroxyprogesterone acetate and HIV by use of random-effects models***

	Number of studies	I^2 (95% CI)	Pooled hazard ratio (95% CI)
Combined oral contraceptive pills			
Primary analysis[16–20,26,39,44,45,47]	10	0% (0–48·6)	1·00 (0·86–1·16)
MSM-IPTW analysis[16–18,2147]	5	0% (0–55·2)	1·03 (0·81–1·32)
Subgroup analysis			
Higher risk women[16,39]	2	0% (0–0)	1·49 (1·04–2·13)
Women in the general population[17–20,26,44,45,47]	8	0% (0–0)	0·92 (0·78–1·18)
Prospective cohort[20,39]	2	52% (0–88·3)	··
Sample from randomised controlled trial[16–19,26,44,45,47]	8	0% (0–0)	0·91 (0·75–1·10)
Sensitivity analysis			
Reference group includes women using non-hormonal or no methods[16–20,39,45,47]†	8	0% (0–64·8)	1·00 (0·85–1·17)
Intersurvey interval of up to 3 months[16–18,20,39,44,45,47]‡	8	0% (0–64·3)	1·00 (0·86–1·16)
Norethisterone enanthate			
Primary analysis[17–19,40,47]	5	0% (0–74·6)	1·10 (0·88–1·37)
IPTW-MSM analysis[17,47]	2	36% (0–78·1)	1·08 (0·77–1·52)

IPTW-MSM=inverse probability of treatment weighted marginal structural model. *All pooled analyses were restricted to published, prospective studies of incident HIV infection in which the exposure category was predominantly (or exclusively) combined oral contraceptive pills or norethisterone enanthate, the comparison group was women using non-hormonal or no contraceptive method (including condoms, unless noted), the model was adjusted for potential confounders of the hormonal-contraception–HIV relation, including condom use and age, and no more than 30% of the study population was lost to follow up. †Two studies[26,44] in which condom users were excluded from the reference group were excluded. ‡Two studies with intersurvey intervals of 6 months[19] and 10 months[26] were excluded.

Table 4: **Comparison of results for primary and subgroup analyses of the combined oral contraceptive pills–HIV and norethisterone enanthate–HIV relationship using random-effects models***

showed an increased risk of HIV acquisition in users of combined oral contraceptives or oral contraceptive pills (pooled HR 1·49, 95% CI 1·04–2·13; table 4). There was only one study that assessed progestin-only pills as an exposure;[18] thus, we were not able to pool effect estimates for this specific exposure.

Estimates of the relation between norethisterone enanthate and HIV did not show an increased risk of HIV acquisition (pooled HR 1·10, 95% CI 0·88–1·37) and showed minimum heterogeneity (I^2 0%, 95% CI 0–74·6; table 4). Similar estimates were obtained for the two studies with inverse probability of treatment-weighted marginal structural model (pooled HR 1·08, 95% CI 0·77–1·52; table 4). The results of the influence analysis were not significant (data not shown) and subgroup analyses were not possible because of the small number of studies.

Discussion

The results of our meta-analysis showed that in observational studies with similarly and precisely defined exposures, adjustment for key confounders, minimum selection bias, and sound analytical approaches, there was a small but increased risk of HIV acquisition associated with use of depot medroxyprogesterone acetate. Consistent with the results of an earlier meta-analysis of oral contraceptive pills,[48] risk was not increased for users of oral contraceptive pills or combined oral contraceptives in the general population. Furthermore, there was no increased risk in users of norethisterone enanthate; however, the few studies in this analysis preclude any definitive statements about an association of norethisterone enanthate with HIV.

The results from this analysis, particularly for depot medroxyprogesterone acetate, should be used as an input parameter in ongoing modelling studies to quantify the compromises associated with removing injectables from the contraceptive method mix. For example, Butler and colleagues[6] used both a hypothetical (relative risk [RR] 1·2) and a single study (odds ratio 2·19)[16] estimate to predict changes in the numbers of HIV and maternal deaths after reductions in use of injectable hormonal contraception. Their findings suggest that, except in southern Africa where both HIV incidence and use of injectable contraception are high, the effect of removing hormonal contraception on the number of maternal and HIV-related deaths is sensitive to the chosen effect estimate. In view of these results, it is possible that an increased risk of magnitude found in our study (HR 1·4; figure 2), particularly for women in the general population, would not merit complete withdrawal of depot medroxyprogesterone acetate because maternal mortality would still exceed HIV-related deaths in most settings, particularly if women did not have immediate access to and uptake of alternate, effective contraceptive options in the absence of depot medroxyprogesterone acetate, one of the assumptions in Butler and colleagues' models.[6] Moving forward, we encourage Butler[6] and others[5,7] to apply our estimates and more fully explore regional or geographic and

subpopulation differences so that context-specific contraceptive policy can be developed.

Our analysis also provides an insight into potential sources of heterogeneity in results. Studies in women in the general population, representing most of the studies in our analysis, provide estimates of the average population effect of hormonal contraception on women's risk of HIV acquisition. By contrast, studies in women at high risk, of which there were two in our analysis, provide estimates of the effect of hormonal contraception conditioned on a high likelihood of HIV exposure. For the millions of users of hormonal contraception worldwide, most of who are not in serodiscordant or other high-risk partnerships, this distinction is crucial. Although the increased risks for users of depot medroxyprogesterone acetate and users of combined oral contraception or oral contraceptive pills reported in the two studies with commercial sex workers[39] and women in serodiscordant partnerships[16] might warrant consideration of changing contraceptive guidelines for these populations, it would be too early to do so based on the results of just two studies. Furthermore, it is important that the results of these two studies are not generalised to women in the general population, who according to the results of our study had a smaller increase in risk that might 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 reduced power in our planned secondary analyses or analysis of heterogeneity through meta-regression, only comparable estimates were combined. Contrary to the perception that these studies are too diverse for meta-analysis, we did not find heterogeneity that would preclude pooling estimates in most analyses. One notable exception is that although the studies done as secondary analyses of randomised trials contribute to the primary pooled analyses, we were unable to present a separate pooled estimate specific to this subset of studies for depot medroxyprogesterone acetate. The heterogeneity statistic for this group (I^2 51·1%; table 3) is borderline between moderate and substantial according to current Cochrane guidance.[49] Compared with the prospective cohort studies, each of which was designed specifically to examine the relation between hormonal contraceptive use and women's risk of HIV, the randomised trials had divergent research objectives. This might partly explain the higher level of heterogeneity noted in this subgroup. Hence, a very conservative application of our findings would be to use the pooled HR and 95% CI from only the prospective cohort studies. However, the randomised trials have many strengths, notably their large sample sizes, assessment of contraceptive method use and switching, and efforts to ensure high retention. In the absence of another prospective cohort study or data from the proposed randomised trial of the association of hormonal contraception and HIV,[50] the results of which will not be available for several years, other HIV prevention trials are the primary source of data to study this association in the near future.[51]

Our study findings have several limitations. First, meta-analyses of observational studies, like observational studies themselves, are inherently prone to bias and cannot be used to address whether the association between hormonal contraception and HIV is causal.[14] There has been extensive discussion about whether studies so far have sufficiently addressed the potential confounding effects of misreported condom use,[25,52] particularly because many study populations were drawn from HIV prevention trials in which condom use is strongly encouraged and women might feel pressure to report socially desirable behaviours.[53,54] However, the results of recent modelling studies suggest that the practical effects of misreporting condom use might be overstated. For example, Smith and colleagues[55] show that only a substantial amount of condom use under-reporting by non-hormonal contraceptive users, an unlikely scenario, could explain the increased effect estimate in the study by Heffron and colleagues[16] (HR 2·19 for all injectable contraception and 3·93 for depot medroxyprogesterone acetate specifically). Furthermore, our own work with biomarkers of unprotected sex has shown that misreporting of condom use is not significantly different between women using hormonal contraception and those using other methods, and therefore might not bias effect estimates to the extent suggested.[56] Even a randomised controlled trial is not likely to overcome many of the measurement challenges inherent to studying whether an association exists between HIV and use of hormonal contraception.[5,57] Likewise, the limitations of the original studies are also 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 hormonal contraception and subsequent acquisition of HIV in women.

A second limitation is that, despite our efforts to ensure systematic inclusion of all studies of the association between hormonal contraception and HIV and publication bias with funnel plots, like all meta-analyses, our results might 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. However, if studies with positive and significant effects of hormonal contraception on women's risk of HIV acquisition were more likely to be published, that would imply that our findings are an overestimate of the true association.

Although our study findings are similar to what was previously presented qualitatively in two systematic reviews[8–10] (ie, there is evidence of a moderate increase in the risk of HIV infection for users of injectable hormonal

contraception, specifically in women at high risk), this study is the first in which existing evidence is quantitatively summarised, particularly for depot medroxyprogesterone acetate, and a series of weighted, pooled estimates of effect and their variances are reported by type of hormonal contraceptive method used, for all studies published until May 31, 2014. Since we approached data extraction and definitions of study quality independently from the other reviews, our study provides another perspective of methodological rigour of the existing evidence.

In view of the concerns about the observational evidence gathered so far, efforts are underway to fund a randomised trial to investigate the relation between hormonal contraception and HIV. Arguably, the increase in risk noted for users of depot medroxyprogesterone acetate in our study, who would comprise one of the intervention groups, might violate the principle of equipoise required for a trial.[58] Another important concern is whether, with the methodological challenges inherent in studying the association between hormonal contraception and HIV,[57] the randomised trial will provide evidence superior to current evidence, especially when also considering the personal and financial investments required for a trial.[1] Our pooled estimates can inform contraceptive policy now, without waiting several years for trial data. Additionally, our findings emphasise an immediate need to refocus secondary analyses on commercial sex workers and women in serodiscordant partnerships because evidence for these women at high risk is inadequate but suggests an increased risk of HIV infection. Meanwhile, basic science research must continue so that the biological mechanisms underlying the association found here can be more precisely defined.[59] Imperative for public health is the continued need to promote a wide array of existing methods and develop and promote long-term options for reversible contraceptives for women worldwide.

Contributors

LJR, SIM, and NSP conceptualised 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 studies that met the eligibility criteria. LJR did all the statistical analyses with input from SIM and NSP. All authors contributed to manuscript preparation.

Declaration of interests

We declare no competing interests.

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References

1 Gollub E, Stein Z. Living with uncertainty: acting in the best interests of women. *AIDS Res Treat* 2012; **2012:** 524936.
2 Affairs UNDoEaS. World contraceptive use 2011. http://www.un.org/esa/population/publications/contraceptive2011/wallchart_front.pdf (Dec 10, 2014).
3 Singh S, Darroch JE, Ashford LS, Vlassoff M. Adding it up: the costs and benefits of investing in family planning and maternal and newborn health. New York: Guttmacher Institute and United Nations Population Fund, 2009.
4 Hormonal contraception and HIV: technical statement. Geneva, Switzerland: WHO, 2012.
5 Jain AK. Hormonal contraception and HIV acquisition risk: implications for individual users and public policies. *Contraception* 2012; **86:** 645–52.
6 Butler AR, Smith JA, Polis CB, Gregson S, Stanton D, Hallett TB. Modelling the global competing risks of a potential interaction between injectable hormonal contraception and HIV risk. *AIDS* 2013; **27:** 105–13.
7 Rodriguez MI, Reeves MF, Caughey AB. Evaluating the competing risks of HIV acquisition and maternal mortality in Africa: a decision analysis. *BJOG* 2012; **119:** 1067–73.
8 Polis CB, Curtis KM. Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence. *Lancet Infect Dis* 2013; **13:** 797–808.
9 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:** 263–84.
10 Polis CB, Phillips SJ, Curtis KM, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. *Contraception* 2014; **90:** 360–90.
11 Greenland S. Can meta-analysis be salvaged? *Am J Epidemiol* 1994; **140:** 783–87.
12 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000; **283:** 2008–12.
13 Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6:** e1000097.
14 Egger M, Davey Smith G, Altman D, eds. Systematic reviews in health care: meta-analysis in context. 2nd edn. London: BMJ Publishing Group, 2001.
15 Heffron R, Rees H, Mugo N, Baeten JM. Use of hormonal contraceptives and risk of HIV-1 transmission. *Lancet Infect Dis* 2012; **12:** 510–11.
16 Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis* 2012; **12:** 19–26.
17 Morrison CS, Skoler-Karpoff S, Kwok C, et al. Hormonal contraception and the risk of HIV acquisition among women in South Africa. *AIDS* 2012; **26:** 497–504.
18 McCoy SI, Zheng W, Montgomery ET, et al. Oral and injectable contraception use and risk of HIV acquisition among women in sub-Saharan Africa. *AIDS* 2013; **27:** 1001–09.
19 Myer L, Denny L, Wright TC, Kuhn L. Prospective study of hormonal contraception and women's risk of HIV infection in South Africa. *Int J Epidemiol* 2006; **36:** 166–74.
20 Morrison CS, Richardson BA, Mmiro F, et al. Hormonal contraception and the risk of HIV acquisition. *AIDS* 2007; **21:** 85–95.
21 Morrison CS, Chen P-L, Kwok C, et al. Hormonal contraception and HIV acquisition: reanalysis using marginal structural modeling. *AIDS* 2010; **24:** 1778–81.
22 Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; **11:** 550–60.
23 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–60.
24 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.
25 Gray RH. Use of hormonal contraceptives and risk of HIV-1 transmission. *Lancet Infect Dis* 2012; **12:** 507.
26 Kiddugavu M, Makumbi F, Wawer MJ, et al. Hormonal contraceptive use and HIV-1 infection in a population based cohort in Rakai, Uganda. *AIDS* 2003; **17:** 233–40.
27 Hernan MA. The hazards of hazard ratios. *Epidemiology* 2010; **21:** 13–15.

28 Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd edn. Philadelphia, PA: Lippincott, Williams, and Wilkins, 2008.

29 Plummer FA, Simonsen JN, Cameron DW, et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. *J Infect Dis* 1991; **162:** 233–39.

30 Saracco A, Musicco M, Nicolosi A, et al. Man-to-woman sexual transmission of HIV: Longitudinal study of 343 steady partners of infected men. *J Acquir Immune Defic Syndr* 1993; **6:** 497–502.

31 Laga M, Manoka A, Kivuvu M, et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS* 1993; **7:** 95–102.

32 Bulterys M, Chao A, Habimana P, Dushimimana A, Nawrocki P, Saah A. Incident HIV-1 infection in a cohort of young women in Butare, Rwanda. *AIDS* 1994; **8:** 1585–91.

33 Sinei SK, Fortney JA, Kigondu CS, et al. Contraceptive use and HIV infection in Kenyan family planning clinic attenders. *Int J STD AIDS* 1996; **7:** 65–70.

34 Ungchusak K, Rehle T, Thammapornpilap P, Spiegelman D, Brinkmann U, Siraprapasiri T. Determinants of HIV infection among female commercial sex workers in northeastern Thailand: results from a longitudinal study. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; **12:** 500–07.

35 Kilmarx PH, Limpakarnjanarat K, Mastro TD, et al. HIV-1 seroconversion in a prospective study of female sex workers in northern Thailand: continued high incidence among brothel-based women. *AIDS* 1998; **1998:** 1889–98.

36 Martin HL, Nyange PM, Richardson BA, et al. Hormonal contraception, sexually transmitted diseases, and risk of heterosexual transmission of human immunodeficiency virus type 1. *J Infect Dis* 1998; **178:** 1053–59.

37 Kapiga S, Lyamuya EF, Lwihula GK, Hunter DJ. The incidence of HIV infection among women using family planning methods in Dar es Salaam, Tanzania. *AIDS* 1998; **12:** 75–84.

38 Lavreys L, Baeten JM, Martin HL Jr, et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. *AIDS* 2004; **18:** 695–97.

39 Baeten JM, Benki S, Chohan V, et al. Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women. *AIDS* 2007; **21:** 1771–77.

40 Kleinschmidt I, Rees H, Delany-Moretlwe S, et al. Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort. *Contraception* 2007; **75:** 461–67.

41 Kumwenda NI, Kumwenda J, Kafulafula G, et al. HIV-1 incidence among women of reproductive age in Malawi. *Int J STD AIDS* 2008; **19:** 339–41.

42 Watson-Jones D, Baisley K, Weiss HA, et al. Risk factors for HIV incidence in women participating in an HSV suppressive treatment trial in Tanzania. *AIDS* 2009; **23:** 415–22.

43 Feldblum PJ, Lie CC, Weaver MA, et al. Baseline factors associated with incident HIV and STI in four microbicide trials. *Sex Transm Dis* 2010; **37:** 594–601.

44 Reid SE, Dai JY, Wang J, et al. Pregnancy, contraceptive use, and HIV acquisition in HPTN 039: relevance for HIV prevention trials among African women. *J Acquir Immune Defic Syndr* 2009; **53:** 606–13.

45 Wand H, Ramjee G. The effects of injectable hormonal contraceptives on HIV seroconversion and on sexually transmitted infections. *AIDS* 2012; **26:** 375–80.

46 Lutalo T, Musoke R, Kong X, et al. Effects of hormonal contraceptive use on HIV acquisition and transmission among HIV-discordant couples. *AIDS* 2013; **27** (suppl 1)**:** S27–34.

47 Crook AM, Ford D, Gafos M, et al. Injectable and oral contraceptives and risk of HIV acquisition in women: an analysis of data from the MDP301 trial. *Hum Reprod* 2014; **29:** 1810–17.

48 Wang CC, Reilly M, Kreiss JK. Risk of HIV infection in oral contraceptive pill users: a meta-analysis. *J Acquir Immune Defic Syndr* 1999; **21:** 51–58.

49 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Oxford: Cochrane Collaboration, 2011.

50 Cates W, on behalf of the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Consortium. Research on hormonal contraception and HIV. *Lancet* 2014; **383:** 303–04.

51 Polis CB, Westreich D, Balkus JE, Heffron R. Assessing the effect of hormonal contraception on HIV acquisition in observational data: challenges and recommended analytic approaches. *AIDS* 2013; **27** (suppl 1)**:** S35–43.

52 Schwartz SR, Pettifor A, Stuart GS, Cohen MS. Hormonal contraception and HIV: the methods have confused the message. *AIDS* 2013; **27** (suppl 1)**:** S45–53.

53 Gallo MF, Behets FM, Steiner MJ, et al. Validity of self-reported 'safe sex' among female sex workers in Mombasa, Kenya-PSA analysis. *Int J STD AIDS* 2007; **18:** 33–38.

54 Warner P. Concerns regarding design, analysis, and interpretation of the Morrison study on hormonal contraceptive use and acquisition of cervical infections. *Sex Transm Dis* 2005; **32:** 644.

55 Smith JA, Butler AR, Polis CB, Gregson S, Stanton D, Hallett T. Programmatic implications: balancing maternal mortality and HIV risk. 20th Conference on Retroviruses and Opportunistic Infections; Atlanta, GA, USA; March 3–6, 2013.

56 McCoy SI, Ralph LJ, Padian NS, Minnis AM. Are hormonal contraceptive users more likely to misreport unprotected sex? Evidence from a biomarker validation study in Zimbabwe. *AIDS Behav* 2014; **18:** 2259–64.

57 Ralph LJ, McCoy SI, Hallett T, Padian N. Next steps for research on hormonal contraception and HIV. *Lancet* 2013; **382:** 1467–69.

58 Jones HE. Time to focus on improving the contraceptive method mix in high HIV prevalence settings and let go of unanswerable questions. *Contraception* 2014; **90:** 357–59.

59 Murphy K, Irvin SC, Herold BC. Research gaps in defining the biological link between HIV risk and hormonal contraception. *Am J Reprod Immunol* 2014; **72:** 228–35.