Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence

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Whether or not the use of hormonal contraception affects risk of HIV acquisition is an important question for public health. We did a systematic review, searching PubMed and Embase, aiming to explore the possibility of an association between various forms of hormonal contraception and risk of HIV acquisition. We identified 20 relevant prospective studies, eight of which met our minimum quality criteria. Of these eight, all reported findings for progestin-only injectables, and seven also reported findings for oral contraceptive pills. Most of the studies that assessed the use of oral contraceptive pills showed no significant association with HIV acquisition. None of the three studies that assessed the use of injectable norethisterone enanthate showed a significant association with HIV acquisition. Studies that assessed the use of depot-medroxyprogesterone acetate (DMPA) or non-specified injectable contraceptives had heterogeneous methods and mixed results, with some investigators noting a 1·5–2·2 times increased risk of HIV acquisition, and others reporting no association. Thus, some, but not all, observational data raise concern about a potential association between use of DMPA and risk of HIV acquisition. More definitive evidence for the existence and size of any potential effect could inform appropriate counselling and policy responses in countries with varied profiles of HIV risk, maternal mortality, and access to contraceptive services.

Lancet Infect Dis 2013; 13: 797–808

Published Online July 19, 2013 http://dx.doi.org/10.1016/S1473-3099(13)70155-5

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See Online for appendix

Introduction

HIV and unintended pregnancy are both important public health concerns. HIV infection carries burdens beyond morbidity and mortality, including the complication of efforts to reduce poverty and improve access to education.[1] Contraception prevents unintended pregnancies, which reduces maternal and infant morbidity and mortality, decreases recourse to abortion, and provides non-health-related benefits (eg, increased education for women).[2] Furthermore, studies in which the association between pregnancy and HIV acquisition has been assessed have had conflicting results; the results of some (but not all) studies suggest that pregnancy could potentially increase risk of HIV acquisition in women, or transmission from women to men.[3–6] Hormonal contraceptives are among the most effective methods of pregnancy prevention. WHO continues to emphasise the need to better understand whether hormonal contraception affects the risk of HIV acquisition in HIV-negative women, HIV progression in HIV-positive women,[7] and female-to-male HIV transmission,[8] and whether or not it interacts with antiretroviral therapy.[9]

Several biological mechanisms by which use of hormonal contraception could theoretically increase the risk of HIV acquisition have been postulated.[10,11] Previous systematic reviews concluded that the overall epidemiological data did not suggest an association between use of hormonal contraception and HIV acquisition in the general population, but that data were equivocal in groups such as sex workers.[12,13] We aimed to update previous systematic reviews by examining reports of longitudinal studies that assessed the relation between use of hormonal contraception and HIV acquisition in HIV-negative women.

Methods

Search strategy and selection criteria

We did a systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[14] We searched PubMed and Embase for relevant articles published in any language up to Dec 15, 2011, and followed up additional references found in the reference lists of the reports identified. Appendix p 1 shows the full search strategy. The results of this search were supplemented by in-press reports that were brought to our attention. We included all longitudinal studies of HIV-negative women that measured incident HIV infections in women who used hormonal contraception (injectables, oral contraceptive pills, implants, patches, rings, or levonorgestrel intrauterine devices; not including emergency contraception) compared with women who did not use hormonal contraception. We excluded studies that did not report on the association between use of hormonal contraceptives and HIV acquisition; cross-sectional studies; studies for which updated data were available (earlier publications were used for background information); and studies that assessed only emergency contraception, which is not typically used as a regular hormonal contraceptive method.

We used EROS (Early Review Organizing Software; (Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina) for selection of relevant reports. One author (CBP) did the database search and screened titles and abstracts to identify studies for full-text review; both authors reviewed full-text reports and agreed about final study inclusion. Abstraction forms underwent expert review and pilot testing. Both reviewers independently assessed study quality and resolved differences by discussion. When necessary, we attempted

to contact study authors for clarifications. We used a standardised form to extract relevant data.

Quality assessment

For comprehensiveness, we examined all 20 studies that met our inclusion criteria. However, many of these studies had severe methodological flaws, and do not meaningfully contribute to the evidence base. Thus, we include information about all studies to provide a comprehensive report, but focus on the more robust studies.

To examine the quality of included studies, we used a component approach based on potential sources of bias particular to the topic under review.[14,15] For systematic reviews of observational studies, primary risks that should be assessed include selection bias and confounding, but also any other sources of bias that are specific to the topic. First, to identify the studies most likely to provide relevant information about our question of interest (ie, does hormonal contraception increase the risk of HIV acquisition via a biologic mechanism?), we assessed whether or not our included studies met a set of minimum quality criteria, which we developed on the basis of important methodological considerations in work on this topic.

Studies did not meet the minimum quality criteria if they contained at least two of three flaws: unclear definitions of exposure to hormonal contraception, high loss to follow-up, and inadequate consideration of potential confounders. We regarded the definitions of exposure as unclear if studies did not use time-varying exposure information, included other methods of hormonal contraception in the comparison group, or did not present separate estimates for different methods of hormonal contraception. For example, depot-medroxyprogesterone acetate (DMPA) is a progestin-only contraceptive, which could have different biological effects from combined oral contraceptive pills that contain both oestrogen and progestin.[11] Although different progestin-only methods, such as DMPA and norethisterone enanthate, might have different biological effects, few studies examined these two types of injectables separately; we present estimates for each method separately where possible.

We defined high loss to follow-up as a loss of 20% or more at 12 months.[16] We specified studies in which multivariate analyses (including, at minimum, assessment of condom use) were not done as having inadequate consideration of potential confounders. Additionally, since our aim was to identify those studies most likely to minimise bias, we determined that one study[17] did not meet the minimum quality criteria on the basis of a discussion with the study investigators. The investigators agreed with our concern that their data were unlikely to provide information about the biological effect of hormonal contraception on HIV acquisition, noting that in their data use of hormonal contraception indicated lack of condom use. The parameterisation and control for condom use in the study addressed condom use during only one sex act (last sex), and did not address condom use between surveys.

Data analysis

We created summary graphs of risk using Microsoft Excel 2007 (Microsoft, Redmond, WA, USA). However, because of between-study heterogeneity in design, analysis, and point estimates, we did not do a statistical meta-analysis.[18] Instead, we describe how various design or analytical factors might have contributed to heterogeneity.

Methodological considerations in studies that met the minimum quality criteria

Potential for confounding

For the studies that met our minimum quality criteria, we assessed several methodological features, similar to those taken into account in our systematic review of hormonal contraception and female-to-male transmission of HIV.[8] These factors included potential for confounding, handling of condom use, frequency and accuracy in variable measurement, and the reason for data collection.

Hormonal contraception users and non-users can differ in ways that also affect exposure to HIV—eg, users might have more frequent sexual encounters, less consistent condom use,[19–21] or be in longer-term relationships[22,23] than non-users. Since whether or not users and non-users are equally likely to have HIV-infected sexual partners is unknown, analysis of serodiscordant couples or adequately controlling for partner risk could provide a methodological advantage, although proxy measures of partner risk might not be very useful.[24] Users of hormonal contraception can differ from non-users with respect to other important factors that might relate to HIV risk, such as age, parity, education, marital status, behavioural risk, and pregnancy status. Pregnancy is strongly associated with non-use of hormonal contraception, and might be associated with HIV acquisition;[3] ideal methods to address pregnancy in analyses of hormonal contraceptive use and HIV acquisition are unclear. Users of hormonal contraception who use different contraceptive methods might have unequal distributions of other potentially important factors—eg, users of injectable contraceptive might be more likely than users of oral contraceptive pills to be post partum or breastfeeding, to use contraception covertly, or to use vaginal drying agents where a cultural preference for a dry rather than a lubricated vagina exists (J Stanback, FHI 360, personal communication).[25,26]

Statistical adjustment is not always sufficient to eliminate confounding—eg, self-reported information about condom use is often inaccurate.[27–29] Statistical

adjustment with inadequately measured information (or failure to adjust for important covariates) can leave residual confounding. Some researchers[30] have argued that studies of sex workers or mutually disclosed serodiscordant couples might contain less potential behavioural confounding than studies in other groups since these individuals are aware of their increased HIV risk, but this possibility has not been empirically established.

Factors that vary over time could potentially cause time-dependent confounding affected by previous exposure to hormonal contraceptives. In such cases, marginal structural models fitted with inverse probability weights might be preferred to other statistical approaches.[31–33] These models are complex and require several assumptions to be made. As with traditional statistical approaches, causal inference relies on the assumption that all confounders have been adequately measured and controlled for, or addressed by the study design.

Handling of condom use

Condom use, one of many potential confounders, is especially important with respect to the possibility of an association between use of hormonal contraception and HIV acquisition. Non-users of hormonal contraception might use condoms for pregnancy prevention, prevention of HIV and other sexually transmitted infections (STIs), or both. Users of hormonal contraception already use an effective contraceptive method, and the results of some studies[34–37] suggest that their use of condoms for prevention of HIV and other STIs is less consistent than use by women who use condoms for pregnancy prevention. In some studies,[38] consistent condom use, but not inconsistent condom use, is associated with reduced HIV risk, so controlling for consistency of condom use—rather than for any condom use—could be important.

The success of statistical adjustment for differences in condom use depends on accurate measurement and parameterisation of this variable. If users and non-users of hormonal contraception have differential validity of self-reported condom use, results could be biased towards or away from the null. Furthermore, asking participants about the entire inter-survey interval might produce different responses from asking them about a specified or typical period of time and extrapolating to a longer interval.

Comparison of users of hormonal contraception with women who use condoms as a primary contraceptive method could be problematic if condom use or consistency of use differs and is not adequately controlled for. Comparison of users of hormonal contraception with non-users who do not report condoms as a primary contraceptive method (with statistical adjustment for remaining differences in condom use for prevention of infection) could potentially equalise dimensions of condom use that are difficult to measure accurately (eg, consistency, use with partners of varied risk profiles), but reasons for condom use might not be clear, and associations between reasons for and patterns of condom use are unknown. Analyses stratified by condom use could help to decrease confounding, but for populations in which condom use is common, this strategy might have low statistical power. The best approach to handling condom use is unclear and might depend partly on the population studied. Use of several approaches could help to assess the robustness of results. Assessment of the association between self-reported consistent condom use and reductions in HIV or pregnancy could help to confirm the validity of self-reported data in this context, which would enhance confidence in successful adjustment for condom use.

Frequency and accuracy of variable measurement

Use of hormonal contraception and HIV status should be measured repeatedly and frequently to ascertain whether the hormonal contraception was used at the time of HIV infection and to minimise potential misclassification of exposure. Use of time-varying information, preferably collected within short inter-survey intervals, can reduce misclassification. Long inter-survey intervals increase the chances of recall bias, complicate the establishment of a temporal relation between exposure and outcome, and might not capture contraceptive switching. We regarded an inter-survey interval of 6 months or less as a methodological advantage. Most contraceptive information was self-reported, but validation with clinical records can enhance accuracy. Collection of information about exposure to hormonal contraception exclusively from patients' medical records could result in poor measurement, but an association between information about hormonal contraceptive use and reduced pregnancy rates could enhance confidence.

Aim of data collection

Studies that aimed mainly to assess the relation between use of hormonal contraception and HIV acquisition could theoretically collect more comprehensive information about important variables than studies with a different primary aim. For secondary analyses, the effects of inclusion and exclusion criteria and the quality of information about relevant variables are important considerations. Secondary analyses should specify analytical plans a priori to discourage selective reporting of significant results from post-hoc analyses.

Statistical power and precision

Studies can have low statistical power to detect an effect if the sample size is small, users of hormonal contraception are few, or HIV incidence is low. In attempting to draw causal inference, particularly from observational data, caution is warranted if 95% CIs are wide and p values are marginal,[39] especially for small point estimates.

Results

All included studies

From 634 records, we identified 20 eligible reports (figure 1);[5,17,40–57] all were of observational studies. Of these eligible studies, 17 used data from African countries,[5,17,40,42–44,47–57] two from Thailand,[45,46] and one from Italy.[41] 16 included estimates specific to oral contraceptive pills,[5,17,40–42,44–50,54–57] 14 included estimates specific to injectable contraception,[5,17,45–52,54–57] and two did not distinguish between methods of hormonal contraception, but the investigators noted that most of the users of hormonal contraception used injectables.[43,53] None of the eligible studies examined the contraceptive patch, ring, implant, or levonorgestrel intrauterine device.

Appendix pp 3–8 describes the 20 eligible studies and states whether or not they met the minimum quality criteria. Figure 2 summarises the 16 results for oral contraceptive pills, and figure 3 summarises the results for injectables (the two studies with non-specified methods of hormonal contraception are included with the 14 that reported estimates specific to injectables). In figures 2 and 3, all studies are shown irrespective of methodological quality, and are in decreasing order of risk estimate. For both oral contraceptive pills and injectables, study results are heterogeneous, and in several studies the power to detect an effect was low. Of the 16 studies that examined oral contraceptive pills, two reported significantly increased HIV risk.[40,49] The remainder showed no significant differences: six reported a non-significant increase in risk,[44,46–48,55,56] six reported a non-significant decrease,[5,17,42,45,50,57] the direction of the estimate varied in one study dependent on the statistical approach used,[23,54] and the investigators of one[41] could not calculate risk because no seroconversions occurred in the hormonal contraception group (figure 2). Of the 16 studies that examined injectables, seven[17,45,49,52,54–56] reported significantly increased risks of HIV associated with contraceptive use (one[54] was not significant when an alternative Cox proportional hazards approach was used in the original analysis[23]), three[43,46,53] reported a non-significant increase in risk, four[5,47,48,50] reported a non-significant decrease in risk, and two[51,57] reported non-significant point estimates separately for norethisterone enanthate and DMPA (figure 3).

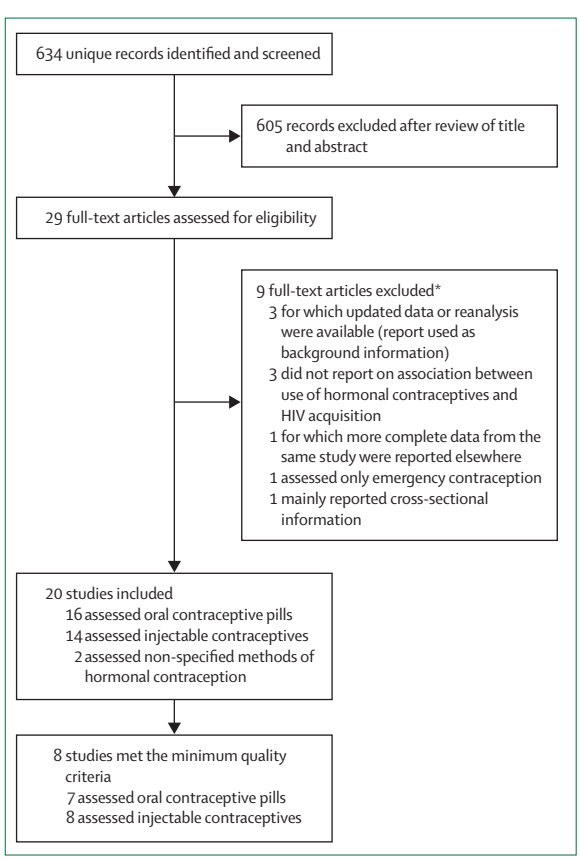

Figure 1: **Study selection**
*Excluded articles are listed in the appendix (p 2).

Studies that met minimum quality criteria

Of the 20 eligible studies, eight met the minimum quality criteria (appendix pp 9–12).[5,48–51,54,56,57] Of the seven of these that assessed oral contraceptive pills (figure 4), one[49] reported a borderline-significant increase in risk (p=0·05; adjusted hazard ratio [HR] 1·5, 95% CI 1·0–2·1). Three[48,54,56] reported non-significant increases in risk, and three[5,50,57] reported non-significant decreases in risk.

Of the eight analyses for injectables that met the minimum quality criteria, three[49,54,56] reported significant increases in risk (figure 5). Estimates by Morrison and colleagues[23,54] were significant when marginal structural model analysis[54] was done (adjusted HR 1·5, 95% CI 1·0–2·2), but not when a Cox proportional hazards model[23] was used (adjusted HR 1·3, 95% CI 0·9–1·8). Four studies[5,48,50,57] reported non-significant findings, including the largest study,[57] which reported an adjusted HR for DMPA of 1·3 (95% CI 0·9–1·8). Kleinschmidt and colleagues[51] reported an unadjusted incidence risk ratio (IRR) for any injectable of 1·1 (95% CI 0·5–2·8), and also presented unadjusted and adjusted HRs for norethisterone enanthate (adjusted HR 1·8, 95% CI 0·6–4·8) and DMPA (adjusted HR 0·5, 0·1–3·8). Unadjusted and adjusted estimates for each individual contraceptive method were similar, but the DMPA estimate was based on an analysis with only one seroconverter and should be interpreted cautiously. None of three estimates specific to norethisterone enanthate[50,51,57] were significant. A comparison of norethisterone enanthate with DMPA did not show a consistent pattern whereby one method generated a higher risk estimate than the other.

All eight studies that met the minimum quality criteria included, or assessed the need for, statistical control for some parameterisation of condom use, age, number of sexual partners, and at least one genital symptom or infection. Other factors, such as marital status, frequency of sexual encounters, or partner risk, were accounted for only in some of the studies (appendix p 13).

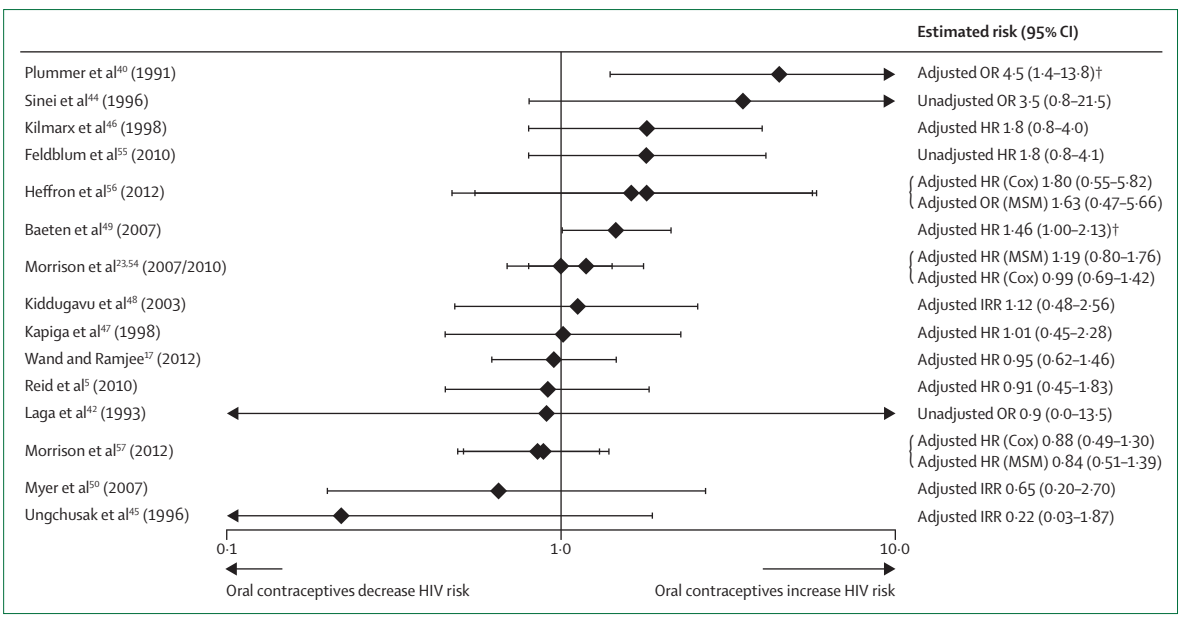

Figure 2: **Use of oral contraceptive pills and HIV acquisition (all 16* studies)**
For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. OR=odds ratio. IRR=incidence risk ratio. HR=hazard ratio. *Data from Saracco and colleagues' study[41] are not shown because risk could be calculated since no seroconversions occurred in the hormonal contraception group. †Analysis showed significant findings.

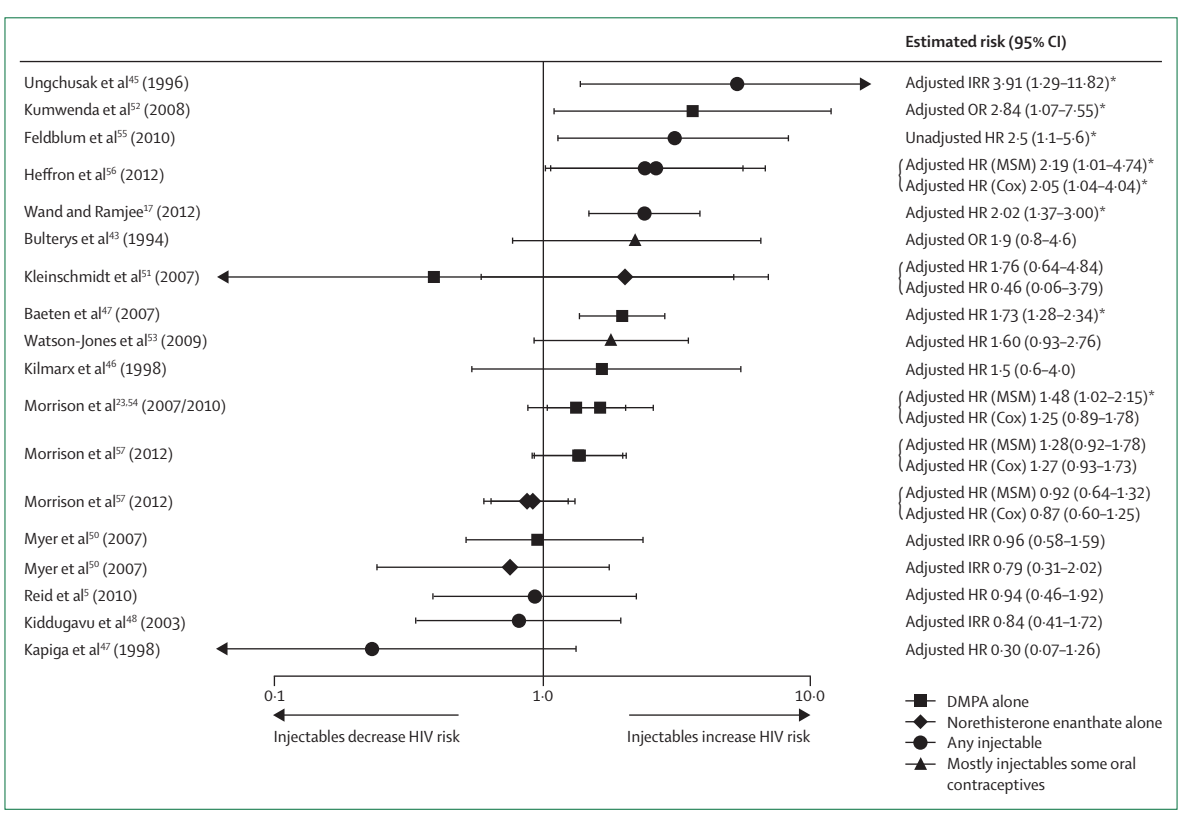

Figure 3: **Use of injectable contraceptives and HIV acquisition (all 16 studies)**
For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. IRR=incidence risk ratio. OR=odds ratio. HR=hazard ratio. DMPA=depot-medroxyprogesterone acetate. *Analysis showed significant findings.

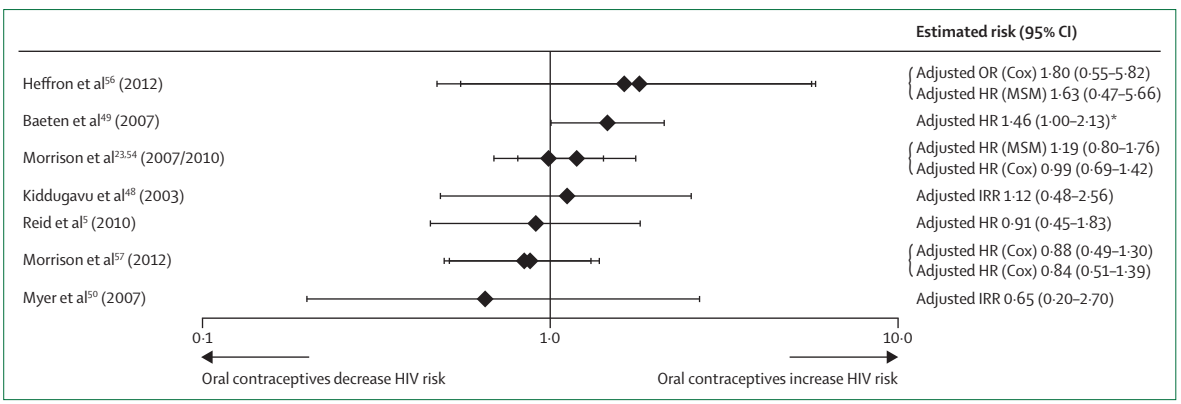

Figure 4: **Use of oral contraceptive pills and HIV acquisition (seven studies that met minimum quality criteria only)**
For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. OR=odds ratio. HR=hazard ratio. IRR=incidence risk ratio. *Analysis showed significant findings.

Considerations of findings for injectables

For the studies of injectables that met the minimum quality criteria,[5,48–51,54,56,57] we considered how differences in study design or analysis might have contributed to heterogeneity in the results. We examined several factors that did not seem to account for the heterogeneity of results, including source of study population, HIV incidence, study size, number of seroconverters, statistical approach, and handling of pregnancy information. We identified four factors that merit further consideration: length of inter-survey interval, handling of condom use, analysis of serodiscordant couples, and reason for data collection.

In one study women were interviewed at intervals of roughly 1 month,[49] in five studies every 2–4 months,[5,51,54,56,57] and in two studies every 8 or 10 months.[48,50] The three studies with significant findings had inter-survey intervals of 4 months or less, including one with intervals of about 1 month.[49,54,56] Three other studies with inter-survey intervals of less than 4 months showed no significant differences in risk.[5,51,57] Two studies with intervals of more than 4 months also did not show significant associations.[48,50]

Six studies addressed condom use via statistical adjustment alone,[49–51,54,56,57] including all three that reported significant increases in risk.[49,54,56] Myer and colleagues[50] addressed condom use via statistical adjustment alone and did not report a significant association, but low overall condom use might have minimised the potential for confounding from this factor. The remaining two studies,[5,48] neither of which reported increased risk, addressed condom use differently. Reid and colleagues[5] compared users of hormonal contraception with women who did not report use of hormonal contraception or condoms as a primary contraceptive method, and statistically adjusted for unprotected sex and other factors. In Kiddugavu and colleagues' study,[48] no HIV seroconversions occurred among self-reported consistent condom users, but self-reported inconsistent condom use was a marker for HIV acquisition, and most condom use (70%) was inconsistent. In a multivariate analysis, the investigators compared users with non-users of hormonal contraceptives who reported no condom use. The non-users who also did not use condoms had a lower unadjusted HIV incidence than did the non-users of hormonal contraception who used condoms. The effect of analysis with this reference group is unclear; such analysis could theoretically dilute a potential adverse effect of hormonal contraception if users of hormonal contraception also used condoms concurrently and consistently (which might have occurred in very few women), but this approach might have been the most conservative, since the reference group had the lowest unadjusted incidence of HIV. For both of these studies, the effect of exclusion of women who used condoms for contraception is unclear, and other potential explanations for the null findings are possible.

In addition to their main analyses, four studies also restricted analysis to women with no condom use;[23,48,50,51] none showed significant increases in risk associated with injectable contraceptives, but approaches and estimates varied and 95% CI s were wide. Morrison and colleagues[23] restricted analysis to the subgroup of women who reported no condom use and adjusted for all covariates in the main Cox proportional hazards statistical model (adjusted HR for DMPA 1·6, 95% CI 0·9–3·1). Myer and colleagues[50] restricted analysis to the subgroup of women who reported never or sometimes using condoms and adjusted for age (adjusted IRR for DMPA 1·0, 95% CI 0·6–1·7; adjusted IRR for norethisterone enanthate 0·7, 0·3–2·0; L Myer, University of Cape Town, personal communication). Kiddugavu and colleagues[48] and Kleinschmidt and colleagues[51] restricted analysis to women who reported never using condoms, but did not adjust for other covariates (unadjusted IRR for any hormonal contraception 1·6, 95% CI 0·9–2·7;[48] unadjusted IRR for injectables 0·8, 0·1–4·7).[51] None of the three studies that reported increased risks associated with

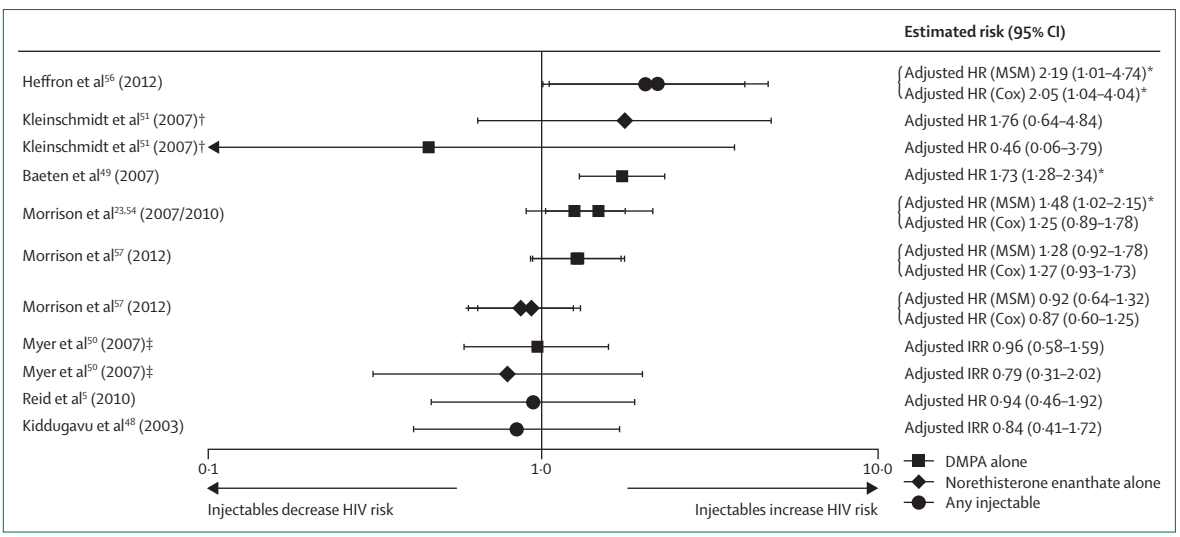

Figure 5: **Use of injectable contraceptives and HIV acquisition (eight studies that met minimum quality criteria only)**
For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. HR=hazard ratio. IRR=incidence risk ratio. DMPA=depot-medroxyprogesterone acetate *Analysis showed significant findings. †Kleinschmidt and colleagues[48] also reported a combined estimate for DMPA and norethisterone enanthate (unadjusted IRR 1·12, 95% CI 0·45–2·78). ‡Myer and colleagues[47] also reported a combined estimate for DMPA and norethisterone enanthate (adjusted IRR 0·94, 95% CI 0·59–1·49).

injectables in the main model provided estimates stratified by condom use. Across the studies that met the minimum quality criteria, reporting on the association between self-reported consistent condom use and outcomes such as pregnancy or HIV varied, which complicated assessment of the validity of self-reported condom use.

The results of the only study done in serodiscordant couples,[56] in which potential confounding by differential exposure to HIV-positive partners might be less of a concern than in other studies, suggested significantly increased risk of HIV associated with use of injectables.

In three studies[23,49,51,54] data were obtained specifically to address the relation between hormonal contraception and HIV acquisition. Kleinschmidt and colleagues[51] detected no significant effects, but had low statistical power, particularly for DMPA. The results reported by Baeten and colleagues[49] and Morrison and colleagues[23,54] suggested significantly increased risks of HIV associated with DMPA (Baeten and colleagues[49] also reported an association with oral contraceptive pills).

Effect modification

Several factors that might modify the possible effect of hormonal contraceptives on HIV acquisition were assessed in some of the eight studies, including age, infection with herpes simplex virus 2 (HSV2) or other STIs, site in multisite studies, and condom use or participant behavioural risk. In their marginal structural model analysis, Morrison and colleagues[54] reported that both DMPA and oral contraceptive pills were associated with increased HIV acquisition in women aged 18–24 years (adjusted HR for DMPA 2·7, 95% CI 1·6–4·7; adjusted HR for oral contraceptive pill 2·0, 1·2–3·6), particularly in women aged 18–20 years (adjusted HR for DMPA 9·29, 2·72–31·69; adjusted HR for oral contraceptive pill HR 3·68, 0·88–15·31), but not in women aged 25 years and older (adjusted HR for DMPA 0·8, 0·5–1·4; adjusted HR for oral contraceptive pill 0·7, 0·4–1·3). In a subsequent study,[57] Morrison and colleagues reported a significant (p=0·03) interaction for young age and increased risk associated with norethisterone enanthate, but did not report whether interactions were significant for oral contraceptive pills or DMPA (although they described their findings as providing "modest evidence" of an increased risk of HIV acquisition in young women who used DMPA). Kleinschmidt and colleagues[51] reported higher adjusted point estimates for HIV acquisition in women aged 15–19 years than in older women, but differences from other age groups were not significant. Neither Kiddugavu and colleagues,[48] Baeten and colleagues,[49] nor Heffron and colleagues[56] detected effect modification by age, nor did Myer and colleagues,[50] although their study was done in women aged 35–49 years.

In their marginal structural model analysis, Morrison and colleagues[54] reported that DMPA was associated with increased HIV risk in HSV2-negative (adjusted HR 4·5, 95% CI 2·0–10·2), but not HSV2-positive (adjusted HR 1·0, 0·7–1·6) women. Neither Baeten and colleagues[49] nor Heffron and colleagues[56] noted an effect modification by HSV2 status, although both studies included few HSV2-negative women. In their later study, Morrison and colleagues[57] reported no evidence of an interaction between use of hormonal contraception and prevalent chlamydia or gonorrhoea that affected HIV acquisition.

Morrison and colleagues[23] reported a significant interaction by study site (point estimates of HR for both oral contraceptive pills and DMPA were above 1·0 in Uganda, but below 1·0 in Zimbabwe) on the basis of their original Cox proportional hazards analysis, but in their reanalysis of these data[54] with a marginal structural models approach they did not assess this interaction. In their later study,[57] Morrison and colleagues reported no evidence of effect modification between hormonal contraception and condom use as reported at baseline, or by participant behavioural risk.

Discussion

Included studies

The results of 20 prospective, observational studies that investigated a possible association between the use of hormonal contraception and HIV acquisition were heterogeneous. We identified eight of these studies that met our minimum quality criteria, which we therefore believe are the most likely to provide insight into this question.

Oral contraceptive pills

Most available evidence does not suggest that oral contraceptive pills are associated with an increased risk of HIV acquisition. Baeten and colleagues[49] reported that oral contraceptive pills were associated with a 46% increase in risk among sex workers in Kenya (p=0·05). Heffron and colleagues[56] reported non-significant point estimates for oral contraceptive pills of 1·6 (adjusted OR, marginal structural model) to 1·8 (adjusted HR, Cox proportional hazards model), which is slightly higher than those reported by Baeten and colleagues,[49] but the results included only three seroconverters who used oral contraceptive pills, which resulted in low statistical power and precision. Morrison and colleagues[54] assessed the most seroconverters who were using oral contraceptive pills of the seven studies that met the minimum quality criteria (appendix pp 9–12), and reported no increase in HIV risk. The marginally significant findings for oral contraceptive pills reported by Baeten and colleagues[49] might be related to factors specific to sex workers, short inter-survey intervals, chance, or residual confounding.

Injectable contraceptives

The observational data for use of injectable contraceptives and risk of HIV acquisition are difficult to interpret. Residual confounding could generate a spuriously increased estimate, mask a real effect, or both. We attempted to discern whether specific methodological factors could help to account for the heterogeneity of the findings from the studies that met our minimum quality criteria. Since users of hormonal contraception might be less likely to use condoms consistently than non-users,[34–37] we hypothesised that failure to adequately capture and control for differences in patterns of condom use is more likely to generate spuriously increased risks than to mask an effect, but bias could work in either direction. Of the three studies that reported significant associations,[49,54,56] all had short inter-survey intervals (although three other studies with short inter-survey intervals[5,51,57] did not show significant associations), and one of these studies[56] was the only reported analysis in serodiscordant couples. Of the three studies intended to assess a potential association between hormonal contraception and HIV acquisition,[23,49,51,54] one[49] suggested an increased risk from both oral contraceptive pills and DMPA; one[23,54] suggested an increased risk from DMPA with one statistical model, but not with another; and one[51] suggested no increased risk from DMPA, but had low statistical power. Of the three studies with significant results,[49,54,56] other methodological strengths included that two addressed the potential for time-dependent confounding[54,56] (as did one study with non-significant results[57]), and one validated reports of contraceptive method with clinical records.[54] Some evidence raises questions about potential subgroup effects in young women or HSV2-negative hormonal contraception users, but findings were inconsistent. Possible mechanisms for such interactions have been postulated,[23,54] but have not been proven. Reported effect modification by country is also difficult to interpret.[23] Differential ability to control for confounding across various strata (eg, age or site) could generate spurious findings about effect modification.

Our critiques of studies that have generated non-significant estimates are generally related to length of the inter-survey intervals, measurement of contraceptive use, and concern about low or potentially differential exposure to HIV. For example, Kiddugavu and colleagues[48] and Myer and colleagues[50] had inter-survey intervals greater than 6 months, which could reduce accuracy in measurement of exposure and other time-varying variables, as well as the relative timings of exposure and outcome. Reid and colleagues[5] used self-reported contraceptive data captured in patient medical records and abstracted into a database at the end of the study, which complicated assessment of how systematically exposure information was collected; however, use of hormonal contraception was associated with reduced risk of pregnancy in their study. If users of hormonal contraception are less likely to have HIV-infected partners, this difference could mask a harmful effect of the contraception, and none of the studies with non-significant findings assessed serodiscordant couples. Some studies had low statistical power, and none of the studies had an upper-bound 95% CI inconsistent with an up to 60% increase in risk of HIV acquisition. The study with the greatest statistical power[57] had a non-significant adjusted HR for DMPA, but a lower-bound 95% CI close to 1.

Our critiques of studies that have generated significant estimates are generally related to whether potential differences in condom use or other sexual behaviours were

adequately controlled for, and whether increased risk from several methods of hormonal contraception or outcomes (eg, both acquisition in women and transmission to men) might suggest potential residual confounding. For example, in Morrison and colleagues' study[23,54] self-reported consistent condom use did not decrease HIV risk, which complicated assessment of the success of control for condom use. In this study, most (84%) non-users of hormonal contraception reported using condoms at baseline, and large differences in self-reported condom use between users and non-users of hormonal contraception persisted throughout the study.

Use of marginal structural model analysis in recent studies should reduce the potential for time-dependent confounding, but these models cannot correct for issues related to variable measurement. In Heffron and colleagues' study,[56] less than 8% of study intervals included any self-reported unprotected sex, and despite low reported coital frequency, HIV incidence was 4·09 per 100 person-years, which could potentially suggest underreporting of unprotected sex. Such underreporting, if it occurred, could generate a spurious result if users of hormonal contraception underreported differentially, although the scale of differential reporting might need to be large to account for the doubling in risk of HIV acquisition reported (J Smith, Imperial College London, personal communication). In none of the studies with significant estimates of HIV risk from injectables were women asked about condom use during the entire preceding inter-survey interval, which has unknown effects on response validity. Both Heffron and colleagues[56] and Baeten and colleagues[49] reported increased point estimates of risk for both oral contraceptive pills and injectables, and Heffron and colleagues[56] reported increased point estimates of risk for both HIV acquisition in women and transmission to men. Such findings could represent actual increases in risk for several methods and mechanisms, or systematic bias from uncontrolled differences between users and non-users of hormonal contraceptives.

Limitations

We have described several limitations of the available evidence on the relation between use of hormonal contraception and HIV acquisition. All eight minimum-quality studies were observational and could be affected by residual confounding with effects in either direction, and several have low statistical power. Little evidence is available for methods of hormonal contraception other than oral contraceptive pills and injectables, and for whether length of time using hormonal contraception affects risk. Although none of the eight studies specifically investigated hormone dosages, earlier analyses of data in Baeten and colleagues' study[49] reported higher point estimates for high-dose than for low-dose oral contraceptive pills (adjusted HR 2·6, 0·8–8·5 *vs* 1·3, 0·7–2·4),[58] and non-significantly increased estimates for a contraceptive implant (adjusted HR 1·6, 0·5–5·7), a progestin-only contraceptive with a lower dose than DMPA.[59] Whether or not any potential increase in HIV risk might be related to the presence of hormones or follow a dose-response relation is unknown.

Systematic assessment of the risk of bias in individual observational studies is a difficult and necessarily subjective process.[14,60,61] We used the component approach, in which risk of bias items are specific to the topic under review.[14] We examined all available evidence, and attempted to identify studies with reduced risk of bias through the development of minimum quality criteria. Other investigators might have chosen different criteria, which could have led to the inclusion of a different subset of studies. For example, Reid and colleagues' study[5] has been criticised for its measurement of contraceptive exposure and for having some proportion (7·6%) of missing data; but this study met our minimum quality criteria, provided some evidence for the validity of information about exposure to hormonal contraception (hormonal contraception reduced pregnancy risk), assessed missing data as a separate exposure, and included desirable components in terms of control for condom use.

Similarly, we excluded Wand and Ramjee's study,[17] which included a very small number of implant users within the injectable group, because of concerns about potential residual confounding related to condom use. We excluded that study because our aim was to identify the studies most likely to isolate an unconfounded effect of hormonal contraception on HIV acquisition. However, Wand and Ramjee's study is similar to other secondary analyses from HIV prevention trials that met our minimum quality criteria, and an argument for its inclusion could be made.

WHO technical consultation

A draft of this systematic review was presented at a WHO technical consultation in Geneva, Switzerland, in January, 2012, alongside presentations on related issues.[62] Using the GRADE system,[63] the eight studies reviewed were given a rating of low quality because of serious limitations and inconsistencies. After vigorous discussion, 75 experts concluded by consensus that WHO should recommend no restriction on use of any method of hormonal contraception for women at high risk of HIV, but added a strong clarification that, because of the inconclusive nature of the evidence, women who use progestin-only injectables should be strongly advised to also always use male or female condoms and other HIV preventive measures (see technical statement[62] for full clarification).

Users and providers of contraceptives should be informed about the risks and benefits of all available options. As interpretations evolve and new evidence emerges, WHO will continue to review their recommendations and communications. For example, studies

reported in academic journals since the cutoff for inclusion in this review will be carefully examined and incorporated at the next technical consultation on this issue. This future assessment will include sensitivity analyses by Heffron and colleagues in support of their original findings;[64] a study by McCoy and colleagues[65] in which injectables (DMPA and norethisterone enanthate), but not oral contraceptive pills, were associated with a significant 32% increase in risk in a model adjusted only for site, and a similar but non-significant point estimate in a marginal structural model, as well as any additional studies that are reported in the interim.

Conclusions and future directions

Many women need safe and effective means to prevent pregnancy and STIs. Pending availability of multipurpose prevention technologies,[66] use of a highly effective contraceptive method in addition to condoms can provide protection against both pregnancy and STIs, including HIV. Most available evidence does not suggest an association between use of oral contraceptive pills and HIV acquisition. No evidence suggests a significant association between norethisterone enanthate and HIV acquisition, but few data are available.

Data for other injectable contraceptives and HIV acquisition are difficult to interpret. Some observational data suggest a possible association between use of DMPA and risk of HIV acquisition, but these findings are not supported by the results of several other studies. Moreover, some of the effect, if present, of DMPA on HIV acquisition could be mediated by differences in sexual behaviours; and a causal effect exclusive of behavioural differences has not been shown. The available data raise sufficient concern that women at high risk for HIV who choose to use progestin-only injectables should be strongly urged to also use condoms and to take other measures to prevent HIV.

More definitive evidence for whether or not a causal association exists (and if such an effect does exist, its size) is needed to inform appropriate policy responses in countries with varied profiles of HIV risk, maternal mortality, and access to contraceptive services. Similarly, a more precise measurement of any possible effect size, including for subpopulations such as young age groups, could help women to assess different available contraceptive options with respect to the risks of HIV and unintended pregnancy. Modelling studies suggest that even if DMPA were to double the risk of HIV acquisition, in most contexts—with the possible exception of southern Africa—withdrawal of DMPA is unlikely to be of overall public health benefit, although recommendations might vary by epidemiological context and by an individual woman's circumstances.[67–69] As discussions continue about the best approaches to clarify this important issue and to communicate the risks and benefits of all contraceptive methods to users and providers, the HIV, family planning, and global health communities must work together to ensure accurate communication of existing knowledge, and to create an enabling environment for prevention of HIV and unintended pregnancy.

Contributors

CBP did the database search and identified studies for full-text review. CBP and KMC assessed the included studies and wrote the report.

Conflicts of interest

CBP was involved in a study to assess the acceptability of two types of injectable contraceptive methods in HIV-positive women in Uganda; one of the products for that study was donated by Pfizer, but the company did not provide any financial or other support. KMC declares that she has no conflicts of interest.

Acknowledgments

The US Agency for International Development (USAID) and Centers for Disease Control and Prevention (CDC) contributed staff time for work on this systematic review. The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of USAID or the CDC. We thank Mary Lyn Gaffield, Sharon Phillips, and Nathalie Kapp for support and guidance; Roger Chou, Mark Helfand, and Zdenek Hel for expert advice; Jared Baeten, Renee Heffron, Charlie Morrison, and Ron Gray for in-depth comments on an earlier draft of the report; Agustin Ciapponi and Demián Glujovsky for support with the EROS software; and Nellie Kamau and LaToya Armstrong for assistance with the search strategy. A subgroup of the advisory committee for the WHO Hormonal Contraception and HIV technical consultation provided valuable comments on an earlier draft of the report; members included Tim Farley, Phil Hannaford, Bert Petersen, Michael Mbizvo, Trisha Wood-Santos, Monica Kerrigan, and Siobhan Malone. We thank those study investigators who provided additional information about their analyses, and all the individuals who have participated in studies that have advanced our understanding of this important topic.

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