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Review article

Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence☆

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Abstract

Whether use of various types of hormonal contraception (HC) affect risk of HIV acquisition is a critical question for women's health. For this systematic review, we identified 22 studies published by January 15, 2014 which met inclusion criteria; we classified thirteen studies as having severe methodological limitations, and nine studies as "informative but with important limitations". Overall, data do not support an association between use of oral contraceptives and increased risk of HIV acquisition. Uncertainty persists regarding whether an association exists between depot-medroxyprogesterone acetate (DMPA) use and risk of HIV acquisition. Most studies suggested no significantly increased HIV risk with norethisterone enanthate (NET-EN) use, but when assessed in the same study, point estimates for NET-EN tended to be larger than for DMPA, though 95% confidence intervals overlapped substantially. No data have suggested significantly increased risk of HIV acquisition with use of implants, though data were limited. No data are available on the relationship between use of contraceptive patches, rings, or hormonal intrauterine devices and risk of HIV acquisition. Women choosing progestin-only injectable contraceptives such as DMPA or NET-EN should be informed of the current uncertainty regarding whether use of these methods increases risk of HIV acquisition, and like all women at risk of HIV, should be empowered to access and use condoms and other HIV preventative measures. Programs, practitioners, and women urgently need guidance on how to maximize health with respect to avoiding both unintended pregnancy and HIV given inconclusive or limited data for certain HC methods.
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1. Introduction

Whether various types of hormonal contraception (HC) affect the risk of HIV acquisition remains a critical question for women's health, particularly in populations where HIV is common. In 2012, the World Health Organization (WHO) convened a group of 75 experts to review epidemiological, biological, and other data on this issue, and concluded by consensus that WHO should recommend no restriction on use of any method of HC for women at high risk of HIV. However, the group added a clarification that, because of the inconclusive nature of the evidence relating to progestin-only injectables, women at high risk for HIV who choose progestin-only injectables should be strongly advised to always use male or female condoms and to take other HIV preventive measures (see technical statement [1] for full clarification).

☆ Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the United States Agency for International Development, the Centers for Disease Control and Prevention, or the World Health Organization.

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The systematic review of epidemiological data relating to HC and HIV acquisition conducted for the 2012 WHO meeting included all relevant studies published (or in press) by December 15, 2011 [2]. Separate systematic reviews examined the epidemiological evidence on two related issues: whether various methods of HC affect HIV disease progression in women living with HIV [3] or female-to-male HIV transmission [4].

Following the 2012 WHO consultation, the global health community responded with new modeling analyses [5–8], anatomical, microbiological, and immunological data [9–24], supplementary epidemiological analyses [25,26], commentaries [27–29], overviews and guideline updates based on the systematic reviews [30–33], technical briefings [34], and analytical recommendations for future observational analyses of HC and HIV acquisition [35]. Conversations continue about the feasibility and scientific benefit of a randomized trial of various HC methods and HIV risk [28,36,37].

This issue is of substantial public health importance: for example, one impact simulation model estimated that if injectable contraception increases HIV risk by 20%, this would contribute to 27,000 additional infections per year, and that a doubling of HIV risk due to injectables would lead to an additional 130,000 HIV infections per year — the vast majority of which would occur in southern and Eastern Africa [5]. On the other hand, the same model estimated that if there is no causal effect of injectable contraception on HIV acquisition, but injectable use decreases due to fears of this possibility (and is not replaced by more effective contraceptive alternatives), we could expect a large increase in unintended pregnancies, unsafe abortions, unintended births, and at least 16,000 more maternal deaths per year worldwide, largely in southern and eastern Africa and southern Asia.

Therefore, it is imperative that new data on this issue is continually assessed and incorporated into our overall understanding of this complex body of literature, to ensure that contraceptive users, health care providers, and policy makers have the maximum amount of information available when making decisions. This paper updates the previous systematic review on HC and HIV acquisition in women by incorporating new epidemiological evidence published between December 15, 2011, and January 15, 2014. Our goal was addressing the question of whether specific methods of HC influence a woman's risk of HIV acquisition. Data included in this systematic review were presented at a WHO meeting in March 2014. Official WHO guidance on hormonal contraception and HIV stemming from that meeting is expected to be disseminated in mid-2014. This systematic review was conducted independently of the WHO guidance development process, and served as an input in those deliberations.

2. Methods

We conducted this systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [38].

2.1. Inclusion criteria

We included published primary research reports on women who were HIV-negative at baseline in longitudinal studies (observational studies or randomized trials) which measured incident, laboratory-confirmed HIV infection among women who used a specific method of HC [injectables, oral contraceptives (OCs), implants, patches, rings, or levonorgestrel intrauterine devices (IUDs)] compared with incident HIV infection in women who used either a non-hormonal contraceptive method (e.g., condoms, sterilization, withdrawal, etc.) or did not use a contraceptive method.

We determined a priori that any study comparing incident HIV infections among HIV-negative women using one specific method of HC against HIV-negative women using another method of HC (i.e., in a head-to-head comparison), would provide indirect evidence of risk, and would thus be discussed separately. We excluded cross-sectional studies and studies that assessed only emergency contraception (which is not typically used on a continual basis). We did not include conference abstracts or other reports not published in the peer-reviewed literature.

2.2. Search strategy and data extraction

We relied upon our earlier systematic review to identify articles published prior to December 15, 2011, and searched PubMed and Embase for relevant articles published in any language between December 15, 2011 and January 15, 2014. We also hand-searched reference lists of related studies. Appendix A details the complete search strategy. CBP conducted the literature search and identified potentially relevant articles; CBP and SJP read full text articles to determine eligibility for inclusion. We used standardized abstraction forms developed and used in a previous review to extract relevant data [2]. When we needed to clarify details of a particular analysis, we attempted to contact the study authors directly.

2.3. Quality assessment

For comprehensiveness, we reviewed all studies that met our inclusion criteria. However, many studies had severe methodological flaws, and were considered unlikely to contribute meaningfully to the evidence base. Therefore, our main analysis focused on the studies we considered most methodologically robust, using the study quality assessment framework defined below. However, we note that *all* studies had important limitations and should be considered in that context. All authors participated in updating the study quality assessment framework and in classifying each study as either "informative but with important limitations" or "unlikely to inform the primary question."

Studies were considered "unlikely to inform the primary question" if they had one or more of the following flaws:

Table A1
Description of studies, ordered by publication year

First author, publication year, location	Design, purpose, period of data collection	Number enrolled, description of population	Results (point estimate and 95% confidence intervals)	Multivariate analysis included condom use?	Met criteria for being considered "Informative but with important limitations"?*
Plummer 1991 [43] Nairobi, Kenya	Cohort; to determine incidence and risk factors for HIV acquisition 1985–1987	196 sex workers	Crude OR OCs: 3.1 (1.1–8.6) adjOR OCs: 4.5 (1.4–13.8) Stratified (no condom use) crude OR OCs: 3.7 (1.1–11.4) Crude HR OCs: not reported, but log rank $p<.05$.	Yes	No. Unclear measurement of exposure (no time-varying HC exposure in main analysis, referent group included other hormonal method users). Additional limitations: large loss to follow-up (37% at 12 months). Association between HC and HIV was not primary objective of either data collection or data analysis.
Saracco 1993 [44] Italy	Cohort; to determine incidence and risk factors for male-to-female sexual HIV transmission in serodiscordant couples 1987–1991	368 women in stable, monogamous serodiscordant relationships	None of the 22 OC users became infected vs. 19/283 non-users	No multivariate analysis	No. Unclear measurement of exposure (no time-varying HC exposure, referent group unclear). Additional limitations: association between HC and HIV was not primary objective of either data collection or data analysis; strong likelihood of confounding, inability to perform multivariate analysis due to small numbers of OC users. Loss to follow-up unclear (7% at 6 months, but median follow-up time was 24 months).
Laga 1993 [45] Kinshasa, Zaire	Nested case-control; to determine if treatable ulcerative and non-ulcerative STD were risk factors for HIV 1988	431 female sex workers	Crude OR ever OC use: 0.6 (0.2–2.4); Crude OR OC use during study: 0.7 (0.1–3.4); Crude OR OC use during exposure interval: 0.9 (0–13.5)	No multivariate analysis	No. No adjustment for condom use and unclear measurement of exposure (no time-varying HC exposure). Additional limitations: association between HC and HIV was not primary objective of either data collection or data analysis. Few OC users and minimal OC use during exposure interval. Information on total loss to follow-up not provided (mean monthly follow-up 76%).

Bulterys 1994 [46] Southern Rwanda	Cohort; to determine incidence of HIV in young, sexually active women in Rwanda 1989–1993	1524 sexually active women <30 years old in mixed rural and urban population who were pregnant or attending a prenatal clinic	Crude OR ever HC use: 3.2 (1.6–6.5) Age-adjOR ever HC uses: 2.9 (1.4–6.2) adjOR ever HC use: 1.9 (0.8–4.6) Results not provided separately for OCs and DMPA, but "incidence of HIV infection did not differ by the type of HC method used (data not shown)"	Multivariate analysis did not include condom use, but condom use was rare	No, unclear measurement of exposure (did not distinguish between HC methods leading to lack of clarity on utility of estimates, HC use not collected prospectively; asked about use in past 24 months). Additional limitations: association between HC and HIV was not primary objective of either data collection or data analysis.
Sinei 1996 [47] Nairobi, Kenya	Nested case-control; pilot study to demonstrate feasibility of larger study. 1990–1992	1537 women in a family planning clinic	Crude OR for OC use in last 6 months: 3.5 (0.8–21.5) Attempted to adjust for multiple confounders including condom use, but association persisted	No, and estimates from multivariate analysis not provided	No, unclear measurement of exposure (no time-varying HC exposure), and condom use not addressed. Additional limitations: high loss to follow-up (71% at 12 months).
Ungchusak 1996 [48] Khon Kaen, Thailand	Cohort; to investigate risk factors of HIV 1990–1991	365 sex workers in 24 illegal brothels in Thailand	Crude IRR OCs: 0.17 (p=.11, 95% CI not provided) adjIRR OCs: 0.22 (0.03–1.87) Crude IRR inj: 2.90 (p=.06, 95% CI not provided) adjIRR inj: 3.91 (1.29–11.82) (based on comment published after original publication) [83]	Multivariate analysis did not include condom use	No, unclear measurement of exposure (no time-varying HC exposure), and condom use not addressed. Additional limitations: association between HC and HIV was not primary objective of either data collection or data analysis. High loss to follow-up; 34% at 3 months.
Kilmarx 1998 [49] Chiang Rai, Thailand	Cohort; to examine demographic, behavioral, and other STIs associated with HIV infection in FSWs 1991–1994	340 sex workers in STD clinic, medical clinic, or workplace	Crude RR OCs: 2.5 (1.1–5.3) adjRR OCs: 1.8 (0.8–4.0) Crude RR DMPA: 1.5 (0.6–4.0) adjRR DMPA: N/A	Multivariate analysis did not include condom use	No, unclear measurement of exposure (referent group contains women using other forms of HC), and multivariate analysis does not include condom use. Additional limitations: association between HC and HIV was not primary objective of either data collection or data analysis. High loss to follow-up (29% at 12 months, 46% at 24 months), and differential loss to follow-up.

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Table A1 (*continued*)

First author, publication year, location	Design, purpose, period of data collection	Number enrolled, description of population	Results (point estimate and 95% confidence intervals)	Multivariate analysis included condom use?	Met criteria for being considered "Informative but with important limitations"?*
Kapiga 1998 [50] Dar Es Salaam, Tanzania	Cohort; to study HIV incidence in low-risk women and examine associations with contraceptive methods 1991–1995	2471 women in three family planning clinics in Dar es Salaam	Age-adjusted HR OCs: 1.28 (0.58–2.81) adjHR OCs: 1.01 (0.45–2.28) Age-adjusted HR injectables: 0.27 (0.06–1.12) adjHR injectables: 0.30 (0.07–1.26) Analyses on duration of HC use were not statistically significant for any method. Stratified on condom use: "adjusted results not altered"	Considered controlling for condom use in multivariate analysis	No, unclear measurement of exposure (no time-varying HC exposure (ever/never during follow up). Additional limitations: high loss to follow-up (44.5%, unclear at what time point), and differential loss to follow-up. Frequency of follow-up visits unclear and may have varied by participant.
Kiddugavu 2003 [51] Southwestern Uganda	Cohort; ongoing population-based cohort established as part of a community randomized trial 1994–1999	5117 sexually active women aged 15–49 years	adjIRR any HC: 0.94 (0.53–1.64) Crude IRR OCs: 1.70 (0.85–3.04) adjIRR OCs: 1.12 (0.48–2.56) Crude IRR injectable: 1.47 (0.82–2.45) adjIRR injectable: 0.84 (0.41–1.72) Stratified by no condom use: Crude IRR any HC: 1.59 (0.90–2.66)	Yes	No. The intersurvey interval was 10 months, with contraceptive use collected only at each interval endpoint. Note, this study was considered to meet minimum quality criteria in our previous review.
Baeten 2007 [52] (update of Martin 1998 [84]and Lavreys 2004 [66]) Mombasa, Kenya	Cohort; to define HIV seroincidence in female CSWs and examine relationship between HC, STDs, and HIV incidence 1993–2003	1498 female sex workers attending clinic for STD	Crude HR OCs: 1.58 (1.12–2.24) adjHR OCs: 1.46 (1.00–2.13) Crude HR DMPA: 2.05 (1.56–2.70) adjHR DMPA: 1.73 (1.28–2.34)	Yes	Yes
Myer 2007 [53] Cape Town, South Africa	Cohort; RCT to evaluate cervical cancer screening approaches 2000–2004	4555 women aged 35–65 enrolled in a cervical cancer trial	*All estimates based on subset of participants followed through 6 months* adjIRR OCs: 0.66 (0.09–4.78) adjIRR NET-EN: 1.60 (0.63–4.09) adjIRR DMPA: 0.75 (0.33–1.68)	Yes	Yes; but only for estimates based on participants followed through 6 months; subsequent visits had an intersurvey intervals of greater than 6 months.

Kleinschmidt 2007 [54] Orange Farm, South Africa	Cohort; to investigate prospectively if HIV incidence is higher among sexually active women using progestin 1999–2002	634 sexually active women aged 18–40	Crude IRR injectables: 1.12 (0.45–2.78) Crude IRR NET-EN: 1.77 (0.77–4.11) adjIRR NET-EN: 1.76 (0.64–4.84) Crude IRR DMPA: 0.26 (0.03–1.97) adjIRR DMPA: 0.46 (0.06–3.79) Stratified analysis among "never" condom users: Crude IRR injectables: 0.8 (0.1–4.7)	Yes	Yes
Kumwenda N 2008 [55] Blantyre, Malawi	Cohort; RCT to assess effect of intravaginal antibiotic on genital tract infections 2003–2005	842 non-pregnant women of childbearing age attending general reproductive health services, enrolled at a central hospital or one of two health centers	Crude OR DMPA: 3.57 (1.37–9.31) adjOR DMPA: 2.84 (1.07–7.55)	Multivariate analysis did not include condom use	No, no assessment of condom use, and unclear measurement of exposure (no use of time-varying HC, and referent group unclear, appears to include women using other methods of HC) Additional limitations: association between HC and HIV was not primary objective of either data collection or data analysis; strong likelihood of confounding.
Watson-Jones 2009 [56] Northwestern Tanzania	Cohort; RCT assessing effect of acyclovir on HIV incidence 2004-end date unclear	821 HSV2+ women aged 16–35 years working in bars, guesthouses, or other food and recreational facilities	Age-adjusted HR HC at baseline: 1.17 (0.71–1.93) Age-adjusted HR current HC: 1.63 (0.95–2.80) adjHR HC: 1.60 (0.93–2.76)	Multivariate analysis did not include condom use	No, unclear measurement of exposure (did not distinguish between HC methods), and condom use not addressed. Additional limitations: association between HC and HIV was not primary objective of either data collection or data analysis; strong likelihood of confounding. Potentially high loss to follow-up, unclear (20% did not complete follow-up defined as attending until seroconversion or end of study).
Morrison 2010 [57] (reanalysis of Morrison 2007) [64] Uganda, Zimbabwe	Cohort; to examine association between OC and DMPA use and HIV 1999–2004	6,109 sexually-active, non-pregnant women in family planning clinics, plus some high-risk referral women from STI or primary healthcare	2010 MSM reanalysis: Crude HR DMPA: n/a adjHR DMPA: 1.48 (1.02–2.15) Crude HR OCs: n/a adjHR OCs: 1.19 (0.80–1.76)	Yes	Yes

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Table A1 (*continued*)

First author, publication year, location	Design, purpose, period of data collection	Number enrolled, description of population	Results (point estimate and 95% confidence intervals)	Multivariate analysis included condom use?	Met criteria for being considered "Informative but with important limitations"?*
		clinics, sex worker networks, or military bases.	2007 Cox PH analysis Crude HR DMPA: 1.24 (0.90–1.71) adjHR DMPA: 1.25 (0.89–1.78) Crude HR OCs: 1.02 (0.72–1.43) adjHR OCs: 0.99 (0.69–1.42) 2007 stratified analysis restricted to no condom use: adjHR OCs: 1.47 (0.78–2.80) adjHR DMPA: 1.61 (0.85–3.06) Sensitivity analyses did not change results.		
Feldblum 2010 [58] Nigeria, Ghana, Benin, Uganda, India, South Africa	Cohort; data from four Phase III RCTs on microbicides 2004–2007	7364 women at "higher than average risk of HIV" (variably defined between studies)	Crude HR OCs: 1.84 (0.83–4.05) Crude HR injectables: 2.51 (1.12–5.60) "Use of injectable contraception and condom use were significantly associated with incident HIV initial models, but dropped from the final model; only age and education were significantly associated with incident HIV in the final model."	Considered controlling for condom use in multivariate analysis	No, unclear measurement of exposure (no use of time-varying information, all covariates assessed at baseline). Additional limitations: association between HC and HIV was not primary objective of either data collection or data analysis. High loss to follow-up in some but not all sites (up to 30% in Nigeria site).
Reid 2010 [41] South Africa, Zambia, Zimbabwe	Cohort; HPTN 039 study, RCT to assess effect of acyclovir on HIV incidence 2003–2007	1358 (analyzed, n enrolled unclear) HSV2-positive women recruited from family planning, well-baby, and VCT clinics, and community venues.	Crude HR OCs: 0.93 (0.48–1.82) adjHR OCs: 0.91 (0.45–1.83) Crude HR injectables: 1.01 (0.51–1.98) adjHR injectables: 0.94 (0.46–1.92)	Yes	Yes

Heffron 2012 [59] Seven countries in East and Southern Africa	Cohort; RCT assessing effect of acyclovir on HIV incidence 2004–2010	1314 (analyzed, n enrolled unclear) M+F-serodiscordant couples (83% of observations from an acyclovir RCT, 17% of observations from cohort study of immune correlates of HIV protection)	HC Crude HR (Cox): 1.73 (0.95–3.15) adjHR (Cox): 1.98 (1.06–3.68) adjOR (MSM): 1.84 (0.98–3.47) OCs Crude HR (Cox): 1.53 (0.48–4.90) adjHR (Cox): 1.80 (0.55–5.82) adjOR (MSM): 1.63 (0.47–5.66) Injectables Crude HR (Cox):1.80 (0.92–3.52) adjHR (Cox): 2.05 (1.04–4.04) adjOR (MSM): 2.19 (1.01–4.74) Censoring at pregnancy adjHR HC: 1.84 (0.97–3.49)	Yes	Yes
Heffron 2012 [Authors' reply] (Subanalysis of study shown above) [61] Seven countries in East and Southern Africa *New since last systematic review*	Same as above	Same as above (n=1314), except for certain sub-analyses	Injectables; analysis adding total number of unprotected sex to statistical model: adjHR (Cox): 2.04 (1.03–4.04) Injectables; analysis replacing woman's report of unprotected sex with male partner's report: adjHR (Cox): 2.03 (0.95–4.32) DMPA; analysis excluding women from South Africa (who may use NET-EN) (unpublished estimate) [65]: adjHR (Cox): 2.04 (0.81–5.15) DMPA; analysis excluding women from South Africa and also excluding women who switched	Yes	Yes

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Table A1 (*continued*)

First author, publication year, location	Design, purpose, period of data collection	Number enrolled, description of population	Results (point estimate and 95% confidence intervals)	Multivariate analysis included condom use?	Met criteria for being considered "Informative but with important limitations"?*
			contraceptive status at any time in the study: adjHR (Cox): 3.93 (1.38–11.22)		
Morrison 2012 [60] South Africa	Cohort; RCT assessing the effectiveness of the microbicide Carraguard, 2004–2007	5567 (analyzed, n enrolled unclear), recruited from community venues	OCs adjHR (Cox): 0.88 (0.49–1.30) adjHR (MSM): 0.84 (0.51–1.39) DMPA adjHR (Cox): 1.27 (0.93–1.73) adjHR (MSM): 1.28 (0.92–1.78) NET-EN adjHR (Cox): 0.87 (0.60–1.25) adjHR (MSM): 0.92 (0.64–1.32)	Yes	Yes
Wand 2012 [42] South Africa	Cohort; RCT assessing the effectiveness of vaginal microbicide, dates of data collection not provided	2236, recruited from community venues	OCs adjHR: 0.95 (0.62–1.46) Injectables adjHR: 2.02 (1.37–3.00) DMPA adjHR: 1.61 (1.10–2.37) [85] NET-EN adjHR: 2.54 (1.61–3.97) [85]	Yes	Yes Note: this study was considered not to meet minimum quality criteria in our previous review given concerns about the adequacy of control for condom use.
McCoy 2013 [62] South Africa and Zimbabwe *New since last systematic review*	Cohort; RCT assessing effectiveness of diaphragm and lubricant gel for HIV prevention, 2003–2006	4948 in HIV-endpoint analytical dataset (5048 enrolled). Women reporting at least 4 sex acts per month recruited from FP, well-baby, general health clinics, community based organizations, and printed media and radio	adjHR Cox, site-adjusted only OC overall: 0.82 (0.58–1.15) COC: 0.78 (0.53–1.12) POP: 0.91 (0.49–1.50) Injectables overall: 1.32 (1.00–1.74) DMPA: 1.18 (0.84–1.62) NET-EN: 1.40 (0.72–2.35) adjHR Cox, model adjusted for baseline covariates OC overall: 0.84 (0.57–1.22)	Yes	Yes

			COC: 0.80 (0.53–1.19) POP: 0.94 (0.50–1.59) Injectables overall: 1.27 (0.94–1.72) DMPA: 1.22 (0.84–1.74) NET-EN: 1.15 (0.58–1.95) adjHR Cox, model with robust standard errors to account for within-subject correlation and separate baseline hazards for each of the three study sites, adjusted for baseline and time-varying covariates COC: 0.86 (0.58–1.28) POP: 0.98 (0.56–1.73) Injectables overall: 1.37 (1.01–1.85) DMPA: 1.28 (0.90–1.82) [82] NET-EN: 1.33 (0.76–2.33) [82] adjHR IPTW MSM Injectables overall: 1.34 (0.75–2.37) OC overall: 0.86 (0.32–1.78) Note: disaggregated injectable Cox estimates provided in personal communication; disaggregated MSM injectable estimates not possible due to violation of the positivity assumption.		
Lutalo 2013 [63] Rakai, Uganda *New since last systematic review*	Cohort; ongoing population-based cohort established as part of a community randomized trial 1999–2009	190 M+F-serodiscordant couples retrospectively identified from a cohort; none using antiretroviral therapy or condoms	adjIRR OCs: 2.65 (0.82–8.60) Implant: 0.89 (0.11–7.10) DMPA: 1.42 (0.60–3.36) adjIRR with consistent use OCs: 4.51 (0.74–27.45) Implant: 1.47 (0.17–12.67)	If condom use was reported in any study interval by any participant, that observation was excluded from analysis. Thus, condom use was controlled via study design, rather than via statistical control.	No. The intersurvey interval ranged from between 12–16 months, with contraceptive use collected only at each interval endpoint.

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Table A1 (*continued*)

First author, publication year, location	Design, purpose, period of data collection	Number enrolled, description of population	Results (point estimate and 95% confidence intervals)	Multivariate analysis included condom use?	Met criteria for being considered "Informative but with important limitations"?*
			DMPA: 0.36 (0.04–3.6) Age-adjusted ORs from case-control study (n=70 couples) controlling for viral load (results same controlling for condom use): OCs: 1.59 (0.32–97.85) DMPA: 1.44 (0.46–4.51)		

adj, adjusted; CSW, commercial sex worker; HR, hazard ratio; HSV2+, seropositive for herpes simplex virus 2; IRR, incidence rate ratio; OR, odds ratio; RCT, randomized control trial.

* Studies considered "informative but with important limitations" included adjustment for condom use (at minimum), and clear measurement of exposure to hormonal contraception (as defined in the methods section).

- No adjustment for any measure of condom use, or
- Unclear measurement of exposure to HC, including one or more of the following:
  - o Failure to include time-varying analysis of HC exposure, if appropriate.
  - o Failure to provide separate estimates for different *types* of HC methods (e.g., OCs or injectables or implants). We did not exclude studies that grouped together different formulations of a particular method (e.g., combined depot-medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN) into a single exposure category).
  - o Comparison group included a substantial or unclear number of users of another HC method (except in an intentional head-to-head comparison of a specific HC method versus another specific HC method).
  - o The interval of time between study visits ("inter-survey interval") was longer than 6 months, with contraceptive use measured only at each interval endpoint (and thus providing only limited information about possible contraceptive switching during the intersurvey interval). (Note: if variation in length of intersurvey interval occurred within an individual study, such that some intervals were 6 months or less and other intervals were longer than 6 months, we included only data from intervals that were 6 months or less).

Studies considered "informative but with important limitations" had none of the flaws described above.

2.4. Graphical summaries

We created forest plots using Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) to display the estimates from each study of the association between various HC methods and HIV risk, and generated funnel plots using Review Manager 5 [39]. We created graphics to display all available studies of a given method (i.e., OCs, injectables, or implants), as well as separate graphics to display only studies considered "Informative but with important limitations". We declined to include a statistical meta-analysis of these observational data for methodological reasons. For example, experts note that in observational data "potential biases in the original studies, relative to biases in randomized controlled trials, make the calculation of a single summary estimate of effect of exposure potentially misleading." [40] However, such efforts are the focus of ongoing work by other groups [28].

Where possible, we have presented estimates for disaggregated HC methods, and included both Cox and marginal structural model (MSM) estimates when both were provided. We emailed authors of "informative but with important limitations" studies which included women from South Africa (where use of both types of injectable, DMPA and NET-EN, is common) but which did not report separate estimates for each, and requested disaggregated estimates where possible. Disaggregated estimates of effect have reduced statistical power but

are of more clinical importance, an important consideration given the potential for different biological effects by contraceptive type or formulation. All estimates from each study are reported in Tables A1 and A2.

3. Results

3.1. All included studies

Twenty eligible reports were included in the previous review [41–60], and out of 400 references retrieved in our updated search (Fig. 1), we identified one new eligible sub-analysis of a previously included study [61] and two new eligible studies [62,63]. None of these three new analyses were derived from studies designed specifically to assess the relationship between HC and HIV acquisition; all were secondary data analyses, and each included data from African women. None of the studies included head-to-head comparisons of different HC methods.

Among 22 included studies (represented by 23 reports), 18 included estimates specific to OCs [41–,47–53,57–60,62,63], 16 included estimates specific to injectable contraception [41,42,48–55,57–60,62,63], and two did not distinguish between methods of HC although the investigators noted that most of the HC users used injectables [46,56]. No eligible studies assessed the contraceptive patch, ring, combined injectable, or levonorgestrel IUD.

Table A1 briefly describes all 23 reports (of 22 eligible studies) and notes whether they met criteria for being "informative but with important limitations". Fig. 2 displays the estimates from eighteen studies for OCs and Fig. 3 shows the estimates for injectables (two studies with non-specified methods of HC are included with the sixteen that reported estimates specific to injectables). In Figs. 2 and 3 all studies are displayed, regardless of methodological quality, and are shown in decreasing order of effect size.

3.2. Studies considered "informative but with important limitations"

Of 22 included studies, we considered thirteen "unlikely to inform the primary question" [43–51,55,56,58,63], and nine "informative but with important limitations" (Table A2) [41,42,52–54,57,59–62,64]. Each of the "informative but with important limitations" studies included or assessed the need for statistical control for some measure of condom use, age, number of sexual partners, and genital symptoms or genital infection. Other factors, such as marital status, frequency of sexual encounters, or partner risk, were accounted for only in some of the studies (Table A3).

3.2.1. Oral contraceptives

Of the eight "informative but with important limitations" studies that assessed OCs (Fig. 4), one reported a significant increase in risk [p=.05; adjusted hazard ratio (adjHR) 1.5, 95% CI 1.0–2.1] [52]. The other studies reported non-significant estimates [ranging from adjusted incidence rate ratio (adjIRR) 0.66, 95% CI 0.09–4.78 to adjHR 1.80, 95% CI 0.47–5.66] [41,42,53,57,59,60,62,64]. No substantial differences were observed between combined oral contraceptives (COCs) and progestin-only pills (POPs) in the one study that disaggregated these methods [62].

3.2.2. Injectables

Of the nine "informative but with important limitations" studies for injectables, four reported a significant increase in risk with injectables [42,52,57,59], though the statistical significance of one of these studies depended upon the statistical method used. In that study, the association was significant when MSM was used [57], but non-significant when a Cox proportional hazards model was used [64]. The confounders adjusted for in each of these two statistical models differed slightly (Fig. 5) [57,64]. Estimates from studies considered informative but with important limitations that reported significant findings for injectables ranged from adjHR 1.48, 95% CI 1.02–2.15 (specific to DMPA) [57] to adjHR 2.54, 95% CI 1.61–3.97 (specific to NET-EN) [42]. Five studies reported non-statistically significant estimates of effect in their primary analyses [41,53,54,60,62] (although one had a significant result in an analysis combining NET-EN and DMPA using a Cox proportional hazards model [adjHR: 1.37, 95% CI 1.01–1.85] [62]); non-significant estimates ranged from adjIRR 0.46, 95% CI 0.06–3.79 [54] to adjIRR 1.76, 95% CI 0.64–4.84 [54]. No study found a significantly decreased risk estimate.

Two studies reported estimates for DMPA and NET-EN combined. Heffron et al. reported increased HIV risk (ranging between adjHR 2.04, 95% CI 1.03–4.04 [Cox estimate] and adjHR 2.19, 95% CI 1.01–4.74 [MSM estimate], depending on the statistical method used) [59], and Reid et al. reported an estimate of adjHR 0.94, 95% CI 0.46–1.92 [41]. Heffron et al. performed a new sub-analysis excluding women from South Africa (who may have used either NET-EN or DMPA), to attempt to isolate the effect of DMPA. They reported a point estimate (adjHR 2.04, 95% CI 0.81–5.15) [65] similar to the primary findings but with wider confidence intervals; this sub-analysis was based on four seroconverters assumed to be using DMPA (estimate from this restricted sub-analysis not shown in figures to avoid loss of data due to fewer endpoints; complete disaggregation into DMPA and NET-EN users was not possible in this analysis).

Of seven studies reporting DMPA-specific estimates, two reported significantly increased risks (ranging from to adjHR 1.61, 95% CI 1.10–2.37 [42] to adjHR 1.73, 95% CI 1.28–2.34 [52]; one reported a significantly increased risk under an MSM statistical approach (adjHR 1.48, 95% CI 1.02–2.15) but a non-significant increased risk under a Cox proportional hazards model (adjHR 1.25, 95% CI: 0.89–1.78) [57,64]; two reported non-significant elevated estimates (adjHR 1.27, 95% CI 0.93–1.73 and adjHR 1.28, 95% CI 0.90–1.82) [60,62]; and two reported non-significant decreased estimates (adjIRR 0.46, 95% CI 0.06–3.79 and adjHR 0.75, 95% CI 0.33–1.68) (Fig. 6) [53,54].

Table A2
Comparison of studies considered "Informative but with important limitations"

Study, study population, and whether analysis is new since last systematic review [2]	Number seroconverted/ number analyzed, number of seroconverters using HC, overall HIV incidence	Interval between visits, length of follow-up, loss to follow-up and whether follow-up was differential by HC status	Referent group Overall proportion of condom use in population	Handling of condom use	HC/non-HC differences noted at baseline or follow-up?	Results	Summary of strengths	Summary of weaknesses
Baeten 2007 (Kenya) [52] Sex workers	233/1206 seroconverted 38 seroconverters using OCs, 79 using DMPA 8.7/100 person-years	Median 35 days between visits. Median total follow-up: ~ 15 months LTFU: Unclear, Martin 1998, reported 18% at 7.5 months [84]. Unclear if differential.	Used tubal ligation, used condoms, or used no method Overall condom use unclear, reported in Martin 1998 at enrollment as median 100%, range 0–100% [84]	Controlled for condom use, including consistency.	Neither provided.	OCs: Crude HR: 1.58 (1.12–2.24) adjHR: 1.46 (1.00–2.13) DMPA: Crude HR: 2.05 (1.56–2.70) adjHR: 1.73 (1.28–2.34)	Primary objective of data collection. Monthly follow-up. Authors argue that behavioral confounding less of an issue among high-risk women. Presented estimates specific to one type of injectable (DMPA). Met minimum quality criteria.	Assumes self-reported condom use in last week reflects condom use in last month. No attempt to explore validity of self-reported sexual behavior or contraceptive use data presented. High loss to follow-up at 12 months (~45%, open cohort) [86]. Potential for residual/ unmeasured confounding.
Myer 2007 (South Africa) [53] Women older than 35	53/4200 (at 6 months) Number of seroconverters using each method unclear since this review uses only data collected up to 6 months. 2.2/100 person-years	This review utilizes only information collected between baseline and 6 months; thus, 6 month interval. LTFU: 11% at 6 months. Not differential by HC use.	No HC, could use condoms Overall condom use low, 1% at enrollment, 8% most of the time or always during follow-up	Controlled for condom use, control may not have captured consistency.	Both provided.	*All estimates based on subset of participants followed through 6 months* adjIRR OCs: 0.66 (0.09–4.78) adjIRR NET-EN: 1.60 (0.63–4.09) adjIRR DMPA: 0.75 (0.33–1.68)	Large sample. Low condom use in study may have minimized potential for confounding by condom use. Disaggregated between DMPA and NET-EN. Met minimum quality criteria.	Control for condom use combined "always" users and "most always" users which may not address condom use consistency. No attempt to explore the validity of contraceptive use data presented. Potential for residual/ unmeasured confounding.

Kleinschmidt 2007 (South Africa) [54] Family planning clinic attendees	23/551 11 seroconverters using injectables (10 using NET-EN, 1 using DMPA) 4.7/100 person-years	2–4 months between visits Total follow-up: 12 months LTFU: Unclear, at least 12% at 3 months (75/634). Unclear if differential.	Using non-hormonal methods or no contraception, could use condoms Overall condom use, 54.2% at enrollment (measured as any use during last 3 months)	Controlled for condom use, including consistency. Unadjusted analysis stratified by condom use and no condom use during study.	Baseline only.	Injectables Crude IRR: 1.12 (0.45–2.78) NET-EN: Crude HR: 1.77 (0.77–4.11) adjHR: 1.76 (0.64–4.84) DMPA: Crude HR: 0.26 (0.03–1.97) adjHR: 0.46 (0.06–3.79) *All injectables, restricted to "never" condom users:* Crude IRR: 0.8 (0.1–4.7)	Primary objective of data collection. Disaggregated between DMPA and NET-EN. Frequent follow-up. Attempted to explore validity of self-reported sexual behavior data. Met minimum quality criteria.	Lack of clarity on loss to follow-up. Limited statistical power, particularly for DMPA. No attempt to explore the validity of contraceptive use data presented. Potential for residual/ unmeasured confounding.
Morrison 2010 (reanalysis of Morrison 2007) (Uganda, Zimbabwe) [57,64] Family planning clinic attendees with subset of higher-risk women	213/4435 71 seroconverters using OCs, 87 using DMPA 2.8/100 person-years	3 months between visits. Mean total follow-up: 21.9 months LTFU: 8% at 24 months. Not differential by HC use.	At baseline, 84% used condoms, 13% used withdrawal, 10% used rhythm, 3% were sterilized, 5% used a non-HC method During follow-up, consistent condom use was 51% in non-HC, 13% in HC	2010 analysis: Controlled for condom use, but not consistency, authors noted via email that this did not affect results 2007 analysis controlled for condom use, addressed consistency (always condom use or no sex vs. none/some condom use) 2007 adjusted analysis stratified by condom use and no condom use during study	Both provided.	2010 MSM reanalysis: OCs: Crude HR: n/a adjHR: 1.19 (0.80–1.76) DMPA: Crude HR: n/a adjHR: 1.48 (1.02–2.15) 2007 Cox PH analysis OCs: Crude HR: 1.02 (0.72–1.43) adjHR: 0.99 (0.69–1.42) DMPA Crude HR: 1.24 (0.90–1.71) adjHR: 1.25 (0.89–1.78) *2007 stratified analysis restricted to no condom use*: adjHR OCs: 1.47 (0.78–2.80) adjHR DMPA: 1.61 (0.85–3.06)	Primary objective of data collection. Large sample. Frequent follow-up and low loss to follow-up. Contraceptive self-report validated in clinic records. 2010 MSM analysis may have addressed time-dependent confounding. 2007 paper provided stratified analysis on never condom use. Presented estimates specific to one type of injectable (DMPA). Attempted to explore validity of self-reported sexual behavior and contraceptive use data. Met minimum quality criteria.	Self-reported condom use associated with increased HIV, and consistent condom use did not decrease HIV, raising concern about response validity and success of statistical adjustment. Assumes self-reported condom use in "typical month in last 3 months" reflects condom use in last 3 months. Effect modification by study site (detailed in 2007 analysis) lacks a clear biological

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Table A2 (*continued*)

Study, study population, and whether analysis is new since last systematic review [2]	Number seroconverted/ number analyzed, number of seroconverters using HC, overall HIV incidence	Interval between visits, length of follow-up, loss to follow-up and whether follow-up was differential by HC status	Referent group Overall proportion of condom use in population	Handling of condom use	HC/non-HC differences noted at baseline or follow-up?	Results	Summary of strengths	Summary of weaknesses
								mechanism. Potential for residual/ unmeasured confounding.
Reid 2010 (South Africa, Zambia, Zimbabwe) [41] HSV-2 positive women in family planning or other clinics	72/1358 Unclear how many seroconverters using HC 4.0/100 person-years	3 months between visits. Total follow-up: up to 18 months. LTFU: Unclear, unclear if differential.	Women using no contraceptive method (excluded women using condom as a contraceptive method) At enrollment, 42% reported ever using condoms in last 3 months	Women reporting condoms as primary contraceptive method not in referent group. Addressed consistency by controlling for any unprotected sex.	Neither provided.	OCs: Crude HR: 0.93 (0.48–1.82) adjHR: 0.91 (0.45–1.83) Injectable (DMPA and NET-EN): Crude HR: 1.01 (0.51–1.98) adjHR: 0.94 (0.46–1.92)	Frequent follow-up. Excluding women using condoms for contraception from referent group may equalize quality of condom use between groups. Attempted to explore validity of self-reported sexual behavior and contraceptive use data. Women with missing data more likely to become pregnant (and acquire HIV); therefore unlikely to have been using HC — suggesting that their exclusion would likely lead to an effect exaggeration, if anything. Met minimum quality criteria.	Self-reported contraceptive info during follow-up captured in site chart notes and abstracted into database at end of study, which may have affected quality of exposure information. Did not disaggregate between DMPA and NET-EN. Lack of clarity on loss to follow-up. Potential for residual/ unmeasured confounding.
Heffron 2012 (Seven countries in East and Southern Africa) [59] Women in a serodiscordant couple	73/1314 13 seroconverters using HC, 10 using injectables and 3 using OCs 4.09/100 person-years	3 months between visits for HIV-partner. Median follow-up: 18 months LTFU: Reported as 7% at 12 months, 13% at 24 months, unclear if differential.	Had hysterectomy, tubal ligation, used condoms, or used no contraception During follow-up, self-reported condom use was high (only 7.6% of intervals included any self-reported unprotected sex)	Controlled for unprotected sex (thereby incorporating information on self-reported condom use consistency).	Follow-up only.	Any HC Cox crude HR: 1.73 (0.95–3.15) Cox adjHR: 1.98 (1.06–3.68) MSM adjOR: 1.84 (0.98–3.47) OCs Cox crude HR: 1.53(0.48–4.90) Cox adjHR: 1.80 (0.55–5.82)	Analysis of serodiscordant couples increases likelihood that all participants were equally exposed to sexual activity with an HIV-positive partner. Frequent follow-up. Low loss to follow-up. MSM analysis may have addressed	Assumes self-reported condom use in last month reflects condom use in last 3 months. Possible condom over-reporting; only 8% of intervals involved any

						MSM adjOR: 1.63 (0.47–5.66) Injectable (DMPA and NET-EN) Cox crude HR: 1.80 (0.92–3.52) Cox adjHR: 2.05 (1.04–4.04) MSM adjOR: 2.19 (1.01–4.74)	time-dependent confounding. Met minimum quality criteria.	self-reported unprotected sex; yet HIV incidence was 4.09/100 person-years. No attempt to explore validity of self-reported sexual behavior or contraceptive use data presented. Did not disaggregate between DMPA and NET-EN. Potential for residual/ unmeasured confounding.
Heffron 2012 [Authors' reply] (Subanalysis of study shown above) [61] HIV-negative women in a serodiscordant couple *New since last systematic review*	Same as above, except sub-analysis excluding women in South Africa (e.g., DMPA subanalysis) includes 4 seroconverters using DMPA [65]	Same as above	Same as above	Same as above	Same as above	Injectables; analysis adding total number of unprotected sex acts to statistical model adjHR (Cox): 2.04 (1.03–4.04) *Injectables; analysis replacing woman's report of unprotected sex with male partner's report* adjHR (Cox): 2.03 (0.95–4.32) *DMPA; analysis excluding women from South Africa (who may use NET-EN) (unpublished estimate)* [65] adjHR (Cox): 2.04 (0.81–5.15) *DMPA; analysis excluding women from South Africa and also excluding women who switched contraceptive status at any time in the study*	Same as above, and in addition: Sub-analyses offer some additional evidence that incomplete statistical control for sexual behavior may not explain findings. Attempt to isolate estimate for DMPA. Met minimum quality criteria.	Same as above.

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Table A2 (*continued*)

Study, study population, and whether analysis is new since last systematic review [2]	Number seroconverted/ number analyzed, number of seroconverters using HC, overall HIV incidence	Interval between visits, length of follow-up, loss to follow-up and whether follow-up was differential by HC status	Referent group Overall proportion of condom use in population	Handling of condom use	HC/non-HC differences noted at baseline or follow-up?	Results	Summary of strengths	Summary of weaknesses
						adjHR (Cox): 3.93 (1.38–11.22)		
Morrison 2012 (South Africa) [60] Sexually active women aged 16–49, recruited from community venues	270/5567 21 seroconverters using OCs, 103 using DMPA, 55 using NET-EN 3.7/100 person-years	Months 1, 3, and every 3 months thereafter Follow-up from 9–24 months LTFU not reported in manuscript (but 89.9% at 1 yr in Kaplan-Meier analysis), (C. Morrision, personal communication, 2012) unclear if differential.	No use of HC; excluded IUD users and women with hysterectomy; included women using male or female condoms, male or female sterilization, diaphragm, traditional methods, or not using any contraceptive method About 23% reported any condom use at enrollment; varied significantly by contraceptive method	Controlled for condom use, did not address consistency.	Baseline only	OCs Cox adjHR: 0.88 (0.49–1.30) MSM adjHR: 0.84 (0.51–1.39) DMPA Cox adjHR: 1.27 (0.93–1.73) MSM adjHR: 1.28 (0.92–1.78) NET-EN Cox adjHR: 0.87 (0.60–1.25) MSM adjHR: 0.92 (0.64–1.32)	Large sample. Frequent follow-up. Disaggregated between DMPA and NET-EN. Low loss to follow-up. MSM analysis may have addressed time-dependent confounding. Attempted to validate of self-reported contraceptive use. Met minimum quality criteria.	Analysis did not address consistency of condom use. No attempt to explore validity of self-reported sexual behavior presented. Potential for residual/ unmeasured confounding.
Wand 2012 (Durban, South Africa) [42] Women enrolled in a phase III trial testing effectiveness of vaginal gel for HIV prevention *Included in last review, newly considered in this review to meet criteria for "Informative but with important limitations"*	162/2236 seroconverted 8 seroconverters using OCs, 90 seroconverters using injectables (61 using DMPA and 29 using NET-EN [85]) Overall HIV incidence not reported	Quarterly visits. Total follow-up: not reported LTFU: Not reported in manuscript (noted as approximately 10%) [87], unclear if differential	Male or female condoms, tubal ligation, vasectomy, intrauterine device, traditional methods, no contraceptive method At enrollment, 60% of participants reported using condoms at last sex, varied significantly by contraceptive method.	Controlled for condom use at last sex	Baseline only.	OCs adjHR: 0.95 (0.62–1.46) Injectables adjHR: 2.02 (1.37–3.00) DMPA adjHR: 1.61 (1.10–2.37) [85] NET-EN adjHR: 2.54 (1.61–3.97) [85]	Frequent follow-up. Met minimum quality criteria.	Information on loss to follow-up not provided. No attempt to explore validity of self-reported sexual behavior or contraceptive use data presented. Disaggregation of injectable types not reported in publication (though provided on request) [85]. Authors stated

								in personal communication that they "do not think that we can infer any biological conclusion between HC and HIV based on our data." [87] Injectable group contained a very small number (n=3) of Norplant users. Potential for residual/ unmeasured confounding.
McCoy 2013 [62] South Africa and Zimbabwe Sexually active women participating in a phase III effectiveness trial of the diaphragm and lubricant gel for HIV prevention *New since last systematic review*	283/4913 women seroconverted (271/4913 seroconversions included in published estimates) 102 seroconverters using injectables (63 using DMPA, 17 using NET-EN, 22 injectable type unclear) and 61 seroconverters using OCs (44 using COCs, 17 using POPs) 4.06/100 person-years	3 months between visits. Median duration of follow-up: 18 months LTFU: unclear. In parent study [88], 7% did not complete scheduled closing visit. Unclear if differential.	Used condoms, traditional methods, withdrawal, nonhormonal IUDs, diaphragm, spermicides, sterilization, or no contraception At enrollment, 69% reported condom use at last sex, which differed significantly by contraceptive method. At enrollment, condom use as reported in the last 3 months was 29% "Never", 39% "Sometimes", and 31% "Always"; this also differed significantly by contraceptive method.	Controlled for condom use (frequency in the past 3 months) in Cox model adjusted for baseline and time-varying covariates; and in IPTW MSM model.	Baseline only.	adjHR Cox, site-adjusted only OC overall: 0.82 (0.58–1.15) COC: 0.78 (0.53–1.12) POP: 0.91 (0.49–1.50) Injectables overall: 1.32 (1.00–1.74) DMPA: 1.18 (0.84–1.62) NET-EN: 1.40 (0.72–2.35) *adjHR Cox, model adjusted for baseline covariates* OC overall: 0.84 (0.57–1.22) COC: 0.80 (0.53–1.19) POP: 0.94 (0.50–1.59) Injectables overall: 1.27 (0.94–1.72) DMPA: 1.22 (0.84–1.74) NET-EN: 1.15 (0.58–1.95) *adjHR Cox, model with robust standard errors to account for within-subject*	Large sample. Disaggregation of COCs and POPs reported in publication. Frequent follow up. MSM analysis may have addressed time-dependent confounding.	Lack of clarity on loss to follow up. No attempt to explore validity of self-reported sexual behavior or contraceptive use data presented. Disaggregation of injectable types not reported in publication (though provided on request) [82]. Potential for residual/ unmeasured confounding.

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Table A2 (*continued*)

Study, study population, and whether analysis is new since last systematic review [2]	Number seroconverted/ number analyzed, number of seroconverters using HC, overall HIV incidence	Interval between visits, length of follow-up, loss to follow-up and whether follow-up was differential by HC status	Referent group Overall proportion of condom use in population	Handling of condom use	HC/non-HC differences noted at baseline or follow-up?	Results	Summary of strengths	Summary of weaknesses
						correlation and separate baseline hazards for each of the three study sites, adjusted for baseline and time-varying covariates COC: 0.86 (0.58–1.28) POP: 0.98 (0.56–1.73) Injectables overall: 1.37 (1.01–1.85) DMPA: 1.28 (0.90–1.82) [82] NET-EN: 1.33 (0.76–2.33) [82] adjHR IPTW MSM injectables overall: 1.34 (0.75–2.37) OC overall: 0.86 (0.32–1.78) Note: only disaggregated injectable Cox estimates provided in personal communication, disaggregated MSM injectable estimates not possible due to violation of the positivity assumption.		

adj, adjusted; HR, hazard ratio; IRR, incidence rate ratio; LTFU, loss to follow-up; OR, odds ratio.

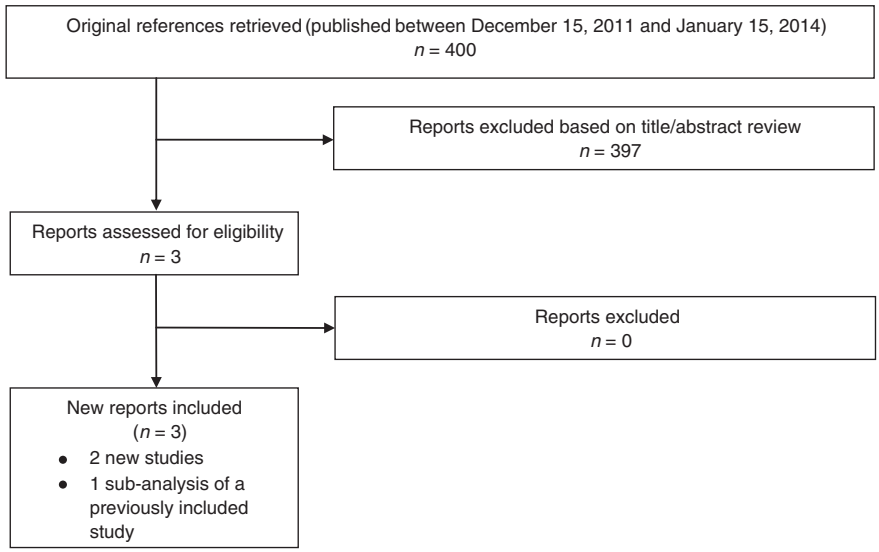

Fig. 1. Study selection. Note: We relied upon the search from a previous systematic review [2] to identify all relevant studies published prior to December 15, 2011.

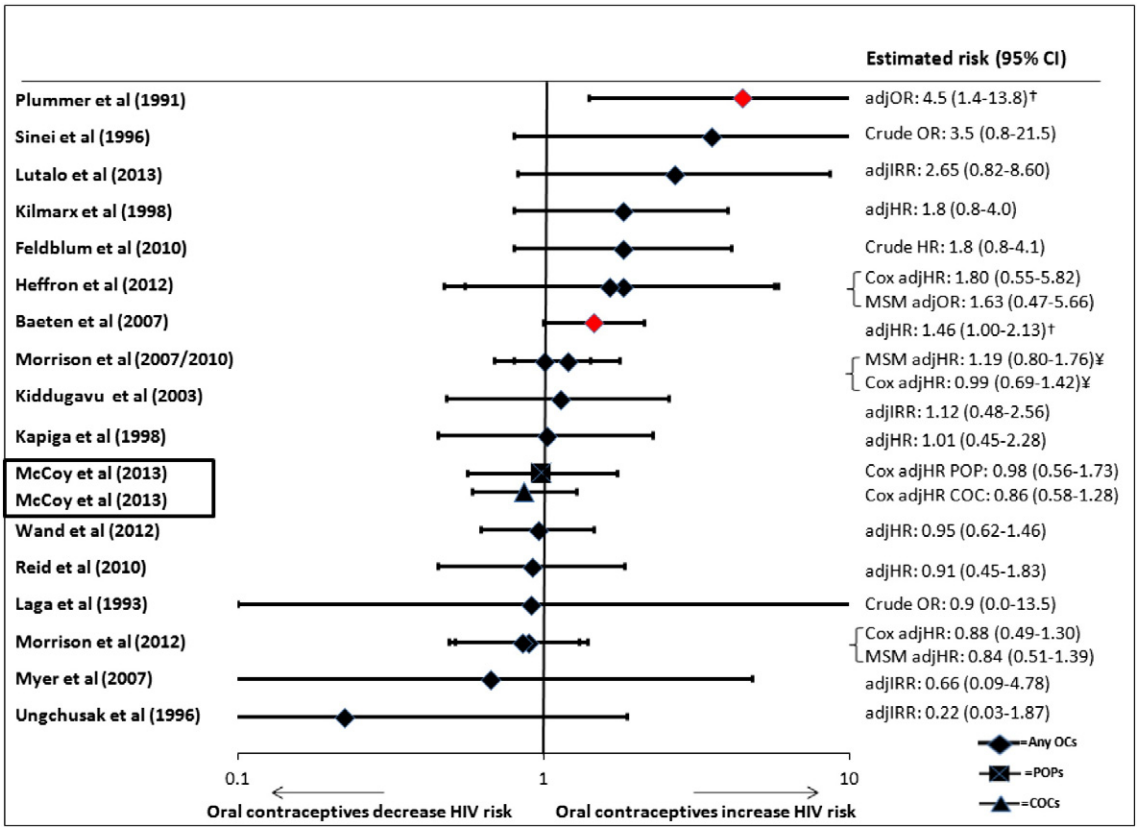

Fig. 2. Use of oral contraceptives and HIV acquisition (all 18* studies, regardless of quality). Error bars show 95% CIs. Studies are arranged in order of decreasing magnitude of risk estimate, except if a single study disaggregated POPs and combined oral contraceptives [COCs], in which case both estimates are adjacent (as indicated by a box around the study identifiers). For studies which reported both Cox and MSM estimates, both estimates are displayed on a single line (also identified by bracket signs). OR, odds ratio, IRR, incidence risk ratio. HR, hazard ratio. * Data from Saracco and colleagues' study are not shown because risk could not be calculated since no seroconversions occurred in the hormonal contraception group. † Analysis showed statistically significant findings at p=.05 (marker also displayed in red). ¥ Different statistical models adjusted for slightly different confounders.

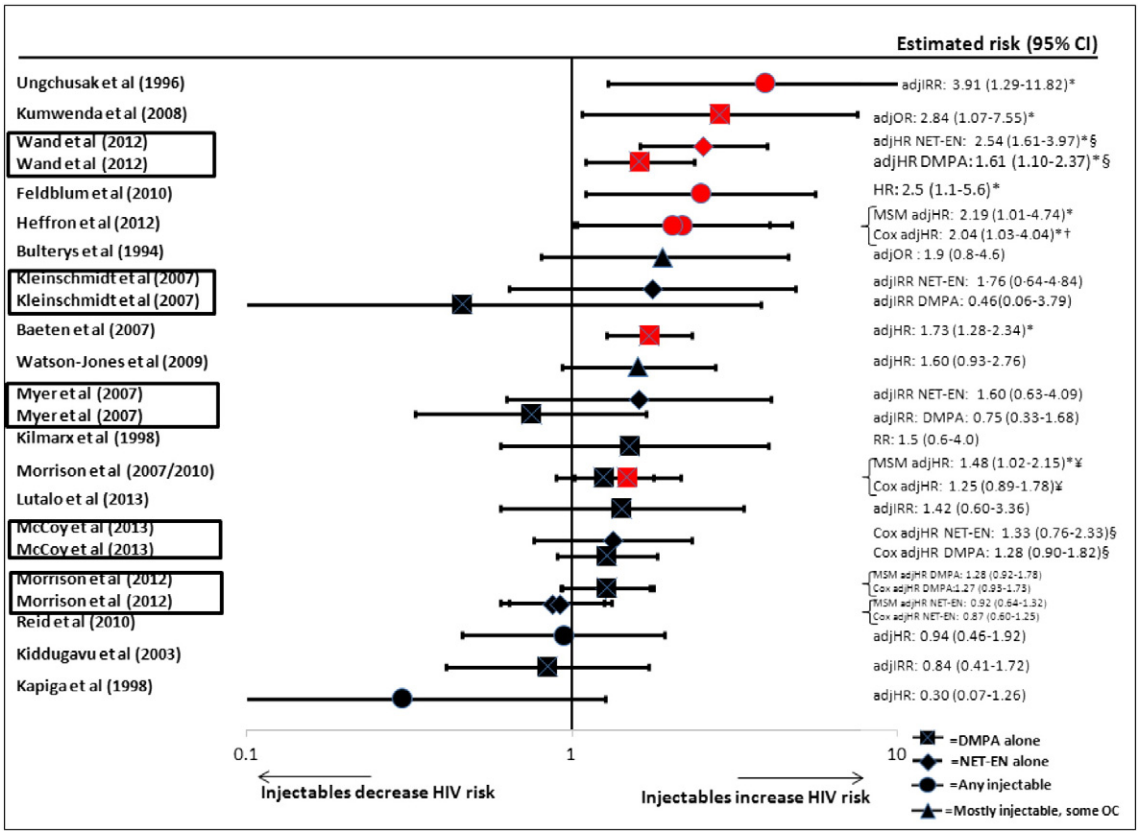

Fig. 3. Use of injectable contraceptives and HIV acquisition (all 18 studies, regardless of quality). Error bars show 95% CIs. Studies are arranged in order of decreasing magnitude of risk estimate, except if a single study provided disaggregated estimates for DMPA and NET-EN, in which case both estimates are adjacent (as indicated by a box around the study identifiers). For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are displayed on a single line (also identified by bracket signs containing two estimates), except for one study in which both Cox and MSM estimates for both DMPA and NET-EN separately were unavailable [62,82]. OR, odds ratio, IRR, incidence risk ratio. HR, hazard ratio. *Analysis showed significant findings at p=.05 (marker also displayed in red). †Estimate for Cox model taken from slightly updated analysis which controlled for total number of unprotected sex acts. § Unpublished estimates disaggregated by injectable type. ¥ Different statistical models adjusted for slightly different confounders.

Of five studies reporting NET-EN estimates, one reported a significantly increased risk (adjHR 2.54, 95% CI 1.61–3.97) [42]; three reported non-significant elevated estimates (ranging from adjHR 1.33, 95% CI 0.76–2.33 to adjHR 1.76, 95% CI 0.64–4.84) [53,54,62]; and one reported non-significant decreased estimates (adjHR 0.87, 95% CI 0.60–1.25 or adjHR 0.92, 95% CI 0.64–1.32, depending upon the statistical model used) (Fig. 7) [60].

Of five studies that provided separate estimates for both DMPA and NET-EN (Fig. 5), four reported estimates within the same study for NET-EN that were slightly or substantially higher than the DMPA estimates [42,53,54,62], while one study reported an estimate for NET-EN that was lower than for DMPA [60].

3.2.3. Implants

Data on implants were limited. Only one study was classified as "informative but with important limitations", and it reported a non-significantly increased risk of HIV acquisition with implants, with a wide 95% confidence interval (adjHR 1.6, 95% CI 0.5–5.7) [66].

3.2.4. Effect modification

One study by Morrison et al. reported that both DMPA and OCs were associated with increased HIV acquisition in women aged 18–24, but not in women aged 25 and older [57]. However, most studies have not detected evidence for effect modification by age [52–54,59], including the second-largest analysis to date (p=.60) [62].

Similarly, the Morrison et al. study reported that DMPA was associated with increased HIV risk (adjHR 4.5, 95% CI 2.0–10.2) in HSV2-negative, but not HSV2-positive women (adjHR 1.0, 95% CI 0.7–1.6) [57]. Other studies have not found evidence for effect modification by HSV2 status [52,59], including a study of 2057 HSV2-negative women and 2856 HSV2-positive women (interaction term p=.21 for the effect of DMPA on HIV acquisition) [62].

The Morrison et al. study also reported a significant interaction by study site (point estimates for both OCs and DMPA were above 1.0 in Uganda, but below 1.0 in Zimbabwe) [64] (an interaction that was not assessed in a later MSM analysis [57]). That study reported no effect modification by reported condom use at baseline, by participant behavioral risk, or by prevalent chlamydia or gonorrhea [64].

Table A3
Factors considered* and controlled for in multivariate analysis, among studies classified as "informative but with important limitations"

		Kiddugavu 2003 [51]	Baeten 2007 [52]	Myer 2007 [53]	Kleinschmidt 2007 [54]	Morrison 2007/10 [57,64]	Reid 2010 [41]	Wand 2012 [42]	Heffron 2012 [59,61]	Morrison 2012 [60]	McCoy 2013 [62]
Condom use	Considered	X	X	X	X	X	X	X	X	X	X
	Controlled	X	X	X	X	X	X	X	X	X	X
Number of sex partners (or concurrent partners)	Considered	X	X	X	X	X	X	X	X	X	X
	Controlled	X	X	X	X	X	X	X		X	X
Age	Considered	X	X	X	X	X	X	X	X	X	X
	Controlled	X	X	X	X	X	X	X	X	X	X
Education	Considered	X	X	X	X	X	X	X		X	X
	Controlled	X	X	X							
Married/lives with partner	Considered	X		X		X	X		X	X	X
	Controlled	X		X		X	X			X	X
Coital frequency	Considered					X	X	X	X	X	X
	Controlled					X			X†		X
Age at sexual debut	Considered				X			X			
	Controlled										
Parity	Considered		X		X	X			X		X
	Controlled		X								X
Pregnancy	Considered					X	X	X	X		X
	Controlled							X	X		
Breastfeeding	Considered					X					
	Controlled										
Sex work	Considered		All SW			X				X	X
	Controlled		All SW			X				X	X
GUD	Considered	X	X				X	X	X		
	Controlled	X	X								
HSV2	Considered		X			X			X		X
	Controlled		X								X
HPV	Considered			X							
	Controlled			X							
BV	Considered		X	X	X	X					
	Controlled		X		X						
Chlamydia/Gonorrhea/ Trichomoniasis	Considered		X	X	X	X	X	X	X	X	X
	Controlled		X	X	X		X				X
Vaginal discharge or discomfort, *Candida*	Considered		X			X				X	
	Controlled		X							X	
Vaginal washing/wiping	Considered		X								X
	Controlled		X								
Abnormal epithelial findings	Considered									X	
	Controlled									X	
Alcohol use	Considered			X							
	Controlled			X							
Partner risk	Considered					X			All HIV+	X	X
	Controlled					X			All HIV+	X	X
Male circumcision status	Considered								X		X
	Controlled										
New sex partners recently	Considered					X	X			X	X
	Controlled					X	X			X	X
Recent HIV+partner	Considered						X		All HIV+		
	Controlled								All HIV+		
Partner plasma VL	Considered								X		
	Controlled								X		
Partner CD4	Considered								X		
	Controlled										
Housing type/status	Considered			X							X
	Controlled										X
Site	Considered					X			X	X	X
	Controlled					X				X	X
Own income	Considered						X	X			
	Controlled										
Partner own income	Considered						X				
	Controlled						X				

(continued on next page)

Table A3 (*continued*)

		Kiddugavu 2003 [51]	Baeten 2007 [52]	Myer 2007 [53]	Kleinschmidt 2007 [54]	Morrison 2007/10 [57,64]	Reid 2010 [41]	Wand 2012 [42]	Heffron 2012 [59,61]	Morrison 2012 [60]	McCoy 2013 [62]
Race	Considered									X	
	Controlled										
Anal sex	Considered							X			X
	Controlled										X
Religion	Considered							X			
	Controlled							X			
Syphilis	Considered										X
	Controlled										X
Injection drug use	Considered										X
	Controlled										X
Diaphragm use over past 3 months	Considered										X
	Controlled										X

BV, bacterial vaginosis; SW, sex worker; GUD, genital ulcer disease; HPV, human papillomavirus; HSV2, seropositive for herpes simplex virus 2; "all HIV+" — all partners were HIV positive as data were collected in study of serodiscordant couples.

* Some confounders were considered but not controlled for due to a lack of confounding in those data; and some factors listed on this table are not relevant to all studies (i.e., site or race in homogeneous populations).

† While most confounding factors are detailed in the original analysis [59], the sensitivity analysis reported in a subsequent publication [61] added a control for total number of unprotected sex acts.

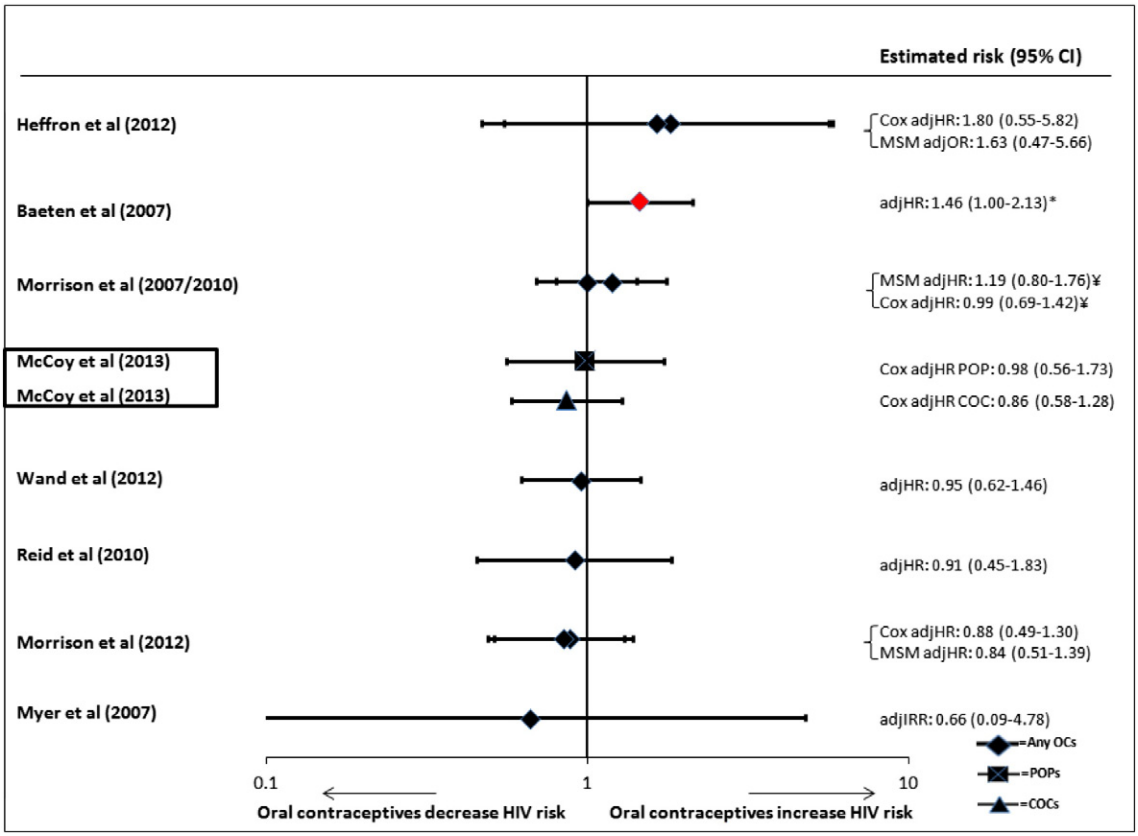

Fig. 4. Use of oral contraceptives and HIV acquisition (eight studies considered informative but with important limitations). Error bars show 95% CIs. Studies are arranged in order of decreasing magnitude of risk estimate, except if a single study disaggregated POPs and combined oral contraceptives [COCs], in which case both estimates are adjacent (as indicated by a box around the study identifiers). For studies which reported both Cox proportional hazards (Cox) and marginal structural model (MSM) estimates, both estimates are displayed on a single line (also identified by bracket signs). OR, odds ratio, IRR, incidence risk ratio. HR, hazard ratio. *Analysis showed significant findings at p=.05 (marker also displayed in red). ¥ Different statistical models adjusted for slightly different confounders.

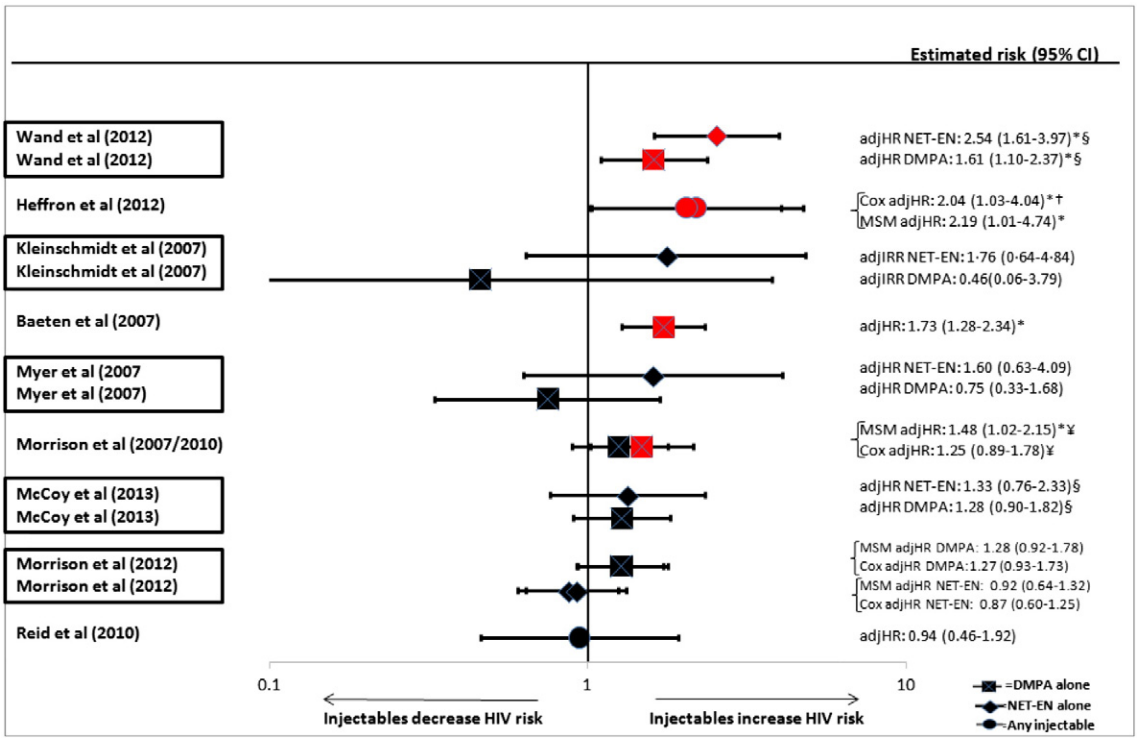

Fig. 5. Use of injectable contraceptives and HIV acquisition (nine studies considered informative but with important limitations). Error bars show 95% CIs. Studies are arranged in order of decreasing magnitude of risk estimate, except if a single study disaggregated DMPA and NET-EN, in which case both estimates are adjacent (as indicated by a box around the study identifiers). For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are displayed on a single line (also identified by bracket signs), except for one study in which both Cox and MSM estimates for both DMPA and NET-EN separately were unavailable [62,82]. OR, odds ratio, IRR, incidence risk ratio. HR, hazard ratio. *Analysis showed significant findings at p=.05 (marker also displayed in red). †Estimate for Cox model taken from slightly updated analysis which controlled for total number of unprotected sex acts. § Unpublished estimates disaggregated by injectable type; only disaggregated Cox estimates provided in McCoy et al. 2013, disaggregated MSM estimates not possible due to violation of the positivity assumption. ¥ Different statistical models adjusted for slightly different confounders.

4. Discussion

4.1. Methodological considerations in studies considered informative but with important limitations

Discussion of multiple key methodological considerations, such as potential for confounding, frequency and accuracy of variable measurement, aim of data collection, and statistical power and precision is available in our previous review [2]. Below, we expand upon the discussion on the handling of confounding by condom use, and provide an overview of considerations related to "total" and "direct" effects.

4.1.1. Considerations on measurement and parameterization of condom use

Analytic approaches to addressing potential confounding by condom use vary considerably across studies (Tables A1 and A2), and is one of several reasons why study findings may vary. Reliable, valid, self-reported measurement of condom use is difficult: individuals may not remember whether, how often, and with whom they used condoms over a given time period; they may deliberately misreport due to embarrassment or social desirability bias [67]; or they may unintentionally misreport (e.g., if they experience an unrecognized condom failure). Adjustment for a poorly-measured confounding variable can in theory lead to adjusted estimates of effect which are more biased than the unadjusted estimates [68].

Studies approached the issue of condom use in different ways. For example, one study restricted analysis to time periods in which no condom use was reported for either contraception or HIV prevention, in an attempt to minimize the potential for differential condom use between users and non-users of HC [63]. Some studies attempt to control statistically for some measure of condom use, such as the proportion of unprotected sex acts, or "never-sometimes-always" condom use. Studies varied with respect to whether questions about condom use were pertinent to the entire intersurvey interval, or only a subset of time during that interval. Some studies asked only about condom use during the most recent sex act and assumed this to be representative of participants' "typical" condom use. This last measure may reduce recall bias, but cannot eliminate intentional or unintentional misreporting; a recent review noted that in several studies semen was detected on vaginal swabs taken from 6–36% of women who reported no sex in the past 2 days, and in 13–39% of women who reported protected sex only [69].

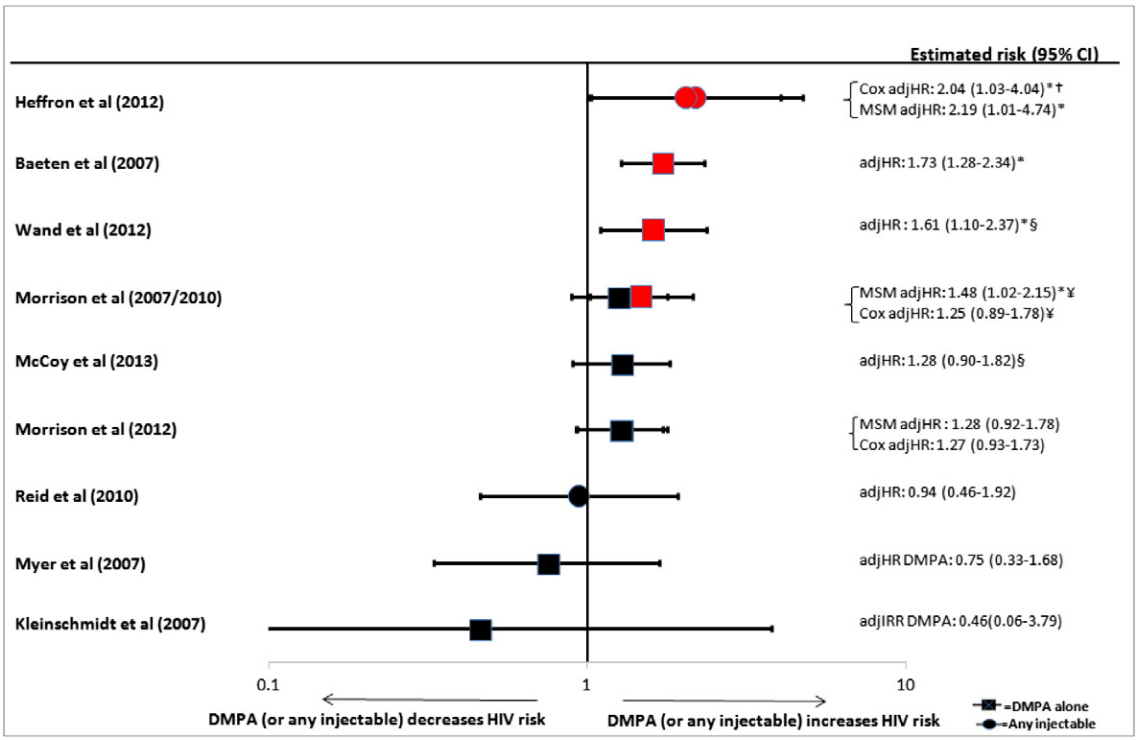

Fig. 6. Use of DMPA (or unspecified injectable) and HIV acquisition (among studies considered informative but with important limitations). Error bars show 95% CIs. Studies are arranged in order of decreasing magnitude of risk estimate. For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are displayed on a single line (also identified by bracket signs) IRR, incidence risk ratio. HR, hazard ratio. *Analysis showed significant findings at p=.05 (marker also displayed in red). †Estimate for Cox model taken from slightly updated analysis which controlled for total number of unprotected sex acts. §Unpublished estimates disaggregated by injectable type; only disaggregated Cox estimates provided in McCoy et al. 2013, disaggregated MSM estimates not possible due to violation of the positivity assumption. ¥ Different statistical models adjusted for slightly different confounders.

4.1.2. Direct versus total effects

As discussed in previous work [35], the analytic approach used by an epidemiologic study has implications for the interpretation of its findings. In particular, model results from reports reviewed here may be estimating a "direct effect" of HC on HIV not mediated by sexual behaviors (which can be roughly conceived of as an estimate of the HIV acquisition risk per coital act unprotected by condoms, comparing HC users to non-users), the "total effect" (which would include these biological effects as well as behavioral changes that may be affected by HC use, such as decreased condom use or increased coital frequency), or neither (due to vague or poor model specification). The authors of this review determined that the "direct effect" (representing a more biological effect) is more desirable for the purpose of the World Health Organization Medical Eligibility Criteria for Contraceptive Use, which is intended to provide global guidance for policy makers. Unfortunately, estimating direct effects may require statistical assumptions additional to those necessary to estimate total effects.

While some argue that a "total effect" is useful to understand the full impact of a given HC method on HIV acquisition, behavioral changes stemming from use of HC may be specific to geography, culture, socioeconomic status, and other factors. Studies estimating a total effect may be less generalizable (if behaviors are affected differently in different populations), and may also be less informative for women for whom use of HC might modify their behavior in ways not represented by population averages. For example, a woman whose partner has always refused to use condoms will not reduce condom use as a result of HC initiation, even if *most* women who initiate HC reduce condom use. DMPA may be an important option for such a client if no direct effect of DMPA on HIV acquisition is expected, even if a total effect (mediated by reduced condom use) is expected. Thus, direct effects (which are not mediated by behaviors of individuals) may be of more use for individual decision-making, and are thus preferred in this discussion.

No published study has explicitly stated whether the analysis attempts to estimate total or direct effects. We assumed that MSMs are generally estimating total effects [70] and time-updated Cox models, which adjust for time-varying mediators such as condom use, are estimating something closer to direct effects. Nonetheless, we included MSM estimates in this review in the hopes of contextualizing direct effects. Although the models should theoretically produce different results, in practice most MSM estimates were very similar to adjusted Cox effects from the same studies. This suggests that mediation by measured sexual behavior was not substantial in this setting: however, since sexual behavior may have been mismeasured, it would be rash to conclude that there is no mediation *per se*.

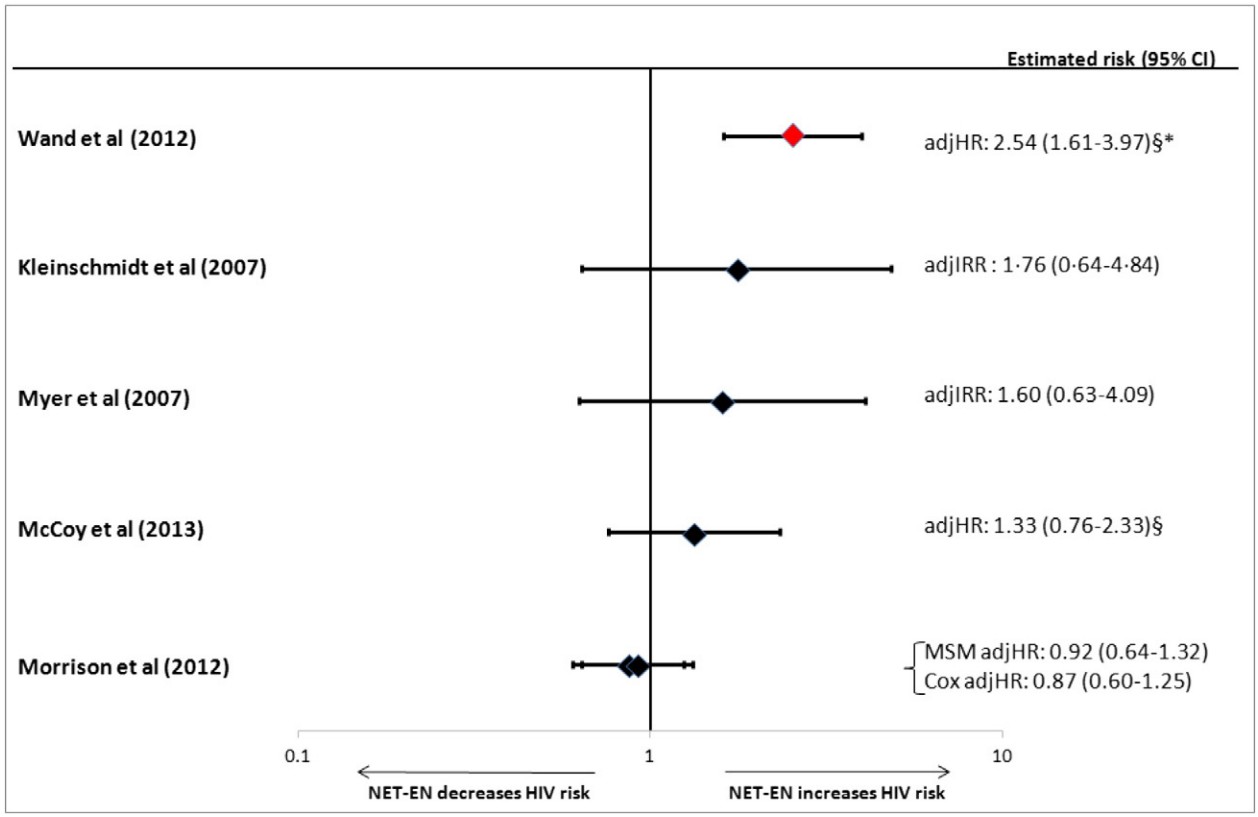

Fig. 7. Use of NET-EN and HIV acquisition (among studies considered informative but with important limitations). Error bars show 95% CIs. Studies are arranged in order of decreasing magnitude of risk estimate. For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are displayed on a single line (also identified by bracket signs). IRR, incidence risk ratio. HR, hazard ratio. *Analysis showed significant findings at p=.05 (marker also displayed in red). § Unpublished estimates disaggregated by injectable type; only disaggregated Cox estimates provided, disaggregated MSM estimates not possible due to violation of the positivity assumption.

4.2. Modifications to quality framework used in previous review

As noted elsewhere, it is imperative to continually refine quality assessment criteria as this complex body of literature continues to grow [35]. For example, older systematic reviews of this issue may have included cross-sectional studies; doing so currently would add little to what is known. As such, we modified the study quality assessment framework used in the previous systematic review [2]. Specific modifications included: (1) relaxing our stipulations about adequate control for condom use (rationale provided below); (2) considering studies lower quality if one out of two (instead of two out of three) major flaws existed; (3) no longer specifying the level of loss to follow up that would be considered a major flaw (as the cutoff chosen could be viewed as arbitrary), and (4) providing additional specificity to our definition of "unclear measurement of exposure to HC," by newly including a requirement that the intersurvey interval be less than or equal to 6 months (or, if over 6 months, that detailed information on use of contraceptives in the interim period be collected and analyzed).

While a Cochrane review estimated that consistent condom use decreased heterosexual HIV transmission by 80% as compared with no condom use [71], a study examining four different measures of condom use (condom use since last visit, condom use at last sex, frequency of condom use, and count of unprotected acts) found that no measure of condom use was significantly associated with reduced risk of sexually transmitted infections or HIV. All four measures were significantly correlated with reduced pregnancy risk; the strongest protective association was observed with the frequency of use condom variable [72]. Since no measurement of condom use has been validated as superior, we did not distinguish between methods of handling condom use, so long as some attempt was made to address this issue.

4.3. Limitations

All currently available epidemiological data on this issue come from observational studies and are vulnerable to residual confounding, which can mask a real effect or generate a spurious effect. Most currently available information relates to OCs and injectables (including DMPA and NET-EN). Separation of data according to specific hormonal content or formulation is not consistently performed across studies. Future analyses should provide disaggregated estimates, given that different hormonal formulations may have different biological effects on risk of HIV acquisition [35]. Data are extremely limited for implants, and no data are available for contraceptive patches, rings, or hormonal IUDs.

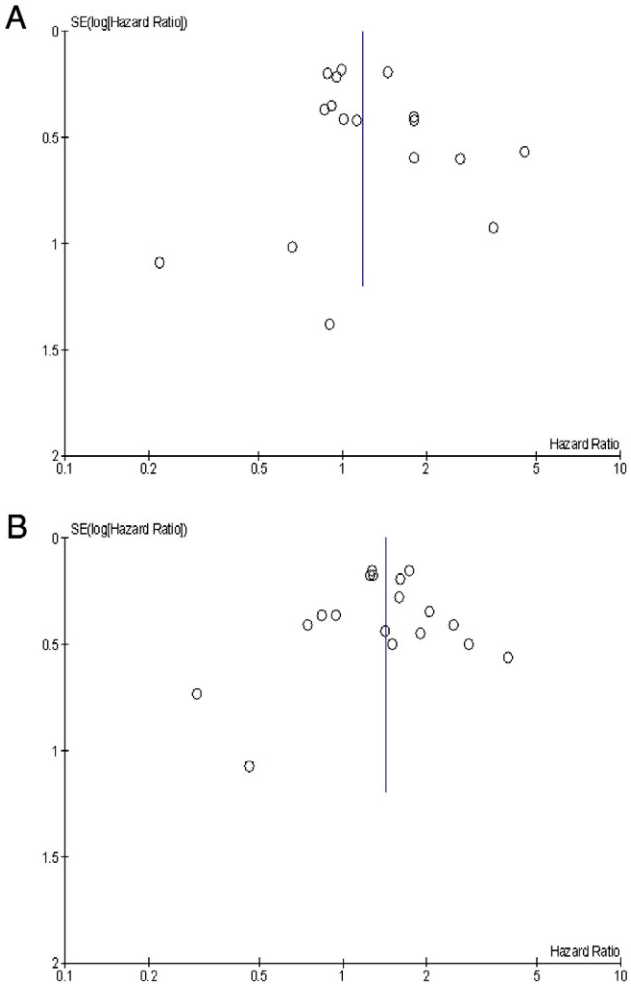

Fig. 8. Funnel plots (A: OCs and HIV acquisition, B: Injectables and HIV acquisition).

Numerous measurement challenges remain in this body of literature, including of measurement of exposure and of potential confounders. For example, measurement of exposure to OC use (which requires daily action by the user) is more challenging than measurement of exposure to injectable contraceptive use (which requires user action only every 3 months). In some HIV prevention trials, women reporting OC use demonstrate comparable pregnancy incidence to women using no contraceptive method; raising the possibility of limited or inconsistent actual exposure to OC use [73]. Thus, the possibility exists that the null effect of OCs reported in most studies reflects a lack of actual exposure, rather than a true lack of association between OCs and risk of HIV acquisition. On the other hand, while pregnancy risk by contraceptive type is not consistently reported, some studies in this review demonstrate a reduction in pregnancy risk among OC users [41]. Given this issue, it is recommended that future observational analyses compare pregnancy rates [35].

Several innovative analytic approaches have been used in recent studies. For example, two studies used data from serodiscordant couples which may help control for differences in exposure to an HIV-infected partner, and both highlight the importance of using various analytic techniques (such as restriction to non-condom users, or assessing male partner report of condom use) to assess whether primary findings remain robust (thereby testing concerns about the validity of data on self-reported sexual behaviors) [61,63]. However, several methodological challenges remain, and are reviewed elsewhere, along with recommended approaches to improve the quality of evidence in future studies [35].

We are aware of anecdotal evidence that a non-significant preliminary finding for the effect of DMPA use on HIV acquisition was not pursued for publication in at least one case, due to the lack of a statistically significant finding. This is problematic; if studies with significant results are more likely to be published, a systematic literature review is unable to capture the universe of relevant information on this issue [74]. However, funnel plots (Fig. 8) displayed only moderate asymmetry.

In addition to the limitations of individual studies, there are limitations to this systematic review. There is no agreed upon, comprehensive, objective method to assessing the quality of studies in this complex body of literature; conclusions may vary depending upon what quality criteria are applied. As noted above, discussions on ideal approaches to evaluating this literature should continue to evolve.

4.4. Unpublished evidence

For methodological reasons, we did not include unpublished analyses in this systematic review. Researchers have noted that differences between data presented in conference abstracts and published papers are "frequent and occasionally major," [75] and that "the inclusion of data from unpublished studies [in systematic reviews] can itself introduce bias" given that "unpublished trials may be of lower methodological quality than published trials." [76] Furthermore, there is no systematic manner in which to search grey literature, and moreover, thorough assessment of study quality is often challenging or impossible based on information provided in a conference presentation. We are aware of one analysis published subsequent to our cutoff date (January 15, 2014) [77], and of four relevant presentations on this issue [78–81]. Any analyses newly reported in academic journals since the cutoff for inclusion in this review will be carefully examined and reported at the next technical consultation on this issue.

4.5. Conclusions

We considered nine of 22 studies to be "informative but with important limitations".

4.5.1. Oral contraceptives

The preponderance of data suggests that OCs do not increase risk of HIV acquisition. Only one study (of eight considered "informative but with important limitations" which assessed OCs) reported a modestly elevated statistically significant risk estimate (adjHR 1.46, 95% CI

1.00–2.13); all other studies found no significant effect, including a study which provided separate information about COCs and POPs [62].

4.5.2. Injectables

4.5.2.1. All injectables (i.e., either DMPA alone, or DMPA and NET-EN combined). The observational data on injectable contraceptive use and risk of HIV acquisition remain difficult to interpret. Modifications to our quality framework for selecting studies changed slightly the group of studies considered to be higher quality (i.e., classified as "meeting minimum quality criteria" in the previous review, or "informative but with important limitations" in the current review). Specifically, we removed one study with non-significant effects for DMPA from the higher quality group [51] and added one study with significant effects for both DMPA and NET-EN [42]. In addition, new sub-analyses by Heffron et al. [61] lend some additional confidence that incomplete statistical control for sexual behaviors (e.g., self-reported condom use, coital frequency) may not explain the statistically significant findings observed for injectables in their original analysis. Another separate new subanalysis by Heffron et al. suggested that the estimate for all injectables (as presented in the original paper) is similar in magnitude to the best possible approximation of an estimate for DMPA (as presented in the subanalysis). However, those sub-analyses contained few incident HIV infections, and some researchers have questioned whether condom use was over-reported based on the high pregnancy rates observed in this study [26,29].

On the other hand, one large, newly included study did not find statistically significant effects on HIV risk for either DMPA or NET-EN. Combining DMPA, NET-EN, and unspecified injectables into a single exposure category resulted in a significant finding (adjHR: 1.37, 95% CI 1.01–1.85) under a Cox proportional hazards model, and a similar but non-significant point estimate under a MSM approach (adjHR: 1.34, 95% CI 0.75–2.37) [62]. In addition, the modification to the quality framework relating to intersurvey interval resulted in the use of HC method estimates for the study by Myer et al. only from the first 6 month survey interval, as subsequent intervals were longer than 6 months [53]. The new DMPA point estimate remained non-significant, and was slightly smaller than the previous one (adjHR 0.96, 95% CI 0.58–1.59 in the previous review vs. adjHR 0.75, 95% CI 0.33–1.68 in the current), while the NET-EN estimate remained non-significant but with the direction of effect changed (from adjHR 0.79, 95% CI 0.31–2.20 previously vs. adjHR 1.60, 95% CI 0.63–4.09 currently). Finally, results from one study [57,64] demonstrate a statistically significant effect of DMPA on HIV risk using a MSM approach but not a Cox model approach. Cox models are a closer approximation to the direct effect, our effect of interest. Thus, new data published between December 15, 2011 and January 15, 2014 for injectables, particularly DMPA, do not resolve the critical question of whether progestin-only injectables increase HIV risk.

4.5.2.2. NET-EN. One previously identified study which was newly classified as "informative but with important limitations" reported a statistically significant increased risk of HIV acquisition with NET-EN [42]. One new study reported no increased HIV risk with NET-EN use [62], and the direction of another estimate (for the study in which we restricted to only data from the 6-month follow-up visit) reversed but remained non-significant (estimate changed from adjIRR 0.79, 95% CI 0.31–2.20 previously, to adjIRR 1.60, 95% CI 0.63–4.09 currently) [53]. These new data add heterogeneity to evidence on NET-EN.

4.5.3. Implants

Data on contraceptive implants and HIV acquisition are extremely limited. No studies have suggested a statistically significant increased risk of HIV acquisition among implant users, though the limited number of studies examining this method and the wide confidence intervals for existing estimates preclude clear interpretation of the effects of implants on HIV acquisition. Ideally, future studies assessing implants will separately assess etonogestrel and levonorgestrel implants, which may have different biological effects.

4.5.4. Summary

In conclusion, and consistent with our previous review, evidence available at present suggests that OCs do not increase risk of HIV acquisition. One new study suggests that this finding may extend to both COCs and POPs, and adds to very limited data assessing non-injectable progestin-only HC methods. Uncertainty persists regarding the association between DMPA and HIV risk. Newly published analyses are in the direction of an elevated risk; taken together with prior evidence, the new data lead to a moderate increase in the consistency of estimates of the effect of DMPA on HIV risk. Still, several of the largest studies reported no statistically significant increased HIV risk among DMPA users, contributing to continued uncertainty. None of three studies in our previous review suggested a significantly increased risk for NET-EN, whereas one of five available estimates in our current review does. Four of the five studies that presented both DMPA and NET-EN estimates reported measures of effect for NET-EN that were slightly or substantially higher than for DMPA, though the 95% confidence intervals overlapped substantially in all cases. Data are limited for implants; neither of two estimates showed a statistically significant increased risk, but only one was considered "informative but with important limitations" and this estimate had limited statistical power.

Women choosing progestin-only injectable contraceptives should be informed of the current uncertainty regarding whether use of these methods is associated with an increased risk of HIV acquisition, and similar to all women at risk of HIV, should be empowered to access and use condoms and

other HIV preventative measures. Access to a range of contraceptive options and to HIV preventive measures is critical. Data for OCs do not suggest an increased risk of HIV acquisition, but programs, practitioners, and women urgently need guidance on how to optimize health decisions in the face of inconclusive data for progestin-only injectable contraception and of limited data for other HC methods.

Acknowledgments

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Appendix A. Search strategy

Our search strategy included papers published in any language, and used the following date limits: Dec 15, 2011 (the date on which the search strategy for our previous systematic review ended) through Jan 15, 2014.

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

The following search strategy was performed in Embase: hormonal AND contracepti* OR 'hormonal methods' OR (progestin* OR 'progestins'/exp OR 'progesterone'/exp OR progestogen* OR progestagen* AND contracept*) OR ('oral'/exp AND contracept*) OR (depo OR depot AND 'medroxyprogesterone'/exp OR depomedroxyprogesterone OR depo OR depot OR dmpa OR 'net en' OR 'norethisterone enanthate'/exp OR 'medroxyprogesterone'/exp AND '17 acetate' AND (contracept* OR inject*)) OR ('levonorgestrel'/exp OR 'etonogestrel'/exp AND 'implant'/exp) OR 'uniplant'/exp OR 'jadelle'/exp OR 'implanon'/exp OR 'norplant'/exp OR norplant2 OR 'sino implant' OR (contraceptives, AND postcoital) OR (contracept* AND ('emergency'/exp OR postcoital OR 'post coital')) OR 'ulipristal acetate'/exp OR 'plan b'/exp OR 'mifepristone'/exp OR ('levonorgestrel'/exp AND ('intrauterine'/exp AND 'devices'/exp OR 'iud'/exp OR 'iucd'/exp OR ius OR 'intrauterine system' OR 'intra-uterine system' OR 'intrauterine device'/exp OR 'intra-uterine device'/exp)) OR 'mirena'/exp OR (combin* AND inject* AND contracept*) OR ('once a month' OR monthly AND inject* AND contracept*) OR 'cyclofem'/exp OR 'lunelle'/exp OR 'mesigyna'/exp OR 'cyclo provera'/exp OR 'cycloprovera'/exp OR ('contraceptive'/exp AND 'devices'/exp OR 'contraceptive'/exp AND agents AND ring) OR 'nuvaring'/exp OR 'nuva ring' OR ('contraceptive'/exp AND 'devices'/exp OR 'contraceptive'/exp AND agents AND patch) OR 'ortho evra'/exp OR orthoevra AND ('hiv seropositivity'/exp OR 'hiv'/exp OR 'hiv infections'/exp OR 'acquired immunodeficiency syndrome'/exp OR 'hiv progression' OR 'hiv disease progression' OR 'hiv shedding' OR 'viral shedding'/exp OR 'hiv transmission' OR 'virus shedding'/exp) AND 'humans'/exp OR (injectable AND contracepti* AND 'hiv'/exp) OR ('oral'/exp AND contracepti* AND 'hiv'/exp) AND [humans]/lim AND [15-12-2011]/sd NOT [15-1-2014]/sd.

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