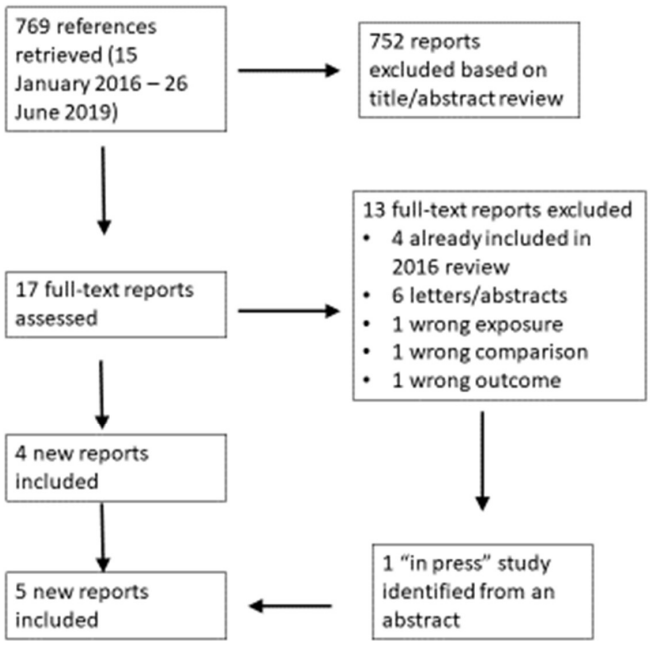
Supplementary Online Figure 1. Identification of newly included studies



Supplementary Online Table 1. Newly included reports for an updated systematic review of hormonal contraception and HIV acquisition among women, 2016-2019

Author, year, location, funding	Design, purpose, period of data collection	Number enrolled, description of population	Number seroconverted/ number analyzed, number seroconverted by exposure group, overall HIV incidence, follow-up time	Results	Strengths	Weaknesses	Quality
Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium, 2019,[1] 12 sites in Eswatini, Kenya, South Africa, Zambia Bill & Melinda Gates Foundation, USAID and PEPFAR, Swedish International Development Cooperation Agency, South African Medical Research Council, UNFPA,	RCT, 2015-2019	7829 HIV negative women seeking contraception	397/7715 seroconverted HIV incidence / 100 woman years Overall: 3.81 DMPA-IM: 4.19 LNG implant: 3.31 Cu-IUD: 3.94 Follow-up time: up to 18 months	**ITT analysis, HR (96% CI):** DMPA-IM vs Cu-IUD: 1.04 (0.82-1.33) DMPA-IM vs LNG implant: 1.23 (0.95-1.59) Cu-IUD vs LNG implant: 1.18 (0.91-1.53) **Continuous use analysis, adjHR (96% CI):** DMPA-IM vs Cu-IUD: 1.10 (0.84-1.44)	Publication of full trial protocol[2] Clear randomization and allocation procedures Good adherence to allocated treatments (99% uptake; continuation 92% of follow-up time), with limited discontinuation or change of contraceptive method	Patients and clinicians not blinded; however, study team made concerted efforts to not provide different information/counselling to women in DMPA-IM group versus other groups	Informative with few limitations

Government of South Africa				DMPA-IM vs LNG implant: 1.29 (0.98-1.71) Cu-IUD vs LNG implant: 1.18 (0.90-1.55) No effect modification by age or HSV-2 status, and no substantial differences by several other factors	Short interval between visits (3 months) Clear exposure groups Outcome assessment, lab testing, and review committees blinded to assignment High rates of follow-up (>91% all visits; 99% at least one visit) Primary intention-to-treat analysis; continuous use analysis with adjustment for baseline and time-varying confounders including vaginal sex without a condom Results reported as per pre-defined analysis plan		

Palanee-Phillips 2019,[3] South Africa NIH	Cohort; from RCT that examined effectiveness of dapivirine ring to prevent HIV; 2012-2015	1136 HIV-negative women from South African clinical study sites	95/1136 seroconverted HIV incidence / 100 woman-years Overall: 5.6 DMPA-IM: 5.79 NET-EN: 6.22 Implant (type not specified): 1.93 Cu-IUD: 4.48 Median follow-up: 1.6 years Total follow-up time: 1771 person-years	**Adj HR (95% CI), compared with Cu-IUD** DMPA-IM: 0.91 (0.44-1.87) NET-EN: 1.02 (0.49-2.12) Implant: 0.46 (0.13-1.70) All 3 hormonal methods together: 0.90 (0.45-1.76) **Adj HR (95% CI), compared with NET-EN** DMPA: 0.89 (0.55-1.44) Implant: 0.45 (0.13-1.53) Cu-IUD: 0.98 (0.47-2.03)	Time-varying analysis of HC exposure, condom use, and other relevant confounders; adjusted for condom use, trial arm, age, menstrual bleeding, number of sexual partners, STIs; clear exposure and comparison groups; short inter-survey interval (monthly)	No information on partners' HIV status; no information on implant type (LNG or etonogestrel); no information on follow-up time or attrition by study group; potential for residual/ unmeasured confounding	Informative but with important limitations
Sabo 2019,[4] Kenya Updated analyses of Baeten 2007[5] and Lavreys 2004[6] NIH	Cohort; long-term open cohort study of female sex workers in Kenya (Mombasa Cohort); 1993-2017	1985 HIV-seronegative female sex workers, presenting for STI screening	307/1985 seroconverted HIV incidence / 100 woman-years Overall: 4.32	**Adj HR (95% CI) compared with no contraception** DMPA: 1.72 (1.34-2.20) OCs: 1.48 (1.05-2.09)	Time-varying analysis of HC exposure, BV diagnosis, and relevant confounders; adjusted for unprotected sex in the last week;	Loss to follow-up not described (median follow-up 1.7 years, IQR 0.5-4.9); assessment of condom use included only self-report of	Informative but with important limitations

			No contraception: 3.28 DMPA: 7.53 OC: 7.36 LNG implant: 2.46 Other (non-hormonal): 2.73 Median follow-up: 1.71 years Total follow-up time: 7127 person-years	LNG implant: 0.99 (0.40-2.45) Other (non-hormonal): 0.82 (0.47-1.43) **Stratified by BV status** **BV present** DMPA: 1.56 (1.08-2.25) OCs: 1.50 (0.94-2.39) LNG implant: 0.65 (0.16-2.72) Other (non-hormonal): 0.54 (0.24-1.3) **BV absent** DMPA: 2.08 (1.46-2.97) OCs: 1.61 (0.99-2.64) LNG implant: 1.39 (0.43-4.46) Other (non-hormonal): 1.20 (0.53-2.68)	clear exposure and comparison groups; short inter-survey interval (1 month)	condom use in the last week which may not be reflective of entire study interval; potential for residual/ unmeasured confounding	
Haddad 2018,[7] Zambia	Cohort; to examine bacterial	564 serodiscordant couples (HIV-	106/564 seroconverted (linked or	**Adj HR (95% CI) compared with non-hormonal**	Time-varying analysis of HC exposure, BV	Various study components not described,	Informative but with important limitations

NIH, Emory University, CDC, USAID, International AIDS Vaccine Initiative Secondary analysis of Wall 2015[8]	vaginosis as an effect modifier of the association between hormonal contraception and HIV acquisition; 1994-2002	negative women with HIV-infected partners) recruited from couples voluntary counseling and testing services	unlinked to partner); Seroconversions by BV and HC status: **BV: Yes** Non-HC: 12 OC: 8 DMPA: 2 LNG implants: 0 Total HIV rate: 12.1/100 couple-years **BV: No** Non-HC: 61 OC: 15 DMPA: 8 LNG implants: 0 Total HIV rate: 8.8/100 couple-years Total follow-up time: 1137.2 person-years	**contraception or no method use** **BV: Yes** DMPA: adj HR 6.55 (1.14-37.77) OCs: adj HR 5.20 (1.68-16.06) **BV: Yes (adj included markers of unprotected sex)** DMPA: adj HR 9.2 (1.3-62.5) OC: adj HR 7.6 (1.9-31.0) **BV: No** DMPA: adj HR 1.35 (0.64-2.85) OC: adj HR 1.36 (0.76-2.42)	diagnosis, and relevant confounders; adjusted for measures of unprotected sex in sensitivity analysis; clear exposure and comparison groups; short inter-survey interval (3 months)	including loss to follow-up, composition of contraceptive methods used in referent group; low statistical power; potential for residual/ unmeasured confounding	
Hofmeyr 2017,[9] South Africa, Effective Care Research Unit,	RCT; to compare rates of incident HIV among women using progestogen-	2493 enrolled, 1246 in injectable arm and 1247 in IUD arm, recruited	20/656 (3%) injectable arm 22/634 (3.5%) Cu-IUD arm	**ITT analysis compared with Cu-IUD**	Appropriate randomization procedures, with good concealment of	No measurement or adjustment for condom use (or	Unlikely to inform the primary question

East London, South Africa	only injectables and those using Cu-IUD; 2009-2012	from women attending pregnancy termination services at two hospitals in South Africa After exclusions of HIV-infected women or women without test results at baseline, 656 women in injectable arm and 634 in IUD arm included for analysis	Median follow-up time: 19-20 months	Injectables: RR 0.88 (0.48-1.59) **Per protocol analysis (according to initial method received) compared with Cu-IUD** Injectables : RR 0.94 (0.52-1.71) DMPA : RR 1.01 (0.55-1.86) NET-EN : RR 0.58 (0.14-2.42)	allocations at point of assignment	other potential confounders) No information on discontinuation or switching, or time-varying analysis of contraceptive use or 19-20 month median interval for HIV testing 37% of follow-up HIV test results by self-report Loss to follow-up for HIV outcome was 25% in injectable arm and 27% in IUD arm	

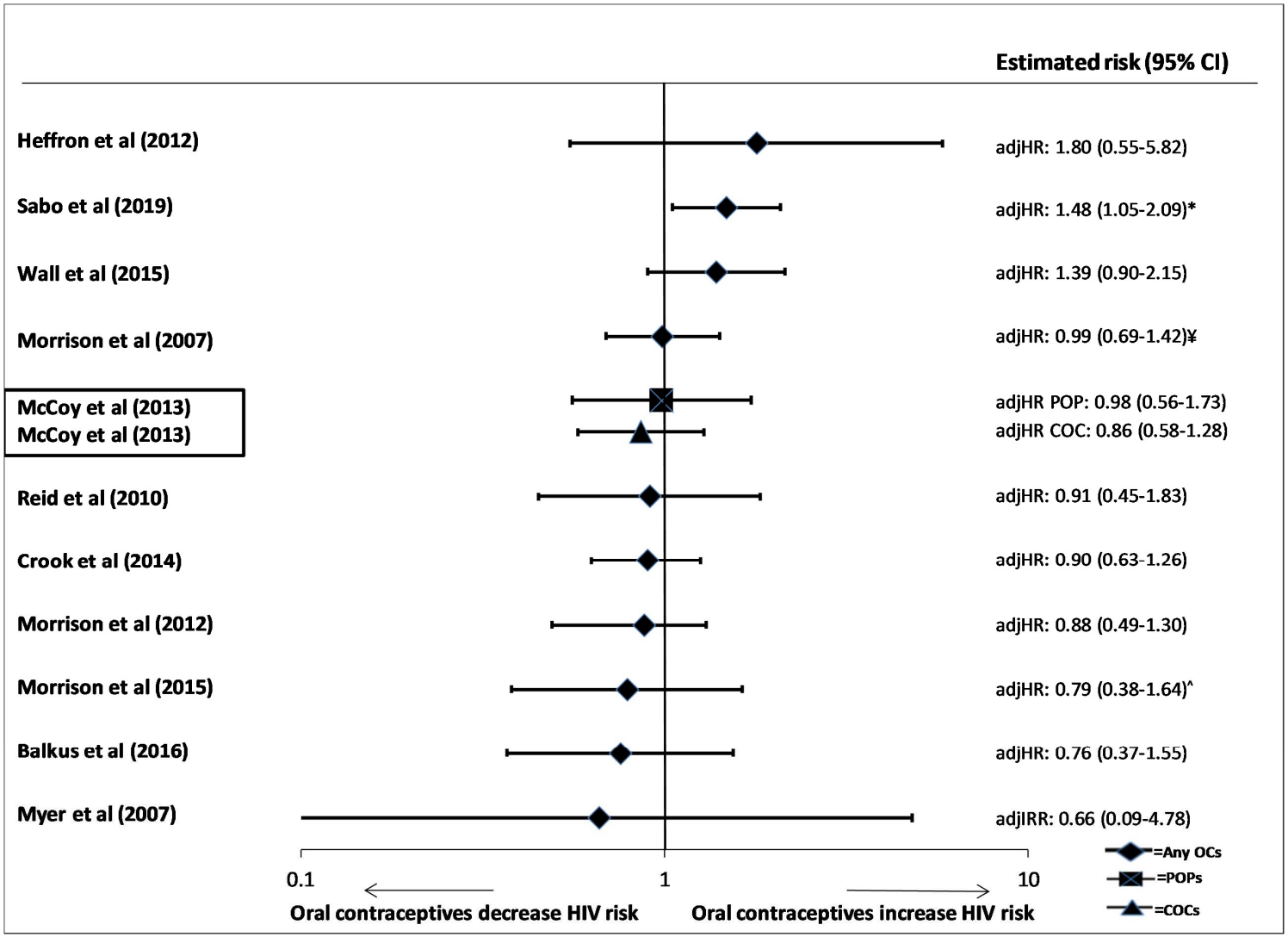
adj HR, adjusted hazard ratio; BV, bacterial vaginosis; CI, confidence interval; Cu-IUD, copper intrauterine device; DMPA, depot medroxyprogesterone acetate; HC, hormonal contraception; HIV, human immunodeficiency virus; IQR, interquartile range; LNG, levonorgestrel; NET-EN, norethisterone enanthate; OC, oral contraceptive; RCT, randomized clinical trial; RR risk ratio; STI, sexually transmitted infection

References for Supplementary Online Table 1.

1. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet* 2019;394:303-313.
2. Hofmeyr GJ, Morrison CS, Baeten JM, et al. Rationale and design of a multi-center, open-label, randomised clinical trial comparing HIV incidence and contraceptive benefits in women using three commonly-used contraceptive methods (the ECHO study). *Gates open research.* 2017;1:17.

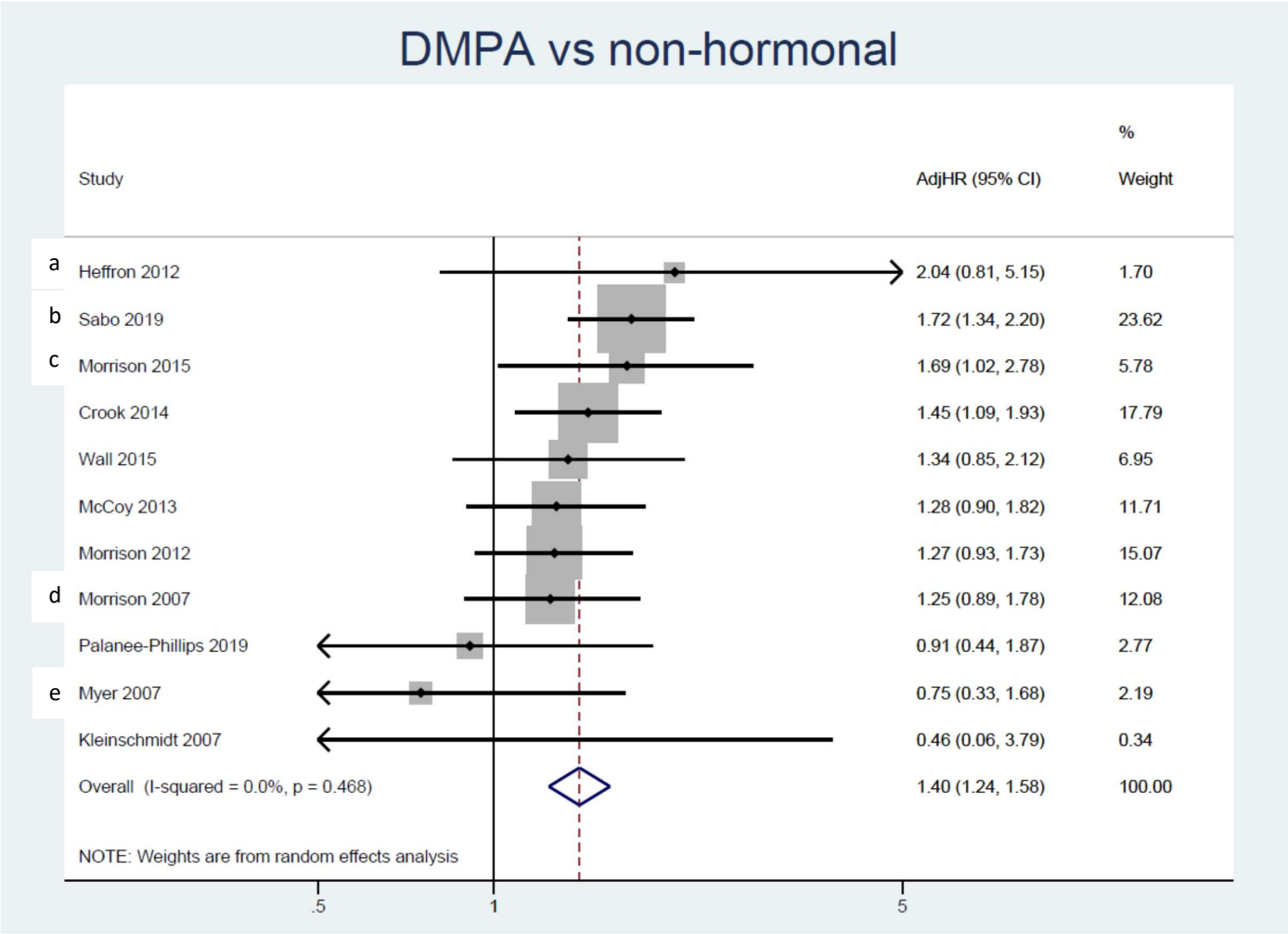
3. Palanee-Phillips T, Brown ER, Szydlo D, et al. Risk of HIV-1 acquisition among South African women using a variety of contraceptive methods in a prospective study. *AIDS* 2019;33(10):1619-1622.
4. Sabo MC, Richardson BA, Lavreys L, et al. Does bacterial vaginosis modify the effect of hormonal contraception on HIV seroconversion. *AIDS* 2019;33(7):1225-1230.
5. Baeten JM, Benki S, Chohan V, et al. Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women. *Aids.* 2007;21(13):1771-1777.
6. Lavreys L, Baeten JM, Martin Jr HL, et al. Hormonal contraception and risk of HIV-1 acquisition: Results of a 10-year prospective study. *AIDS* 2004;18(4):695-697.
7. Haddad LB, Wall KM, Kilembe W, et al. Bacterial vaginosis modifies the association between hormonal contraception and HIV acquisition. *AIDS* 2018;32(5):595-604.
8. Wall KM, Kilembe W, Vwalika B, et al. Hormonal contraception does not increase women's HIV acquisition risk in Zambian discordant couples, 1994-2012. *Contraception.* 2015;91(6):480-487.
9. Hofmeyr GJ, Singata-Madliki M, Lawrie TA, Bergel E, Temmerman M. Effects of injectable progestogen contraception versus the copper intrauterine device on HIV acquisition: Sub-study of a pragmatic randomised controlled trial. *J Fam Plann Reprod Health Care* 2017;43(3):175-180.

Supplementary Online Figure 2. Use of oral contraceptives (versus non-hormonal or no contraception) and HIV acquisition, among 11 studies considered to be informative but with important limitations



Error bars show 95% confidence intervals. Studies are arranged in order of decreasing magnitude of risk estimate, except if a single study disaggregated progestin-only pills and combined oral contraceptives, in which case both estimates are adjacent (as indicated by a box around the study identifiers). Graph does not display estimates from marginal structural models (MSM). adjIRR, adjusted incidence risk ratio. adjHR, adjusted hazard ratio. COC, combined oral contraceptive. POP, progestin-only pills. OCs, oral contraceptives. *Analysis showed significant findings at P=0.05. ^ Unpublished estimates from a sub-analysis of Morrison 2015 meta-analysis, restricted to pooled analysis using databases not previously used to publish estimates on hormonal contraceptive methods and HIV acquisition risk.

Supplementary Online Figure 3. Meta-analysis of risk of HIV acquisition by DMPA compared with non-hormonal or no contraceptive use



a: Unpublished adjusted estimate; b: Updated estimate from previously included study by Baeten et al., 2007; c: Previously unpublished studies only; d: Cox estimate; e: Incidence rate ratio

Supplementary Online Appendix 1. Search strategy

Database	Strategy
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 ((depomedroxyprogesterone OR depo OR depot OR dmpa OR "Sayana Press" OR "net en" OR "NET-EN" OR "norethisterone enanthate" OR norethisterone-enanthate OR Medroxyprogesterone 17-Acetate[MeSH]) AND (contracept* OR inject*)) OR "Depo Provera" OR "Depo-Provera" OR ((levonorgestrel OR etonogestrel) AND implant) OR uniplant OR jadelle OR implanon OR nexplanon OR norplant OR norplant2 OR sino-implant OR 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 OR "human immunodeficiency virus*" OR "Acquired Immunodeficiency Syndrome")) OR (injectable contracepti* HIV) OR (oral contracepti* HIV) January 2016 -
Embase (OVID) 1947-	((hormonal AND contracepti*) OR hormonal methods OR ((progestin* OR progestins OR progesterone OR progestogen* OR progestagen*) AND contracept*) OR ((depo OR depot) AND medroxyprogesterone) OR depomedroxyprogesterone OR depo OR depot OR dmpa OR sayana press OR net en OR net-en OR norethisterone enanthate OR ((medroxyprogesterone AND 17-acetate) AND (contracept* OR inject*)) OR ((levonorgestrel OR etonogestrel) AND implant) OR uniplant OR jadelle OR implanon OR nexplanon OR norplant OR norplant2 OR sino implant OR (contraceptives AND postcoital) OR (contracept* AND (emergency OR postcoital OR post coital)) OR ulipristal acetate OR plan b OR mifepristone OR (levonorgestrel AND intrauterine AND devices) OR iud OR iucd OR ius OR intrauterine system OR intra-uterine system OR intrauterine device* OR intra-uterine device* OR mirena OR (combin* AND inject* AND contracept*) OR ((once a month OR monthly) AND inject* AND contracept*) OR cyclofem OR lunelle OR mesigyna OR cyclo provera OR cycloprovera OR (contracepti* AND ring*) OR nuvaring OR nuva ring OR (contracepti* AND patch) OR ortho evra OR orthoevra OR (injectable AND contracepti*) OR (oral AND contracepti*)) AND (hiv OR human immunodeficiency virus* OR acquired immunodeficiency syndrome) January 2016 -

Supplementary Online Appendix 2. Quality assessment framework

Original categories from 2016 systematic review[1]

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

- No adjustment for any measure of condom use unless authors report trivial differences comparing estimates from models including and not including condom use, or
- Unclear measurement of exposure to hormonal contraception (HC), including one or more of the following:
    - Failure to include time-varying analysis of HC exposure, if appropriate (e.g., time-varying analysis may not be necessary for studies with extremely short follow-up periods).
    - 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).
    - 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).
    - The interval of time between study visits ("intersurvey 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.

Additional category for 2019 update

In 2019, a randomized clinical trial (RCT) was newly included in the systematic review, and we therefore considered whether the previous criteria needed to be modified for RCTs. We determined the following:

1. The previous criteria apply equally to RCTs as well as observational studies
2. Given that RCTs have the potential to have fewer biases and opportunity for confounding, we considered whether such studies might be classified as "informative with few limitations". We decided that such studies might be classified in this way, if most (if not all) of the following elements were present:
    a. Publication of a full trial protocol, including analysis plan, prior to conduct of the study.
    b. Good randomization procedures and completion (clear description of randomization procedures, with good concealment of allocations at point of assignment (ideally via a remote randomization procedure) and, where appropriate, a process which included stratification on key prognostic variables.

c. Good adherence to allocated treatments, with limited discontinuation or change of method of contraception. If occurs in less than 20% of trial participants (and most other criteria are met) may still be deemed 'informative but with few limitations'; if more than 20% affected but investigators adjusted appropriately for this in analysis may be 'informative with important limitations'; if more than 20% affected and no appropriate adjustment made, trial will be deemed 'unlikely to inform the primary question'.

d. Blinding of participants and study personnel to allocated treatments.

e. Independently ascertained outcomes, with personnel responsible for ascertaining the main trial outcomes blind to allocated treatments.

f. High rates ($\geq$ 80%) of follow up of trial participants resulting in high rates of ascertainment of outcomes.

g. Analyses conducted blind to treatment allocation, with time varying analysis of key confounders, including estimates of condom use during the study; with intention to treat analyses the primary comparison between groups.

h. Results reported as per pre-defined analysis plan, with subgroup analyses predefined or clearly designated as post hoc analyses (and with a clear justification for their conduct).

It was recognised that many pragmatic trials in reproductive health care will not fulfill all of these criteria (for example, trials of different contraceptive methods are likely to be open, with participants and clinicians responsible for their routine care unblinded to the treatments allocated). Nonetheless, clarity about how the researchers sought to minimise bias and confounding after treatment allocation should enable a judgement to be made about the extent to which evidence from the trial was limited.

It is possible, although probably highly unlikely, that an observational study purposively established to investigate the possible association between hormonal contraception and HIV acquisition among users meets most of the above criteria. In such a situation a judgement will be made on whether that study was "informative with few limitations".

1. Polis CB, Curtis KM, Hannaford PC, et al. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. *AIDS* 2016;30(17):2665-2683.