Effect of hormonal contraceptive methods on HIV disease progression: a systematic review

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Objective: Systematically assess from the literature whether women living with HIV who use hormonal contraception are at increased risk of HIV-disease progression compared with those who do not use hormonal contraception.

Methods: We searched PUBMED and EMBASE for articles published in peer-reviewed journals through December 15, 2011 for evidence relevant to all hormonal contraceptive methods and HIV-disease progression.

Results: Twelve reports of 11 studies met inclusion criteria. One randomized controlled trial (RCT) found increased risk for the composite outcome of a reduced CD4 cell count or death among hormonal contraceptive users when compared with copper intrauterine device (IUD) users. Ten cohort studies reported no increased risk for HIV disease progression (as measured by mortality, time to a CD4 cell count below 200, time to initiation of antiretroviral therapy, an increase in HIV-RNA viral load, or a decrease in CD4 count) among women who used hormonal contraception compared with those who did not.

Conclusion: The preponderance of evidence indicates that HIV-positive women can use hormonal contraceptive methods without concerns related to HIV-disease progression. Cohort studies consistently found no association between hormonal contraceptive use and HIV-disease progression compared with nonuse of hormonal contraceptives. One RCT found that hormonal contraceptive use was associated with increased risk of HIV-disease progression when compared with IUD use, but this study had important methodological shortcomings. Prevention of unintended pregnancy among women living with HIV remains a public health priority to safeguard women's and infants' health and to prevent vertical transmission of HIV.

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Introduction

The prevention of unintended pregnancy remains a key concern for women living with HIV, both as a core strategy to prevent vertical HIV transmission [1] and to decrease maternal and neonatal morbidity and mortality through reduced unintended pregnancies, improved birth spacing, and lower rates of unsafe abortion [1]. For women living with HIV, who do not wish to get pregnant, family planning is a cost-effective strategy to prevent further vertical transmission of the virus [2].

Family planning is crucial to the health of women living with HIV. However, there are theoretical concerns about the safety of various contraceptive methods for women with HIV [3]. The Medical Eligibility Criteria for Contraceptive Use published by the WHO [4] includes recommendations concerning whether women living with HIV can safely use hormonal contraception. WHO recently held a technical consultation to review evidence regarding the safety of hormonal contraception for women living with HIV [with respect to disease progression, initiation of antiretroviral therapy (ART),

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or death] [5]. An earlier version of this systematic review was prepared for this consultation. This review updates a similar systematic review published in 2009 [3].

Methods

We searched PUBMED and EMBASE for articles in any language published or in press on or before 15 December 2011 (see online Appendix I for search strategy; http://links.lww.com/QAD/A298). We also searched reference lists of relevant articles. We did not attempt to identify unpublished articles or abstracts from scientific conferences.

For the first stages of the article selection process, we used Early Review Organizing Software (EROS) [6]. One author conducted the literature search, screened titles and abstracts of retrieved references, and identified potentially relevant articles. The other two authors then read full texts of these potentially relevant articles to determine which were appropriate for inclusion in this review. If multiple publications were based on the same (or updated) data from a particular study, we reviewed all previous publications, but refer only to the most recent publication unless otherwise indicated.

Participants, interventions, comparison groups, and outcomes

We included primary research reports of women with HIV infection that evaluated the effects of hormonal contraceptive use compared with no hormonal contraceptive use on different measures of HIV-disease progression. We included randomized clinical trials (RCTs) and cohort studies and excluded articles that reported results from all other study designs (because of the relatively large number of cohort studies, we excluded the single case–control study on this topic [7]), as well as articles based on pharmacokinetic studies, studies of emergency contraception and mifepristone, and studies of the copper intrauterine device (IUD) (except those in which copper IUD users served as a comparison group). We considered studies on combined oral contraceptives (COCs), injectables, rings, patches, progestin-only pills, implants, and the levonorgestrel-releasing IUD (LNG-IUD). Measures of disease progression included: changes in viral load or CD4 cell count, progression to AIDS (defined by a threshold CD4 cell count or standard clinical criteria), initiation of antiretroviral therapy (ART), (based on criteria that varied by study), death (either all cause or HIV-related), and a composite outcome of either progression to AIDS, initiation of ART, or death.

Abstraction and study quality assessment

Using standard abstract forms [8], two authors (S.J.P. and K.M.C.) independently assessed the quality of the evidence. We considered multiple methodological factors that could impact study quality, including the following.

Methodology used to minimize confounding

Observational studies carry potential for confounding. We considered several factors associated with minimizing the impact of such confounding on study results, including whether a multivariate analysis including important potential confounding factors had been performed. Studies examining incident (rather than prevalent) cases of HIV may be preferable to minimize confounding by baseline disease state and the effect of time on HIV progression (although this is of less concern in an RCT). Studies examining prevalent cases of HIV that controlled for baseline CD4 in multivariate analysis may similarly be preferable to those that did not control for baseline CD4.

Handling of antiretroviral therapy

Use of ART has a dramatic impact on HIV-disease progression and mortality, and may either confound or modify any effect of hormonal contraception and HIV-disease progression. Using ART initiation as an outcome in and of itself should minimize this effect. For time-to-death analyses, censoring at ART initiation could result in informative censoring.

Accurate measurement and analysis of exposure

Different hormonal contraceptive methods vary significantly, and may influence risk of HIV progression variably. Therefore, studies that analyse different methods separately provide more specific information on exposure than those that group different methods together. In addition, incorporating time-varying exposure information to reflect switching contraceptive methods increases the likelihood of accurate attribution to the exposure group and may reduce bias related to exposure misclassification.

Composition of comparison group

As the underlying risk of progression associated with each individual hormonal contraceptive method is unknown, comparing groups of hormonal contraceptive users to women who are not using any hormonal contraception is preferable to comparing women using one form of hormonal contraception to women using another form of hormonal contraception, as the effect of different hormonal contraceptive methods on disease progression may vary.

Loss to follow-up

Studies with high loss to follow-up may have decreased validity, as results are susceptible to selection bias. There is some evidence that bias associated with nonrandom loss is considerable with 20% or more lost to follow-up [9].

Time of follow-up

Because HIV progresses relatively slowly, the effects of an exposure may not become apparent until years later.

Studies with longer follow-up (e.g. 2 years) may provide greater statistical power to detect an effect.

Additional considerations for randomized clinical trials
In addition to the above considerations, an RCT should ensure adequate randomization (including concealment), and equal distribution of potential confounders among groups. Groups should remain comparable over time; if there is differential attrition or crossover between groups, the benefits of randomization may be lost.

Due to heterogeneity among the studies, summary statistics were not calculated. Results are presented according to outcomes reported: progression to death, AIDS or initiation of ART, composite measures of death and disease progression, and change in HIV plasma viral load or CD4 count.

Throughout this review, we used the term 'oral contraceptives' to describe the contraceptive exposure assessed in a given study if the authors of the study either did not specify the type of oral contraceptive used (combined, progestin-only, or low-dose) or reported results for all oral contraceptive users together.

Results

From the 634 articles identified by our search strategy, 16 met criteria for full-text review (Fig. 1). Four reports were excluded, three for lack of an adequate comparison group [10–12] and one for using case–control methodology [7]; therefore 12 reports were included [13–24], an increase from seven included in the 2009 review.

Relationship between hormonal contraception and progression to AIDS, initiation of antiretroviral therapy, or death

We reviewed nine reports (based on eight studies) in which authors described the relationship between use of hormonal contraception and risk for progression to AIDS, initiation of ART, or death among women living with HIV (online Appendix II; http://links.lww.com/QAD/A298). Studies used various outcome measures to assess progression, including onset of clinical AIDS, decrease of CD4 cell count below 200 (or 250 [19]), initiation of ART, death, or a composite outcome of CD4 below a given threshold, ART initiation, or death. Seven of these studies were observational [13,15,16,18,19, 22,24], and one (the results of which were reported in two articles we reviewed) was an RCT [21,23].

Evidence from randomized clinical trials
One relevant RCT was available, and was conducted among 599 postpartum women with HIV infection in Zambia [21]. In the initial analysis, women allocated to the hormonal contraception arm were noted to have faster HIV-disease progression. However, a subsequent analysis of the same data employing both actual-use and intent-to-treat (ITT) analysis and disaggregation of users of progestin-only contraceptives from those using combined oral contraceptives provides information more pertinent to our outcome of interest [23]. Women were assigned to a copper IUD group ($n = 296$) or a hormonal contraceptive group (in which they chose either oral contraceptives or depot medroxyprogesterone acetate (DMPA)); ($n = 303$). During the 2 years of follow-up 31% of the hormonal contraceptive group and 23% of the IUD group withdrew from the trial or were lost to follow-up. A high proportion of women discontinued their assigned method during the study, and many switched to a new method. Of those assigned to the IUD, 49% discontinued IUD use; of these women, 76% switched to a hormonal method, 6% switched to condoms, and 18% discontinued contraception. Of those assigned to hormonal contraception, 13% discontinued using hormonal methods; of these women, 16% switched to the IUD, 34% switched to condoms, and 50% discontinued contraception. Within the hormonal contraceptive group, 34% of women switched between oral contraceptives and DMPA. Because of the high proportion of women switching contraceptive methods,

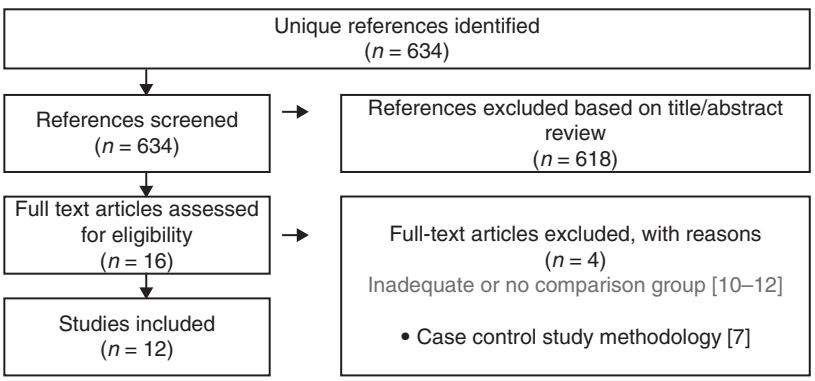

Fig. 1. Article selection flow diagram.

the investigators used both ITT and actual-use analyses to estimate relative risks for HIV-disease progression associated with the use of various contraceptives.

For DMPA, the hazard ratios (HRs) for mortality were slightly elevated, but not statistically significant [HR 1.39. 95% confidence interval (CI) 0.63–3.06] in the ITT analysis and 1.83 (95% CI 0.82–4.08) in the actual use analysis; online Appendix II; http://links.lww.com/QAD/A298, Fig. 2). Similarly, there was no statistically significant association between oral contraceptive use and mortality [HR 1.06 (95% CI 0.38–2.97) in the ITT analysis and 1.24 (95% CI 0.42–3.63) in the actual use analysis]. Oral contraceptives were not associated with a significant increase in progression to a CD4 cell count less than 200 or initiation of ART in the ITT analysis (HR 1.54, 95% CI 0.98–2.42) but the finding was significant in actual use analysis (HR 1.69, 95% CI 1.09–2.64). DMPA was associated with statistically significant estimates in both the ITT and actual use analyses (ITT HR HR 1.81, 95% CI 1.26–2.6; actual use HR 1.56, 95% CI 1.08–2.26) (Fig. 3). Both oral contraceptives and DMPA were also associated with statistically significant elevated risks for a composite outcome of death or CD4 cell count less than 200 or initiation of ART in both ITT and actual use analysis (ITT DMPA HR 1.81, 95% CI 1.30–2.53; actual use DMPA HR 1.62, 95% CI 1.16–2.28; ITT oral contraceptive HR 1.52, 95% CI 1.0–2.32; actual use oral contraceptive HR 1.67, 95% CI 1.10–2.51) (Fig. 4).

Evidence from cohort studies

Of the seven cohort studies identified for review, five were prospective [13,16,18,22,24] and two were retrospective [15,19]. Three took place in Africa [13,18,19], one predominantly in Africa with one site in Asia [22], two in Europe [15,24], and one in Southeast Asia [16]. Four included women with prevalent HIV [13,15,22,24], two included only women with incident infection [18,19], and one included a mix of incident and prevalent cases [16]. Sample sizes ranged from 40 to 625, with one large study enrolling 7846 women [22]. Follow-up ranged from a median of 1–6 years, with six studies having at least 2 years of follow-up [13,15,16,18,19,24].

Six cohort studies used a Cox proportional hazards model to assess the relationship between use of hormonal contraceptives and various measures of HIV progression, baseline covariates that could act as confounders, and the outcomes of interest [13,16,18,19,22,24]. Four also included use of hormonal contraceptive methods as a time-varying variable in the model [13,18,19,22]. None of the cohort studies showed a statistically significant association between hormonal contraceptive use and progression to death, AIDS, or initiation of ART, or composite outcomes of progression to death or AIDS or ART initiation compared with nonuse of hormonal contraception (online Appendix II; http://links.lww.com/QAD/A298; Figs 2–4). Point estimates for mortality among women who used hormonal contraceptives ranged

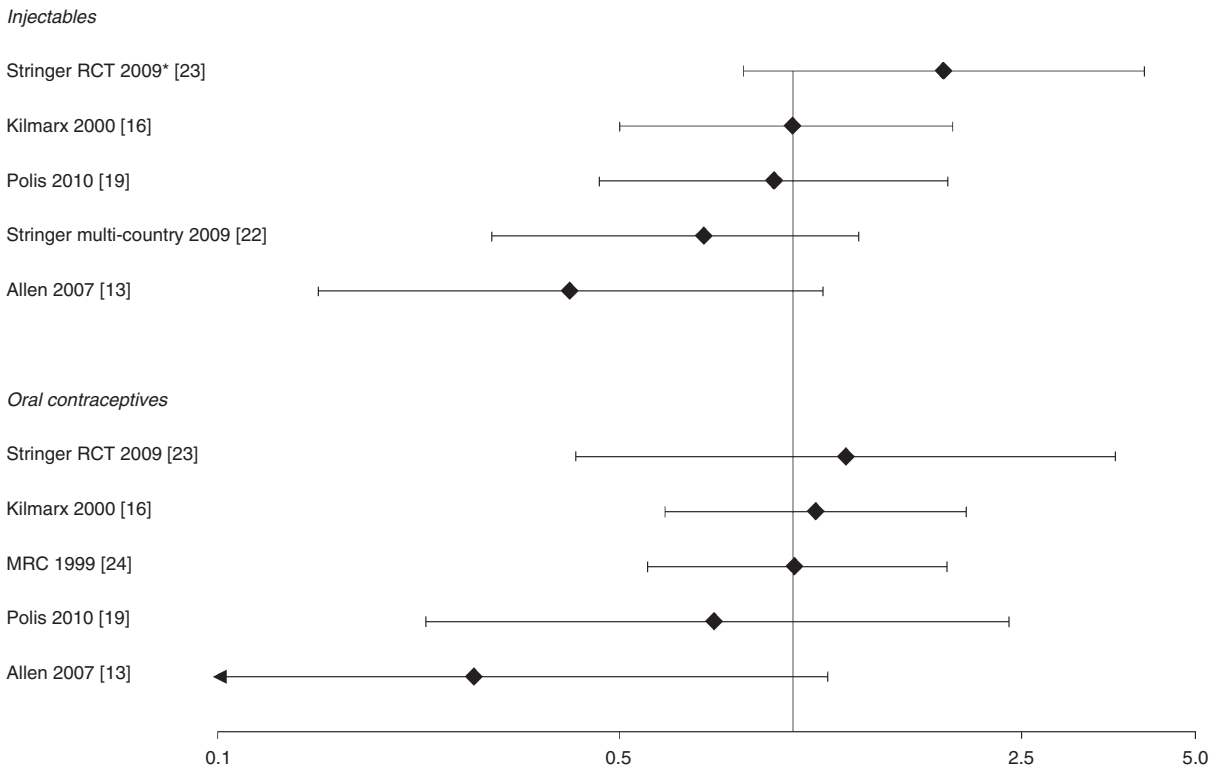

Fig. 2. Mortality associated with hormonal contraceptives. *Actual use analysis, adjusted hazard ratio.

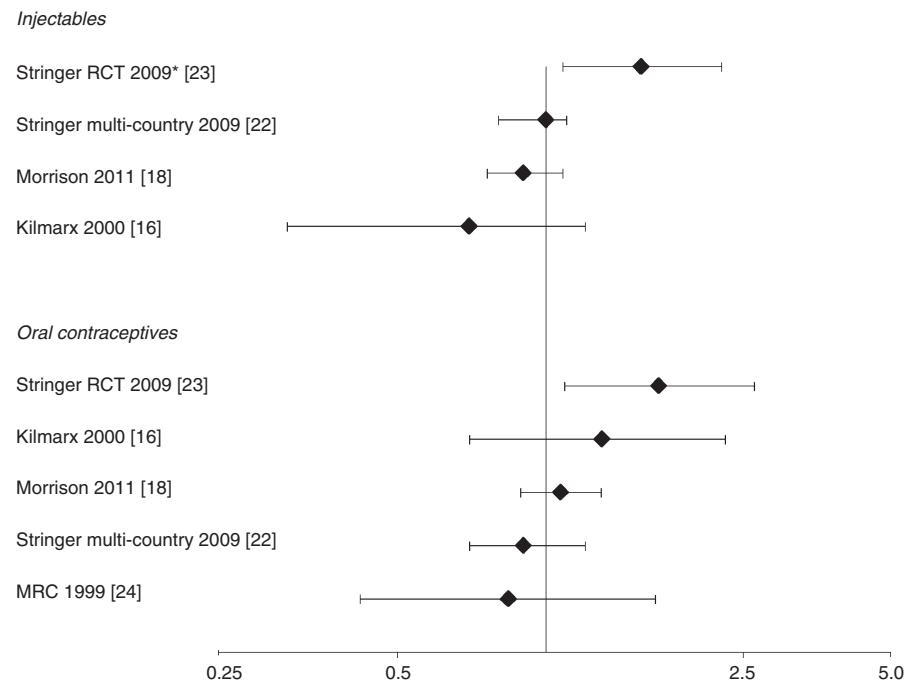

Fig. 3. Progression to AIDS or initiation of antiretroviral therapy (ART). *Actual use analysis, adjusted hazard ratio.

from 0.41 to 1.39 for injectables and from 0.28–1.10 for oral contraceptives (Fig. 2); point estimates for progression to AIDS or initiation of ART ranged from 0.7 to 1.0 for injectables and from 0.84 to 1.3 for oral contraceptives (Fig. 3); and point estimates for combined outcomes ranged from 0.65 to 1.01 for injectables and from 0.72 to 1.02 for oral contraceptives (Fig. 4). The results of one retrospective study [15] addressed the use of the LNG-IUD in women with prevalent cases of HIV. Among those not on ART at study initiation, there was no significant

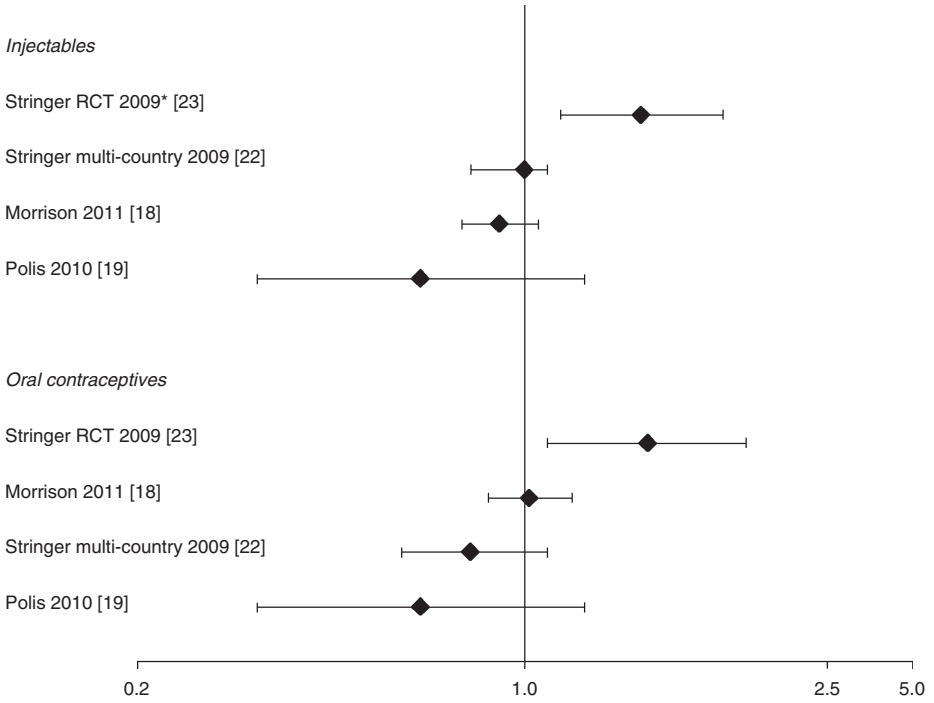

Fig. 4. Composite outcome: progression to AIDS, antiretroviral therapy (ART) initiation, or death. *Actual use analysis, adjusted hazard ratio.

difference between the proportion of LNG-IUD users who did and did not initiate ART (43% of the LNG-IUD group vs. 45% of the comparison group, $P = 0.91$). Although studies used differing methodologies, findings of no association were consistent regardless of statistical method, sample size, length of follow-up, loss to follow-up, patient population studied, and location.

Effect of hormonal contraception on CD4 cell count and HIV RNA viral load

Evidence from observational studies

Five observational studies addressed the effect of hormonal contraceptive use on changes in users' CD4 cell count and HIV RNA viral load, [14–17,20] (online Appendix III; http://links.lww.com/QAD/A298). None found the use of either DMPA or oral contraceptives to be adversely associated with either outcome. One study [14] found a positive association between hormonal contraceptive use and increased CD4 cell count (a mean increase 27.6 cells/μl over 1–2 years of follow-up; $P = 0.01$), this change is of unclear clinical significance. Results of the study of the LNG-IUD [15] showed no significant difference in the change in CD4 count over time between the group using LNG-IUD and the comparison group ($P = 0.97$).

Discussion

Of 11 studies (12 reports) of hormonal contraceptive use and HIV-disease progression, 10 observational studies showed no significant effect of hormonal contraception on HIV disease progression as measured by death, AIDS, ART initiation, a CD4 cell count under 200, or change in viral load or CD4 count. The lone RCT, which examined postpartum women with HIV in Zambia and had as primary outcomes the incidence of pregnancy and pelvic inflammatory disease (PID) among IUD users, is the only study to report adverse effects of hormonal contraception on HIV-disease progression [21]. Compared with randomization to IUD use, randomization to hormonal contraceptive use was associated with 3.72 additional cases of CD4 progression below 200 cells/μl per 100 woman-years.

Although the RCT had many strengths, including randomization of women to study groups to receive either hormonal or nonhormonal contraceptives and use of multivariate analysis that included hormonal contraception as a time-varying variable, we rated it as fair quality due to lack of maintenance of comparable groups, reflected in high levels of switching of contraceptive methods and high and differential loss to follow-up. The authors of the secondary analysis of data from this RCT conducted both an actual-use analysis and an ITT analysis, but actual-use analyses lack the advantages provided by randomization related to control for confounding. Finally, this study compared hormonal contraceptive users with copper-IUD users, whereas all of the observational studies compared hormonal contraceptive users to nonhormonal users or users of no contraceptive method. It is unclear whether having a comparison group consisting of copper-IUD may affect results, either because of some direct effect of the copper-IUD on HIV-disease progression or as a marker of some other factor associated with HIV-disease progression.

Ten observational studies, which ranged from good to poor quality, found no association between hormonal contraception and increased mortality or HIV-disease progression. The two studies rated good [18,19] both included incident cases of HIV, thereby reducing confounding due to factors associated with duration of infection. They also employed multivariate analysis, including use of hormonal contraceptive methods as a time-varying variable, minimizing bias in attribution of exposure. Results from these two good-quality studies were similar to the other studies included in the review, finding no association between hormonal contraceptive use and HIV-disease progression. Studies rated fair [13,14,20,22] generally used prevalent HIV cases and controlled for baseline disease characteristics, such as CD4 cell counts in their multivariate model. Studies rated poor [15,16,17,24] generally did not use multivariate analysis for all outcomes, combined analysis of multiple hormonal contraceptive methods together, or did not exclude users of other hormonal contraceptive methods from their comparison groups.

All observational studies are inherently limited by lack of randomization, and users and nonusers of hormonal contraception differed at baseline on important factors that could affect outcomes in all of the studies that reported on this data [14,15,18–20,22]. None of the studies examined the effects of newer forms of hormonal contraception, such as the contraceptive ring, contraceptive patch, or implants. Most did not specify whether oral contraceptives were COCs or progestogen-only pills, which may have different effects on HIV-disease progression.

A further limitation of this body of evidence is that some of the studies may have lacked sufficient power to detect a difference between groups. As all of the reports analyzed data collected for other purposes, none published power calculations for the outcome of HIV-disease progression. Additionally, assessing the impact of hormonal contraception on HIV-disease progression is increasingly complicated in an era of increased availability of ART. Some of the studies included either no [13,17] or very few users of ART [16,19]. Most used ART initiation as an outcome [15,18,20,22,23], and one study [14] controlled for ART in a multivariate analysis. In one study [24] it was unclear how ART use was handled.

Another factor that may be important in interpreting this evidence is handling of pregnancy. This varied among the studies, ranging from no mention of numbers of pregnancies within the women studied [15–17,20,22,24] to censoring at pregnancy [14,23] to controlling for pregnancy in a time-varying model [13,18,19]. We did not include handling of pregnancy as one of our quality criteria given the lack of consensus regarding the impact of pregnancy itself as a risk factor for HIV-disease progression, although if such an association exists it is likely not strong [25,26]. Of note, those studies reviewed that assessed the impact of incident pregnancy on HIV-disease progression found no association [13,18,19].

Some studies assessed whether use of hormonal contraception at the time of HIV infection may affect characteristics of early infection among women who become infected. Two such characteristics of early HIV infection, elevated viral load setpoint and increased viral heterogeneity, have been positively associated with more rapid HIV progression [27–29]. In one study that followed HIV-negative sex workers in Kenya through HIV seroconversion [17], use of hormonal contraception at the time of infection was associated with higher viral load setpoint. However, in a related analysis of the same data, researchers using a different multivariate model failed to find an association between use of hormonal contraception at the time of infection and higher plasma viral load among users of hormonal contraception and the average plasma viral load among nonusers, although they did find that users were more likely to have heterogeneous genetic variants: for oral contraceptive users, the odds ratio was 2.4 (95% CI 0.9–6.4), and for DMPA users, it was 3.0 (95% CI 1.3–5.6) [30]. Two more recent cohort studies [31,32] assessed whether use of hormonal contraception at the time of infection was associated with viral load setpoint; neither found an association in adjusted analyses. These findings are reassuring, but are not conclusive regarding whether use of hormonal contraception at the time of HIV infection leads to more rapid disease progression for women at high risk of HIV considering various contraceptive methods.

During the WHO technical consultation, the GRADE system [33] was used to evaluate the quality of the evidence from the 11 studies. The overall quality of the body of evidence was rated 'low' because of serious limitations in the studies and serious imprecision in the results for some of the outcomes. WHO continues to recommend that women living with HIV can use all hormonal contraceptive methods (MEC Category '1') without restriction. For women using ART, additional recommendations are provided concerning the potential for drug interactions between hormonal contraception and ART [4]; this is an area requiring ongoing research [34].

Conclusion

The preponderance of evidence indicates that hormonal contraceptive use does not affect HIV disease progression among women with HIV. Results from 10 cohort studies consistently found no association between hormonal contraceptive use and HIV-disease progression compared with nonuse of hormonal contraceptives. A secondary analysis of data from one RCT found that hormonal contraceptive use was associated with increased risk of HIV-disease progression when compared with IUD use; however, this RCT had important methodological shortcomings, and its primary objective was not the assessment of risk for HIV-disease progression among users of hormonal contraceptives. Future studies addressing this issue should assess the safety of newer methods, such as implants and the LNG-IUD and carefully collect information on both exposure and outcome. Preventing unintended pregnancy among women with HIV remains a public health priority, both as a means of safeguarding the health of women living with HIV and as a means of preventing vertical transmission of HIV.

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Conflicts of interest

C.B.P. is collaborating on a study assessing the acceptability of two types of injectable contraceptive methods among HIV-positive women in Uganda; one of the products for that study was donated by Pfizer. S.J.P. and K.M.C. have no conflicts of interest.

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