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Contraceptive Methods and Risk of HIV Acquisition or Female-to-Male Transmission

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Abstract

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Effective family planning with modern contraception is an important intervention to prevent unintended pregnancies which also provides personal, familial, and societal benefits. Contraception is also the most cost-effective strategy to reduce the burden of mother-to-child HIV transmission for women living with HIV who wish to prevent pregnancy. There are concerns, however, that certain contraceptive methods, in particular the injectable contraceptive depot medroxyprogesterone acetate (DMPA), may increase a woman's risk of acquiring HIV or transmitting it to uninfected males. These concerns, if confirmed, could potentially have large public health implications. This paper briefly reviews the literature on use of contraception among women living with HIV or at high risk of HIV infection. The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommendations place no restrictions on the use of hormonal contraceptive methods by women with or at high risk of HIV infection, although a clarification recommends that, given uncertainty in the current literature, women at high risk of HIV who choose progestogen-only injectable contraceptives should be informed that it may or may not increase their risk of HIV acquisition and should also be informed about and have access to HIV preventive measures, including male or female condoms.

Keywords

HIV; AIDS; Contraception; Hormonal contraception; Transmission

Globally, an estimated 41 % of pregnancies are unintended, with even higher rates in South America (64 %), Southern Africa (59%), and North America (48%) [1]. Increased use of contraceptive services to reduce unintended pregnancies is a cost-effective strategy with great personal, familial, and societal benefits, including reduced maternal and child mortality and better educational and economic gender equity [2, 3]. Contraception is also the most cost-effective strategy to reduce the burden of mother-to-child HIV transmission among women living with HIV who wish to prevent unintended pregnancy [4]. Unfortunately, some countries with the highest rates of HIV prevalence also have low rates of contraceptive use and high rates of unintended pregnancy. The World Health Organization (WHO), United Nations, and other global public health organizations recognize that preventions of new HIV infections and unintended pregnancies are both critical to improving health, preventing mother-to-child transmission, and reducing infant and maternal morbidity and mortality [5–7, 8•]. It is therefore a public health priority to improve contraceptive access and use for women living with and at high risk of HIV infection.

All contraceptive methods are not equally effective for pregnancy prevention, and no contraceptive method other than male and female condoms can prevent sexual transmission of HIV. Furthermore, the safety of contraceptive methods may depend on the presence of medical comorbidities, including HIV infection, or interactions with medications such as antiretrovirals (ARVs). Recent systematic reviews have synthesized emerging evidence on whether hormonal contraception affects the risk of HIV disease acquisition, disease progression, or female-to-male transmission [9, 10, 11•, 12•]. This article reviews the literature and potential biologic mechanisms by which hormonal contraception might affect HIV acquisition or female-to-male transmission risk.

Contraceptive Efficacy of Various Methods

While condoms are the only contraceptive method that can reduce the risk of sexually transmitted infections (STIs) including HIV, they have a high failure rate for pregnancy prevention due to poor adherence, with a typical-use rate of 18–21 % within the first year of use [13]. Furthermore, despite three decades of promotion of condoms for HIV prevention, consistent and correct use is reported to occur infrequently among high-risk individuals in settings where the virus is endemic [14].

Hormonal contraceptive methods have higher efficacy for pregnancy prevention than condoms, with a typical-use contraceptive failure rate of approximately 9 % for combined hormonal contraceptives (oral contraceptive pills, patch, or ring), 6% for injectable methods [depot medroxyprogesterone acetate (DMPA) or norethisterone enanthate (NET-EN)], and less than 1 % for contraceptive implant and intrauterine devices (IUDs) [13]. Nonhormonal contraceptives such as the diaphragm, cervical cap, and spermicides have lower contraceptive efficacy (12–28 % failure rate with typical use) [13]. Diaphragms have no proven benefit of reduced HIV infection or STI transmission risk [15], and some forms of spermicide, such as nonoxynol-9, have been associated with an increased risk of sexual HIV acquisition when applied frequently [16, 17]. Fertility awareness methods, such as the symptothermal method, can be highly efficacious when used perfectly [18], but typical-use failure rates for some forms of fertility awareness methods are as high as 24 % [19]. Surgical sterilization, with bilateral tubal ligation for women or vasectomy for men, is an extremely effective contraceptive method with a typical-use failure rate less than 1 %; however, access to these procedures may be limited in low-resource settings and lack of reversibility makes sterilization not ideal for pregnancy spacing [13].

Hormonal contraceptives have high acceptance rates in many communities with infrequent condom use or limited nonhormonal contraceptive options, such as the copper IUD [20]. Injectable contraception alone accounts for nearly half (47 %) of modern contraceptive use in sub-Saharan Africa [20].

Hormonal Contraceptive Methods and HIV Acquisition Risk

Despite excellent contraceptive efficacy and high global uptake, there are growing concerns that hormonal contraception, specifically progestogen-only injectables (such as DMPA or NET-EN), may increase the risk of HIV acquisition in uninfected women or, when used by women living with HIV, the risk of female-to-male HIV transmission [10, 11•, 12•, 21•, 22]. If confirmed, these risks would have important implications for health at the individual and population level.

Research in nonhuman primates demonstrated several-fold increases in the risk of simian immunodeficiency virus (SIV) acquisition in rhesus macaques following exposure to large doses of DMPA [23]. The potential HIV acquisition risk associated with injectable contraception in humans has not been consistently observed across all studies, with some studies reporting no association with DMPA [24–27] and others reporting an increased risk of HIV acquisition [28–31]. Discrepancies in study design, population, sample size, contraceptive methods studied, dose, contraceptive adherence, analytic methods used, and

rate of method discontinuation add to the complexity of interpreting results across these observational studies and limit the conclusions that can be drawn [32]. A recent systematic review [12•] of prospective studies noted that four of nine studies considered *informative but with important limitations* reported a 1.5 to 2.2 times increased risk of HIV acquisition in women using injectable contraception (DMPA or nonspecified injectable contraceptive) [33–36]. Notably, one of these studies [35] that suggested a statistically significant increase in risk using a marginal structural model found no statistically significant association using a Cox proportional hazards model [28]. The other five studies of injectable contraception that were informative but with important limitations reported no statistically significant association [25, 29, 37–39]. Of eight studies [21•, 25, 28, 29, 33–35, 37, 39] considered informative but with important limitations [12•] which evaluated oral contraceptive pills (OCPs), one found an increased risk of HIV acquisition [34]. Figures 1 and 2 present results of epidemiologic studies presented in the systematic review to evaluate the impact of OCPs and injectables on a risk of HIV acquisition in women [12•]. A recent, unpublished meta-analysis examining individual participant data from 18 studies including 37,124 women noted a significantly increased risk of acquisition [adjusted hazard ratio (aHR) 1.5; 95 % confidence interval (CI) 1.24–1.83] [40] for DMPA, with no increased risk from NET-EN or combined hormonal contraceptives. However, when the analysis was restricted to studies with lower risk of bias, the risk associated with DMPA was reduced and no longer statistically significant (adjusted HR 1.22; 95 % CI 0.99–1.50) [40]. A similar conclusion was reported from a recent analysis among 1,393 discordant couples in Zambia, which found that the use of injectable (aHR=1.2; 95 % CI 0.8–1.8), OCP (aHR=1.3; 95 % CI 0.9–1.9), or implant (aHR=0.9; 95 % CI 0.4–2.0) was not associated with HIV acquisition relative to nonhormonal contraceptive users after controlling for woman's age, literacy, sperm on a vaginal swab wet prep, genital ulceration/ inflammation, and time interval post-enrollment [41].

Very limited data exist for the effects of contraceptive implant use on risk of HIV acquisition, with only one study identified in a systematic review [12•] as informative but with important limitations, finding no significant increase in HIV acquisition [22]. Also, no data exist on the effects of contraceptive patch, ring, combined injectable, or levonorgestrel IUD on risk of HIV acquisition [12•].

Hormonal Contraceptive Methods and Female-to-Male HIV Transmission Risk

Data on risk of female-to-male HIV transmission among women using hormonal contraceptive methods are sparse [11•]. A systematic review examining hormonal contraceptive methods and female-to-male HIV transmission risk identified only one study [21•] that evaluated the direct impact of hormonal contraception on HIV transmission, and that study suggested increased female-to-male HIV transmission risk with the use of injectable contraception [21•]. Additionally, the review identified 16 *indirect* studies that evaluated the influence of hormonal contraceptive methods on proxy markers for infectivity (i.e., plasma and/or genital HIV RNA levels) [11•]. Of 11 studies evaluating hormonal contraceptive methods and genital tract virus levels, detectability, or set point, results were

mixed, while seven of eight studies assessing the impact of hormonal contraception on the amount of HIV in the blood reported no increase in plasma viral load or set point. More recent direct evidence from a retrospective cohort in Uganda suggested no increased HIV transmission risk with DMPA or oral contraceptives [42], but this study had some methodological limitations.

Potential Biologic Mechanisms for Increased HIV Acquisition and Transmission Risk Associated with Certain Hormonal Contraceptive Methods

Acquisition of HIV Infection Is a Multifaceted Process of Virus-Host Interactions

In addition to plasma viremia of the transmitter, factors that increase susceptibility of the partner to HIV infection include the presence of STIs, mucosal micro-abrasions, and secreted immune factors—all of which influence local mucosal immunity, the protective integrity of the epithelial barrier in the genital tract, and the activation status of HIV target cells involved in the early stages of infection [43•]. Evidence suggests that the robust nature and functional capacity of the innate and adaptive immune responses are influenced by female sex hormones [43•, 44, 45]. The immunoregulatory influence of estradiol and progesterone ensures a favorable environment for fertilization and pregnancy by altering the local female genital tract (FGT) immunologic milieu and the composition of immune cells.

Animal studies among rhesus macaques have documented that systemic and topical administration of estrogen thickens the vaginal epithelial layer (Fig. 3a) [43•, 46, 47], reduces the population of Langerhans cells within the vaginal epithelium, alters vaginal epithelial tight junctions and mucosal permeability [48, 49], and supports healthy genital tract flora. Through these changes, estrogen makes the mucosa less susceptible to SIV by blocking its access to target cells within the epithelial and subepithelial layers. Contrary to the effect of estrogen, progesterone leads to thinning of the epithelial layer and increased concentrations of susceptible cells in female macaques, allowing SIVeasier access and availability to target cells (Fig. 3b) [50]. However, while animal studies demonstrate potential mechanisms to explain increased risk, these changes have not been robustly demonstrated to occur among humans [51, 52].

Other potential effects of progesterone on immune function that may increase HIV acquisition risk include suppression of antibody production and transepithelial transport within the FGT [53–55], inhibition of cytotoxic immune cell responses [56, 57], and immune cell infiltration within the genital tissue, reducing the functional capacity of antibody-dependent cell cytotoxicity [58–60]. Levels of expression/secretion of chemokines, cytokines, and endogenous antimicrobials in FGT secretions alter over the course of the menstrual cycle, during menopause, and with contraceptive use, suggesting a role for hormones in regulating their release [61–65]. Increased risk of HIV acquisition has been suggested to occur during pregnancy, a high-progesterone state [66]. Progesterone may compromise the integrity of the protective epithelial layers against HIV infection, promote enhanced homing of HIV-susceptible cells to the FGT, and reduce the robust nature of local innate antiviral and adaptive secretory immune responses.

Human data also suggest that progesterone treatment reduces the concentration of lactobacilli in the vaginal microbiota [52, 67]. This divergence from healthy vaginal flora is associated with increased HIV acquisition risk [68, 69]. Although coinfections with ulcerative STIs (e.g., syphilis, herpes, chancroid) or inflammatory STIs (e.g., gonorrhea, chlamydia) can increase the risk of HIV acquisition [70], evidence is conflicting on the influence of hormonal contraceptives on these infections [43•, 71].

For HIV transmission to male partners, several proposed biologic mechanisms could increase risk of female-to-male transmission with hormonal contraceptive methods, although it is unclear which mechanisms, if any, are relevant. Hormonal contraceptive methods could lead to higher genital tract viral loads either directly or indirectly, with increased shedding associated with increased HIV transmission [72]. For example, with increased hormonal levels associated with pregnancy, some studies have documented higher levels of HIV shedding [73–78] and suggested a higher transmission risk to male partners [66, 79]. Further, the immunomodulatory effects noted above that may influence acquisition risk may also impact local immune environment and genital compartmental viral replication, leading to increased shedding. Increases in local inflammation, through hormonal contraceptive influences on STIs or the vaginal microbiome, may additionally increase HIV shedding and, subsequently, transmission risk [80–82]. However, physiologic doses of DMPA in pigtail macaques did not increase plasma viremia or mucosal virus shedding during acute infections [83].

Different contraceptives have variable degrees of estrogenic, androgenic, anti-androgenic, glucocorticoid, and anti-mineralocorticoid activity [84, 85]. Medroxyprogesterone (MPA), for example, has androgenic activity, no anti-mineralocorticoid activity and potent glucocorticoid activity, higher than any other progestogen or endogenous progesterone. Activation of glucocorticoid receptors, seen with MPA, may influence glucocorticoid-like immunosuppressive effects on genes involved with immune function [86, 87]. These differences between contraceptives warrant further investigation and may influence relative contraceptive safety.

Nonhormonal Contraceptives and Risk of HIV Acquisition or Transmission

The copper IUD is one of the most effective contraceptive options available and is generally considered safe in women at high risk of HIV or who are living with HIV, but clinically well [8•]. For women with active stage 3 or 4 HIV disease, IUD insertion is not currently recommended; however, there are no restrictions on its continued use in women who have an IUD in place [8•]. To date, no studies suggest an increased risk of HIV acquisition or viral shedding among women living with HIV with the copper IUD [88, 89], but IUD use results in changes in genital tract immune cell populations which could theoretically alter risk in either direction [90].

Nonoxynol-9, the most common active ingredient in spermicides in the USA, may, with frequent use, cause irritation and vaginal epithelial erosion, which could increase risk of HIV acquisition and transmission. In a study of high-risk women, use of nonoxynol-9 more than three times a day increased the rate of HIV transmission to sexual partners [91].

According to Centers for Disease Control and Prevention (CDC)'s Medical Eligibility Criteria for Contraceptive Use, spermicides generally should not to be used by women with HIV and women at high risk of acquiring HIV [92].

Alternative nonhormonal contraceptives, such as lactational amenorrhea, diaphragms, fertility awareness methods, withdrawal, and cervical caps, are considered lower tier [13] in terms of contraceptive efficacy and do not reduce HIV transmission risk. Male condoms, as discussed above, are an important strategy for STI and HIV prevention but are less effective for pregnancy prevention during typical use than many alternative contraceptive options.

Dual Method Use

Dual method refers to the use of a highly effective form of contraception combined with consistent condom use, and it offers the greatest promise to prevent unintended pregnancy and STIs, including HIV. Reproductive health counseling guidelines recommend the use of a *dual method* strategy [93, 94]. However, rates of reported dual method use are typically low, ranging from 5.5 to 14.6 % in seronegative adolescents [93, 95–97]. Among South African seropositive young women, only 7 % reported dual method use [98]. In a longitudinal cohort study of seropositiveUS adult women, use of a dual method strategy was infrequent [99]. Further, even among dual method users, condom use is often inconsistent or incorrect [100].

Factors that Influence Contraceptive Choice May Impact HIV Risk

Several studies have examined factors associated with seronegative women's selection and use of contraceptive methods [96, 97, 101–103]. Among studies of adult HIV-seropositive women, the majority have been conducted in international settings, primarily in Africa [104–110], with few studies from the USA [111]. These reports highlight the importance of access to health care [104, 105], reporting women's concerns about contraceptive side effects [108] or potential interactions with ARVs [108], convenience of barrier contraceptive methods [104, 105, 111], and desire to have children [107–109] as determinants of contraceptive method use in women living with HIV [104]. Additionally, contraceptive use may differ by partner type; for instance, among a cohort of French women living with HIV, contraceptive use was more prevalent among women reporting recent sexual encounters with casual partners [112].

Some of the behavioral differences between women who choose hormonal contraception and other women may also be related to a woman's underlying risk of acquiring HIV infection. Observational studies can attempt to control for these factors, but unless they are accurately measured, residual (in addition to unmeasured) confounding can occur, complicating our understanding of the impact of hormonal contraceptive methods on HIV risk. For example, unprotected sexual encounters may change with contraceptive use and subsequently alter the risks to uninfected partners through exposure to HIV and other STIs [113–116]. Further, unprotected coitus associated with STI and semen exposure can alter the genital tract inflammatory environment, increasing the risk of HIV transmission. In vitro studies have shown that whole semen can double the rate of HIV infectivity [117], upregulate the expression of proinflammatory cytokines in the female genital tract [118–

120], and increase recruitment of Langerhans cells to the vaginal mucosa [121]. Coinfections with STIs and other genital infections have also been associated with increased HIV shedding and transmission [80, 81, 119, 122]. This increased risk may be due to micro-ulcerations or local recruitment of activated immune cells to the genital tract [123]. Thus, inconsistent condom use, which is difficult to account for in observational studies, can alter HIV susceptibility and infectivity, thereby potentially affecting the association between contraceptive use and HIV acquisition and transmission.

The Influence of Combination Antiretroviral Therapy

Adherence to combination antiretroviral therapy (ART) reduces HIV transmission and clinical disease progression. Plasma viral load (VL) has been shown to be a very strong predictor of heterosexual transmission [124, 125], and ART decreases viral load in plasma and the genital tract. Results from the HIV Prevention Trials Network (HPTN) 052 study demonstrated that individuals living with HIV who initiated ART when their CD4 counts were >350 cells/μl were 96 % less likely to transmit HIV to uninfected partners than those who deferred initiation of ART [126]. Suboptimal adherence to ART remains the primary cause of persistent plasma viremia. Certain at-risk groups (e.g., adolescents and young adults) are more likely to have poor adherence [127–129].

However, several reports have documented detectable HIV in cervicovaginal fluid of women receiving ART, even when the woman has undetectable plasma viral load [125, 130–137]. Thus, it is important to address potential modulating factors that affect viral load in mucosal compartments [138, 139]. The impact of ART on genital HIV-1 RNA shedding in the setting of hormonal contraceptive use is also important, as ART may mitigate any potential increased HIV transmission risk associated with hormonal contraceptives. For example, while evidence is mixed regarding an association between DMPA use and genital HIV-1 RNA shedding among women living with HIV, a recent study in Kenya among women receiving ART demonstrated no association between DMPA use and plasma or cervical HIV-1 RNA [140]. This study suggests that DMPA is unlikely to increase HIV transmission risk among women who are adherent to ART.

Drug interactions have been documented between ART regimens containing certain antiretroviral drugs and certain hormonal contraceptives (primarily combined oral contraceptive pills and possibly implants) due to shared metabolic pathways utilizing the hepatic cytochrome P450 system [92, 141, 142]. Individual concerns about potential interactions between certain ART medications and certain forms of hormonal contraception resulting in decreased contraceptive effectiveness may reduce uptake of certain contraceptive methods. In a qualitative study of South African women, concerns that ART would diminish the efficacy of hormonal contraception were reported [108]. Further investigations are warranted to understand the potential interactions between uses of specific ART medications and various hormonal contraceptive methods.

Summary of the Evidence/Current Recommendations

WHO and CDC have determined that insufficient evidence exists to support a restriction on the use of hormonal contraceptives by women at risk of, or living with, HIV infection [8•,

143]. However, the following clarification applies for women using progestogen-only injectable contraception who are at high risk of HIV:

> Available studies on the association between progestogen-only injectable contraception and HIV acquisition have important methodological limitations hindering their interpretation. Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition; other studies have not found this association. The public health impact of any such association would depend upon the local context, including rates of injectable contraceptive use, maternal mortality, and HIV prevalence. This must be considered when adapting guidelines to local contexts. WHO expert groups continue to actively monitor any emerging evidence. At the meeting in 2014, as at the 2012 technical consultation, it was agreed that the epidemiological data did not warrant a change to the Medical Eligibility Criteria for Contraceptive Use (MEC). Given the importance of this issue, women at high risk of HIV infection should be informed that progestogen-only injectables may or may not increase their risk of HIV acquisition. Women and couples at high risk of HIV acquisition considering progestogen-only injectables should also be informed about and have access to HIV preventive measures, including male and female condoms.

Furthermore, WHO states that women taking ART are eligible for all hormonal contraceptive methods, but *special consideration* may be necessary for women on certain antiretrovirals, specifically efavirenz, nevirapine, or some protease inhibitors [8•]. CDC guide lines for contraceptive use among women with HIV infection or other medical conditions can be found at http://www.cdc.gov/reproductivehealth/unintendedpregnancy/usmec.htm [92]. Global recommendations for contraceptive use among women with HIV infection or other medical conditions can be found at http://www.who.int/reproductivehealth/topics/family_planning/en/ [8•]. These guidelines are regularly evaluated and updated.

Conclusion

The impact of hormonal contraception, specifically progestogen-only injectables, on risk of HIV acquisition or transmission remains inconclusive. If an increased risk is determined with certain contraceptives, this would need to be balanced against consequences of reducing availability of hormonal contraception, especially in regions with high rates of injectable use and maternal morbidity and mortality. However, in certain regions with high HIV prevalence, particularly South Africa, should increased risk of HIV acquisition or transmission via specific contraceptive methods be proven, the overall public health impact of increased HIV incidence might warrant policy changes [144, 145]. Any policies must carefully balance regional HIV risk, contraceptive method safety, regional maternalmortality, and availability and acceptance of alternative effective methods. Both HIV and pregnancy risk reduction strategies, such as the development of female-controlled prevention technology, should be the focus of research efforts. Dual protection with consistent and correct condom use in addition to more effective contraception is a critical

strategy that needs to be further promoted. Lastly high-quality counseling is imperative to optimize patient selection and maintenance of effective contraception.

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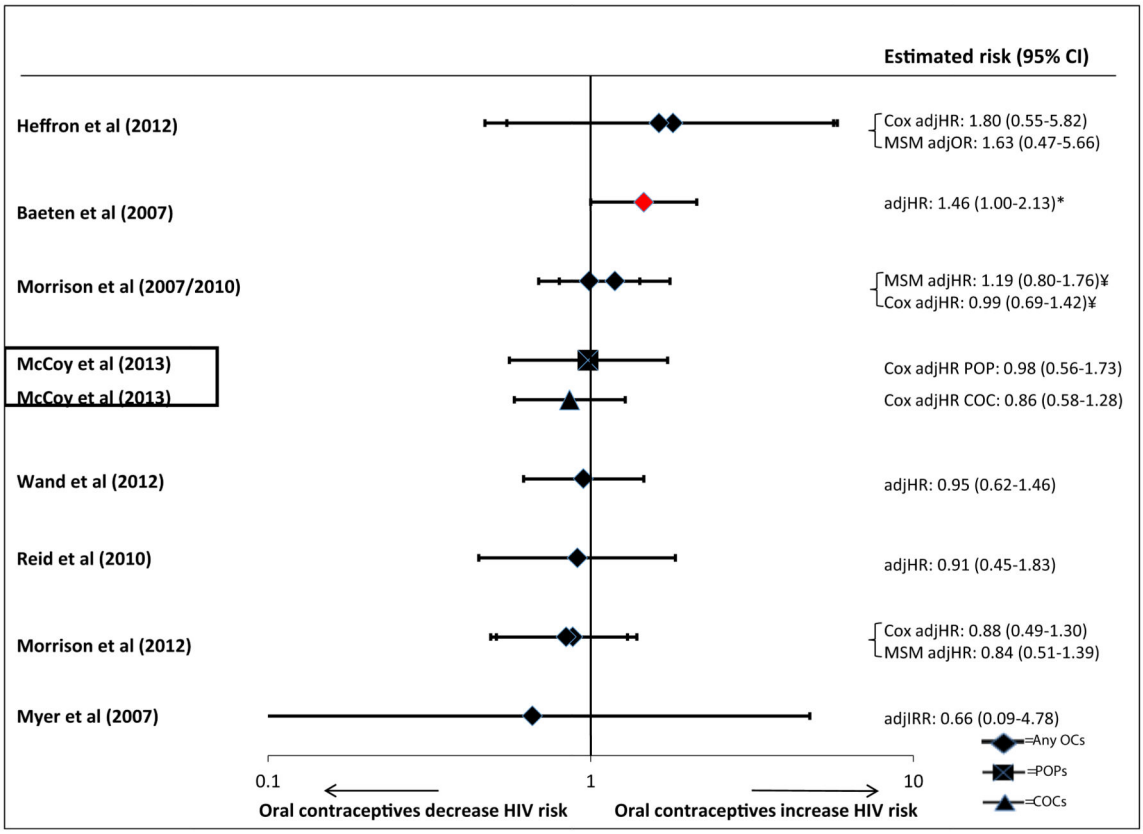

Fig. 1.

Use of injectable contraceptives and HIV acquisition (nine studies considered informative but with important limitations), reproduced with permission from Polis et al. [12•]. *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 *brackets*), except for one study in which both Cox and MSM estimates for both DMPA and NET-EN separately were unavailable [61, 82]. *OR* odds ratio, *IRR* incidence risk ratio, *HR* hazard ratio. *Asterisk* analysis showing significant findings at p=0.05 (*marker also displayed in red*). *Dagger* estimate for Cox model taken from slightly updated analysis which controlled for a total number of unprotected sex acts. *Section sign* unpublished estimates disaggregated by injectable type; only disaggregated Cox estimates provided, in McCoy et al. [39], disaggregated MSM estimates not possible due to violation of the positivity assumption. *Yen sign* different statistical models adjusted for slightly different confounders

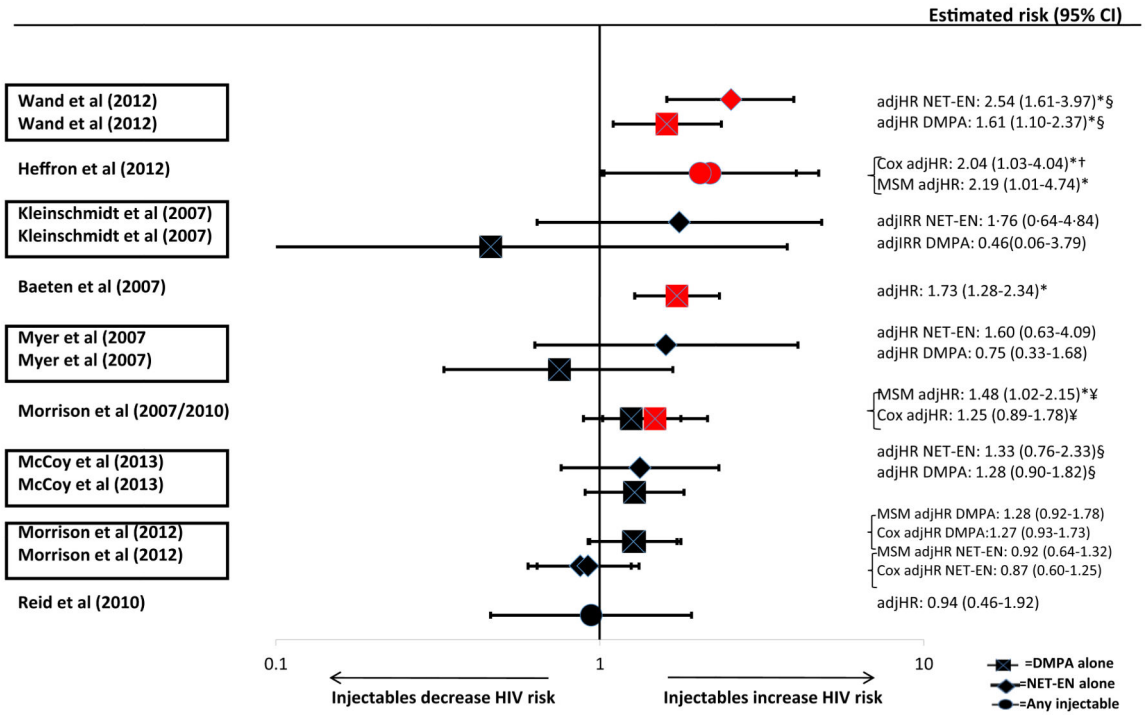

Fig. 2.

Use of oral contraceptives and HIV acquisition (eight studies considered informative but with important limitations) reproduced with permission from Polis et al. [12•]. *Error bars* show 95% CIs. Studies are arranged in order of decreasing magnitude of risk estimate, except if a single study disaggregated progestin-only pills (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 *brackets*). *OR* odds ratio, *IRR* incidence risk ratio, *HR* hazard ratio. *Asterisk* analysis showed significant findings at p=0.05 (*marker also displayed in red*). *Yen sign* different statistical models adjusted for slightly different confounders

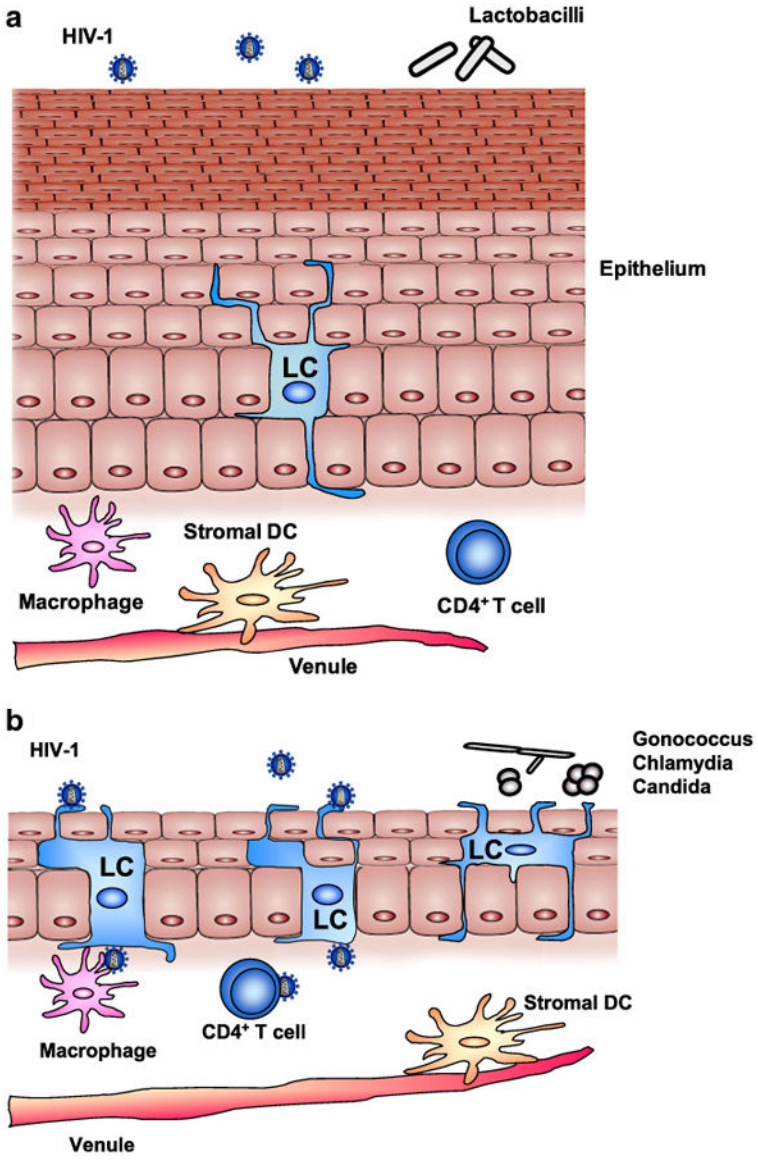

Fig. 3. Potential effects of female sex hormones on the vaginal mucosal tissue. Reproduced with permission from Hel et al. [43•]