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Current and future contraceptive options for women living with HIV

Rena C. Patel^a, Elizabeth A. Bukusi^{b,c}, and Jared M. Baeten^d

^aDivision of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, WA, USA

^bCentre for Microbiologic Research, Kenya Medical Research Institute; Nairobi, Kenya

^cDepartments of Obstetrics and Gynecology and Global Health, University of Washington; Seattle, WA, USA

^dDepartments of Epidemiology, Global Health, and Medicine, University of Washington; Seattle, WA, USA

Abstract

Introduction—Among women living with HIV, half of the pregnancies are unintended. Effective contraception can prevent unintended pregnancies and consequently reduce maternal mortality and perinatal transmission of HIV. While contraceptive options available for all women also apply to women living with HIV, specific considerations exist to the use of contraception by women living with HIV.

Areas covered—First, general principles guiding the use of contraception among women living with HIV are discussed, such as choice, method mix, relative effectiveness, and drug-drug interactions. Second, a detailed discussion of each contraceptive method and issues surrounding the use of that method, such as drug-drug interactions, follows. Third, future contraceptive options in advanced development for use by women or men are briefly discussed.

Expert opinion—Contraceptive methods available to all women should also be accessible to women living with HIV. When the relative effectiveness of a contraceptive method is reduced, for example due to drug-drug interactions with antiretrovirals, the method should still be made available to women living with HIV with the appropriate information sharing and counseling. Greater research on various aspects of contraceptive use by women living with HIV and more comprehensive testing of co-administration of hormonal contraceptives and common medications used by these women are warranted.

Keywords

Female contraception; male contraception; women living with HIV; antiretrovirals; drug-drug interactions; resource-limited settings

CONTACT Rena C. Patel: rcpatel@uw.edu.

Declaration of Interest

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1. Introduction

The majority of people living with HIV are women or girls, for whom decision-making around family planning is a priority during their reproductive years. Among women living with HIV, more than half of the pregnancies are unintended [1]. Effective contraception can prevent unintended pregnancies, subsequently reducing maternal mortality and perinatal HIV transmission [2,3]. In fact, contraception for HIV-positive women is the second of the four pillars of perinatal HIV prevention [3].

Fortunately, a considerable number of options exist for contraception for women and men, all of which are applicable to people living with HIV. Over the last three decades, an increasing number of these contraceptive options have also become more widely available in resource-limited settings, where the majority of women living with HIV reside.

However, certain considerations exist to the use of these contraceptive methods for use by women living with HIV. This review is an overview of contraceptive options for women living with HIV, largely from the perspective of family planning and HIV care provision in resource-limited settings, such as those in sub-Saharan Africa. Nonetheless, because similar contraceptive methods and HIV treatment options are available in resource-rich settings, this review is also applicable to women living in resource-rich settings. In Section 1, we discuss general principles regarding contraceptive provision for women living with HIV who do not wish to become pregnant. In Section 2, we discuss the current contraceptive methods available to women living with HIV and what is known regarding issues specific to women living with HIV. In Section 3, we discuss contraceptive methods that may become available to both women and men living with HIV in the near future.

1.1. Primer on antiretroviral medications

The World Health Organization (WHO) now recommends initiation of lifelong antiretroviral therapy (ART) for all individuals living with HIV regardless of disease status or CD4 cell counts, including in resource-limited settings [4]. Generally, a minimum of a three-drug combination of antiretrovirals from at least two different classes are used to treat individuals living with HIV (Table 1). These combinations, termed ART regimens, generally contain two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and then a third antiretroviral from one of the following classes: non-nucleos(t)ide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry inhibitors (e.g. maraviroc or enfuvirtide). While initially, three NRTIs-containing regimens were used in resource-limited settings, currently leading regimens being used are NNRTI- (e.g. efavirenz, nevirapine), PI- (e.g. lopinavir, atazanavir, darunavir, all boosted with ritonavir), or INSTI- (e.g. raltegravir, dolutegravir) containing regimens. The current WHO recommendations highlight the use of efavirenz-containing ART as first-line therapy for people living with HIV [4].

2. General principles for contraceptive provision

2.1. Choice – allow women and their partners to exercise reproductive health decision-making as part of their fundamental human right to health

Providers and programs should consider reproductive health decision-making, including for family planning, as part of an individual's fundamental human right to their health [5]. Adopting a rights-based approach, a bedrock position for reproductive health decision-making, helps ensure that women living with HIV and their partners are able to choose when and which contraceptive method to use to best suit their lives. While the vast majority of women living with HIV may wish to use effective contraception to prevent pregnancies at some point in their lives, they may also wish to have future children. Too often, women living with HIV perceive provider or community biases against their fertility desires for future children and, in some cases, face coercive use of contraception. Providers and programs must ensure they facilitate women living with HIV to realize their reproductive health goals, whether that is to conceive through safer conception strategies or prevent pregnancies through voluntary effective contraceptive use.

2.2. Method mix, integration of reproductive health into HIV care, fertility intentions

Several approaches help women living with HIV and their partners maximize their reproductive health decision-making. First, family planning programs must optimize the method mix, by making as many options as readily available as possible. For example, injectable contraceptives tend to be the most popular hormonal contraceptive method used in some resource-limited settings [6]. However, the effectiveness of injectable contraceptives over long periods of time, due to user action requirements with having the woman return every 3 months for repeat injections or facility stock-outs, can diminish considerably, sometimes to an extent equivalent to women not using any contraceptive method [7]. Improving the provision of all contraceptive options, including long-acting reversible contraceptives (LARCs), should be a priority for every family planning program. Second, integrating reproductive health services, including family planning, directly into routine HIV care not only improves contraceptive use but also prevents pregnancies [8,9]. Various resources exist now to help integrate family planning services into HIV care and vice versa [10]. Third, in order to help facilitate women living with HIV's decision-making on family planning, they need to be asked in routine, systematic manner their fertility desires or intentions and not have their providers assume that their HIV-positive status deters them from desiring future children. Additional factors, such as improving male involvement in family planning or contraceptive knowledge and counseling tools, are important considerations as well in helping women living with HIV and their partners make optimal decisions.

2.3. Relative effectiveness

Several aspects often play into a woman's choice of her contraceptive method, such as anticipated side effects, delivery mechanism, or ability to use covertly. In addition, contraceptive effectiveness can be highlighted as another aspect (Figure 1). Depending on a woman's needs, more effective contraceptive methods (surgical, intrauterine contraception [IUC; which includes intrauterine devices or systems], and implants) may be more appealing

over less effective contraceptive methods (injectables, oral, or other hormonal contraceptives) or least effective contraceptive methods (barrier or natural methods; Figure 2). Generally, implants are the most effective form of contraception, followed by surgical methods and then IUC [6,11]. Contraceptive effectiveness with injectables and oral contraceptives varies markedly depending on the setting. While many of the least effective contraceptive methods are used by people living with HIV, including in combination with more effective methods at times, their relative effectiveness is not specifically influenced by factors related to HIV.

2.4. Prevention of other sexually transmitted infections (STIs)

Prevention of other STIs ultimately requires usage of barrier methods, such as male or female condoms. However, because condoms are less effective at preventing pregnancy than more effective contraceptive methods, they should not be relied on for both pregnancy and STIs prevention or 'dual protection.' Instead, dual contraceptive method use is recommended if individuals are at high risk for STIs as well as pregnancy, using both barrier methods and more effective contraceptive methods [12]. In practice, dual contraceptive method use is challenging, with reports as low as 25% usage among women living with HIV [13], for likely the same reasons why condom use is a poor method for pregnancy prevention.

2.5. Drug–drug interactions (DDIs) – reducing efficacy of contraceptives

DDIs have the potential to reduce contraceptive efficacy, generally more so for progestin-based contraceptives than estrogen-based contraceptives. However, DDIs may also increase the exposure of either types of contraceptives and result in increased toxicity, particularly of estrogen-based contraceptives. Hormonal contraceptives are generally metabolized by hepatic cytochrome P450 (CYP450) enzymes, specifically by CYP3A4 [14]. Antiretrovirals, including NNRTIs, PIs, and cobicistat-boosted agents, influence the activity of CYP3A4 and 2B6 enzymes; NNRTIs are specifically implicated in CYP3A4 induction [14]. Generally, NRTIs and INSTIs are not considered significant inhibitors, inducers, or substrates of CYP450 enzymes, and, therefore, unlikely to influence hormonal contraceptive exposure [14,15]. Two recent systematic reviews on DDIs between hormonal contraceptives and antiretrovirals for women living with HIV thoroughly cover the aforementioned aspects [15,16]. In Section 3, we highlight pertinent findings for each combination of contraceptive method and antiretroviral classes.

Women using other medications which are known to affect contraceptive exposure, such as antiepileptics or azoles, or affect antiretroviral exposure, such as rifamycins, further complicate understanding and interpreting potential three- or four-way DDIs. Few empiric data exist to aid the understanding of such potential DDIs, but caution is advised in such potential cases.

2.6. Contraception's effect on HIV disease progression

Contraceptive's effect on HIV disease progression may occur through two possible mechanisms. First, DDIs between concomitant hormonal contraceptives and antiretrovirals may reduce antiretroviral efficacy. A systematic review of pharmacokinetic (PK) studies

evaluating such relationships notes that a few studies find statistically significant reduction in exposure to antiretrovirals, but because the reduced exposures still meet US Food and Drug Administration's definition of bioequivalence, they are unlikely to be of any clinical significance [15]. The second mechanism for hormonal contraceptives to negatively affect HIV disease progression is through additional immunosuppression and/or stimulation of viral effects [17].

In the pre-ART era, most studies did not find that hormonal contraceptive use was associated with HIV disease progression, as measured by change in CD4 cell count, eligibility to initiate ART, occurrence of opportunistic infections, or death [18,19]. The one exception is a secondary analysis of women not on ART followed in a randomized trial who had higher declines in CD4 cell counts in the hormonal contraceptive arms of injectables or oral contraceptives, compared to women in the nonhormonal IUC arm (hazard ratio 1.56, 95% confidence interval (CI) 1.08–2.26 and 1.69, 95% CI 1.09–2.64, respectively) [20]. With increasing ART use in resource-limited settings, more recently published studies consistently reported no deleterious effect of hormonal contraceptives on HIV diseases progression, including in HIV plasma viral suppression rates [19,21–23]. With effective ART, any theoretical effects of contraception on HIV disease progression are likely moot.

2.7. Contraception's effect on HIV transmission

Progestin-based injectable use, particularly depot medroxyprogesterone acetate (DMPA) use, has been implicated in potentially increasing the risk of HIV acquisition among HIV-negative women; this is a large, important, and still-unanswered topic, and while outside the scope of this review, it has been reviewed elsewhere [24–27]. A parallel concern is the potential for progestin-based hormonal contraception to increase the risk of HIV transmission from women living with HIV to their partners. Progestin-based contraception may increase viral replication, viral diversity, or set point viral load or decrease immune regulation in the genital tract of women living with HIV [17].

In one analysis, women who had not yet initiated ART and used injectable or oral contraception transmitted HIV to their negative partners at twice the rate of women who did not use hormonal contraception; these women were also more likely to have detectable genital viral shedding [28]. These effects were strongest among women using injectable contraception. In a follow-up analysis of a similar cohort – but now among women initiating ART – the use of hormonal contraceptives, including injectables, did not alter HIV genital shedding in women on ART, with overall high viral suppression in plasma and the genital compartment [23]. Other studies conducted among women on ART using various hormonal contraceptives also report no differences in genital shedding [29,30]. Confirmed plasma viral suppression after ART initiation essentially prevents HIV transmission [31], so the impact of intermittent genital shedding while on ART does not appear to increase risk of HIV transmission.

3. Current contraceptive options

Currently, the full range of contraceptive options available to all women and men are also available to people living with HIV, with a few nuances (Table 2) [12]. Later, we discuss

each category of contraceptive method and any particular nuances applicable to people living with HIV, particularly concerns for reduced efficacy of the contraceptive method. When DDIs are discussed, we start with the known interactions with NRTIs, NNRTIs, PIs, and then INSTIs. The discussion also includes major knowledge gaps pertinent to each contraceptive method category.

3.1. Surgical methods

Currently there are no limitations in surgical methods, which include tubal ligation, hysterectomy, and vasectomy, that can be offered to women or men living with HIV. Some guidelines suggest delaying surgery in case of acute HIV-related infections [12].

3.2. Intrauterine contraception

Currently, most resource-limited settings provide nonhormonal IUC. Hence, DDIs with antiretrovirals are not expected. The levonorgestrel-IUC is beginning to be introduced in such settings, and the potential for DDIs with hormonal IUC and anti-retrovirals impacting contraceptive efficacy seem unlikely (given that despite any reduced local hormonal concentrations, the structural IUC barrier will still maintain overall efficacy). Observational or clinical trial data appear to suggest the levonorgestrel-IUC can be used in women living with HIV, including on ART, without any negative effects [32–35]. Whether any known DDIs with levonorgestrel will reduce the hormonal benefits of the levonorgestrel-IUC, such as lighter bleeding patterns with subsequently improvements in menorrhagia-related anemia, negating the need for the hormonal IUC, remains to be studied.

Due to the potential of higher undiagnosed STIs among women living with HIV at the time of IUC placement and, therefore, hypothetically higher rates of subsequent pelvic inflammatory disease, IUC placement without first screening for undiagnosed STIs or in women with advanced HIV disease has been controversial. However, a recent randomized control trial among women living with HIV demonstrated that the rates of STIs and pelvic inflammatory disease after IUC placement are exceedingly low and IUC placement can safely proceed with only syndromic screening (vs. additional laboratory screening) for STIs [36]. A recent systematic review regarding the safety of IUC in women living with HIV found no differences in infectious complications among women with varying levels of HIV disease severity [37]. Ultimately, the WHO Medical Eligibility for Contraception (MEC) recommends that women living with HIV with severe or advanced HIV clinical diseases (e.g. WHO stage 3 or 4) do not initiate any type of IUC (MEC 3), but if they already have an IUC in place, to not remove it [12].

3.3. Implants

Contraceptive implants, containing either levonorgestrel lasting 5 years or etonogestrel lasting 3 years, are the most effective contraceptives, with failure rates <1% [38–42]. However, recently emerging PK and clinical data have raised concerns for higher failure rates with concomitant use of implants and efavirenz. Nonetheless, this combination is still recommended by the WHO for women living with HIV (MEC 2) [12]. Next, we discuss the existing data on either levonorgestrel or etonogestrel implants in combination with various antiretrovirals.

3.3.1. Nucleos(t)ide reverse transcriptase inhibitors—One study demonstrates no significant impact of NRTIs on levonorgestrel exposure in women using implants[43].

3.3.2. Non-nucleos(t)ide reverse transcriptase inhibitors—Four PK studies now demonstrate markedly reduced etonogestrel or levonorgestrel concentrations in women concomitantly using efavirenz-containing ART [44–47], with one study documenting three pregnancies among the 20 women using efavirenz-containing ART [45]. The same study also demonstrated statistically nonsignificant higher exposure to levonorgestrel among women concomitantly using nevirapine-containing ART as compared to women not on any ART [45].

Among a cohort of Kenyan women using either etonogestrel or levonorgestrel implants, unadjusted pregnancy rates were 2.2 (95% CI 1.4–2.9) and 5.8 (95% CI 3.3–8.4) per 100 women-years in women concomitantly using nevirapine- and efavirenz-containing ART, respectively (adjusted pregnancy rate ratio of 3.0, 95% CI 1.3–4.6) [7]. In a retrospective study of women using levonorgestrel implants, 15 of the 121 women concomitantly using efavirenz became pregnant at a median duration of 16.4 months, while no pregnancies occurred among women concomitantly using nevirapine [48]. Therefore, both the PK and clinical evidence strongly suggests reduced contraceptive effectiveness, likely due to DDIs. However, in the same Kenyan cohort study, the use of alternative contraceptive methods other than permanent methods or IUC resulted in higher pregnancy rates when combined with efavirenz-containing ART; adjusted pregnancy rate ratios ranged from 1.6 for injectables to 2.8 for oral contraceptives when compared to implants [7]. Thus, despite the DDIs likely reducing the implant effectiveness, implants remained one of the most effective methods – and the most effective method readily available – to these Kenyan women. A similar analysis with data pooled from prospective trials from various parts of Africa concluded similar findings [49]. Currently, both the WHO and the US Centers for Disease Control and Prevention MEC recommend implant and efavirenz combination as a category 2 [12,50].

3.3.3. Protease inhibitors—In a PK study mentioned earlier, one arm of the study included women using etonogestrel implants and lopinavir/ritonavir-containing ART and found that the etonogestrel exposure was statistically significantly higher in the lopinavir/ritonavir arm as compared to women not on any ART [44]. In the Kenyan cohort study, the unadjusted pregnancy rates among women concomitantly using either implant with lopinavir/ritonavir-containing ART was 1.7 (95% CI 0–4.1) with an adjusted pregnancy rate ratio of 0.86 (95% CI 0–2.1) when compared to women concomitantly using nevirapine-containing ART [7]. Therefore, it does not appear that lopinavir/ritonavir-containing ART reduces implant efficacy or effectiveness; potential increased exposure of the progestin is unlikely to result in any increased toxicities.

3.3.4. Integrase strand transfer inhibitors—Currently, no direct data exists regarding implant progestins and any INSTIs, but due to lack of DDIs with progestins in oral contraceptives [51–54], INSTIs are believed not to influence implant progestin concentrations.

Overall, regarding implants, prospective clinical studies that overcome limitations of the current retrospective clinical studies, including more frequent and objective ascertainment of contraceptive use, ART regimens, and pregnancy, and PK studies that examine combinations of implants with newer ART regimens, such as those including INSTIs, are needed to more definitively inform clinical practice.

3.4. Injectables

Injectables are commonly used for contraception, and in some settings, are the most popular method used [6]. While most of the data exist for DMPA, several different formulations, doses, and frequency of injectables are available in resource-limited settings. Most practitioners extrapolate from DMPA data to the various other forms of injectables.

3.4.1. Nucleos(t)ide reverse transcriptase inhibitors—NRTIs are thought not to have significant interactions with injectable contraception, as demonstrated by PK and cohort studies among HIV-negative women using tenofovir/emtricitabine for pre-exposure prophylaxis [55,56].

3.4.2. Non-nucleos(t)ide reverse transcriptase inhibitors—Two PK studies exist that have evaluated efavirenz-containing ART with injectable contraception, namely DMPA, with neither finding any significant DDIs [57,58]. One of these studies also evaluated nevirapine-containing ART and similarly found no significant DDIs [58]. No direct PK data exists for norethisterone enanthate or for lower dose medroxyprogesterone acetate (MPA) formulations, such as the self-injection formulation of 104 mg MPA.

In the Kenyan cohort, women using injectables, namely DMPA, and nevirapine- or efavirenz-containing ART had unadjusted pregnancy rates of 8.4 (95% CI 7.5–9.3) and 9.4 (95% CI 7.3–11.5), respectively (adjusted pregnancy rate ratio of 1.2 (95% CI 0.91–1.5)) [7].

3.4.3. Protease inhibitors—One PK study found higher DMPA exposure with lopinavir/ritonavir-containing ART as compared to women not on any ART, but the higher exposure did not appear to lead to higher toxicities [59]. Another study reported no significant changes in DMPA exposure in women using nelfinavir-containing ART [58].

3.4.4. Integrase strand transfer inhibitors—No studies have evaluated any INSTIs and injectable contraception; however, since the potential for DDIs between INSTIs and injectable contraception is considered insignificant, again extrapolating from progestin-based oral contraceptive data [51–54], their concomitant use is not considered to reduce contraceptive efficacy.

Because injectables tend to be one of the most commonly used hormonal contraception in resource-limiting settings, greater research on specific types of injectables, including norethisterone enanthate and lower dose MPA formulations, and leading or newer ART regimens, such as efavirenz- or INSTI-containing regimens, are needed to more definitively guide clinical practice.

3.5. Oral contraceptives

The choice of oral contraceptives needs to be evaluated on a case-by-case basis depending the oral contraceptive components and doses and antiretrovirals being coadministered. Overall, the most number of PK studies pertain to oral contraceptives, as antiretroviral manufacturers generally conduct PK studies in healthy volunteers as part of their regulatory approval application.

3.5.1. Nucleos(t)ide reverse transcriptase inhibitors—Generally, studies find no significant changes in hormone exposure among NRTIs and oral contraceptives [51,60,61].

3.5.2. Non-nucleos(t)ide reverse transcriptase inhibitors—In terms of combining oral contraceptives with NNRTIs, some clear patterns are emerging. Progestin-based hormone exposures, such as etonogestrel and levonorgestrel as the primary hormones or their active metabolites, appear to be lowered by concomitant use of efavirenz [62–64]. Ethinyl estradiol exposure, on the other hand, was not significantly changed in these studies [63,64]. In regards to nevirapine, conflicting data exists on reduction of both the ethinyl estradiol or the progestin-based component [65,66]. As for the newer NNRTIs, etravirine and rilpivirine, being used in second- or third-line ART regimens in resource-limited settings, have been tested with healthy volunteer crossover studies and not shown to significantly alter hormone exposures or markers of ovulation [67,68].

In terms of clinical outcomes, unadjusted pregnancy rates were 10.9 (95% CI 7.8–14.0) and 15.4 (95% CI 8.2–22.6) among Kenyan women concomitantly using oral contraceptives and either nevirapine- or efavirenz-containing ART, respectively (adjusted pregnancy rate ratio of 1.6 (95% CI 0.69–2.5)) [7]. Another cohort study noted similar findings [49]. In a small prospective trial, three (out of 25) women using combined oral contraceptives and efavirenz-containing ART had evidence of ovulation but none became pregnant [62].

3.5.3. Protease inhibitors—Formulations containing PIs in resource-limited settings are coadministered with ritonavir 100 mg once or twice daily as a booster. Ritonavir, when combined as a booster with lopinavir, atazanavir, or darunavir, appear to reduce ethinyl estradiol exposure [69–72]. On the other hand, the effect of boosting ritonavir with PIs on progestins appears less clear, though generally the studies indicate higher or insignificantly lower progestin exposures [69,70,72–74]. Cobicistat-boosted PIs have not become widely available in resource-limited settings, but when cobicistat is combined with elvitegravir, ethinyl estradiol exposure was reduced and progestin exposure was increased [75].

3.5.4. Integrase strand transfer inhibitors—Oral contraceptives evaluated in healthy volunteers receiving either raltegravir or dolutegravir did not demonstrate any significant change in hormone exposures [52,54]. On the other hand, elvitegravir, which is coadministered with a booster of either cobicistat or ritonavir, does impact oral contraceptive exposure. In a healthy volunteer study of elvitegravir coadministered with cobicistat, ethinyl estradiol exposure was reduced by 25% while the norethindrone exposure increased by 126% [75]. While no PK data exist for elvitegravir coadministered with ritonavir, given

ritonavir's known PK profile, it is recommended to use alternative contraceptive methods [76].

3.5.5. Maraviroc—Maraviroc, infrequently used in the resource-rich settings and rarely used in resource-poor settings, has not been shown to change oral contraceptive exposures [77].

As noted, most contraceptive and ART PK studies exist with oral methods, given regulatory approval requirements for manufacturers, though a major limitation for these studies is that they are conducted in healthy volunteers, often with a single dose or crossover designs, that often limit generalizability to women living with HIV.

3.6. Other hormonal methods – vaginal rings, transdermal patches

Overall, limited direct evidence exists to guide concomitant usage of other hormonal contraceptive methods, such as vaginal rings or transdermal patches. The leading vaginal ring, containing etonogestrel and ethinyl estradiol, NuvaRing®, has not been evaluated in any DDIs studies, though one is currently under way with efavirenz and atazanavir/ritonavir (Clinical Trial ACTG A5316). One study evaluating an ethinyl estradiol/progestin-containing transdermal patch with concomitant lopinavir/ritonavir-containing ART found lower ethinyl estradiol but higher progestin exposures [71].

3.7. Barrier or natural methods

Since barrier or natural methods rely on nonhormonal methods of contraception, no DDIs are anticipated with antiretrovirals. However, as noted earlier, the overall effectiveness of barrier or natural methods in preventing pregnancy is low and therefore women living with HIV should be informed of more effective methods of preventing pregnancy.

4. Future contraceptive options

While a robust method mix exists in theory for all women, including women living with HIV, each method has its limitations, whether it is user action, undesired or long-term side effects, or DDIs reducing efficacy. As such, the need to improve the existing options remains. However, the greater need for the field of contraceptive technology development is in producing attractive contraceptive options for use by men; providing better contraceptive options for men embarks on a new vision of family planning choices for all women. Next, we discuss the relatively advanced developments in contraceptive options for women and men, and also the potential use of multipurpose technologies (MPTs), which combine technologies for both pregnancy prevention and antiretrovirals for either prevention or treatment of HIV, that may be of interest to women living with HIV.

4.1. Future methods for women

Generally, the approach to future contraceptive options under development for women relies largely on optimizing the currently available options, given the large method mix that already exists for women [78]. By extending the efficacy period or improving the delivery of that method, the newer approaches aim to improve on existing technologies. Next, we

discuss the technologies under development for four of the existing contraceptive methods, though it remains unclear if and when these products will become available in resource-limited settings.

4.1.1. Intrauterine contraception—One of the major barriers in greater IUC use in many settings, including resource-limited settings, is the programmatic and clinical capacity to place the devices. As such, two smaller, levonorgestrel IUC with narrower inserters than the leading levonorgestrel-IUC Mirena® have been tested in a Phase III clinical trial with failure rates <1% [79]. One of these devices is now available under the tradename Skyla®.

4.1.2. Implants—Removal of the currently formulated implants can prove challenging, including in resource-limited settings, when pregnancy is desired or the recommended efficacy period ends. While biodegradable implants, which would degrade at the end of the efficacy period, developed and tested in the 1990s never made it to market due to various limitations [80,81], newer biodegradable implants devices are under development [78].

4.1.3. Injectables—A monthly combined injectable with 25 mg of MPA and 5 mg of estradiol cypionate, with the latter component intended for more regular bleeding patterns than current progestin-only injectables, is being redesigned for resource-limited settings [82]. The approaches to longer-acting injectables, for example to be used at 6-monthly intervals, are still being investigated in preclinical phases [78].

4.1.4. Vaginal rings—A progestin-only ring lasting 3 months is now available and one combining nestorone and ethinyl estradiol lasting 1 year demonstrated good results in Phase III trials and is awaiting regulatory approval (also see Section 4.3 for MPTs involving vaginal rings) [83].

4.2. Future methods for men

Perhaps the greatest innovation in contraceptive technology is occurring in the field of developing hormonal and nonhormonal contraceptive options for use by men, a field that has not seen any significant development for over 100 years [84]. Improving the contraceptive options for use by men will help all women, including women living with HIV, to better share the responsibility of and improve male involvement in family planning. Next, we discuss the two major types of contraceptive options under development for use by men.

4.2.1. Hormonal methods—Current male hormonal contraceptives are targeted at the goal of reversibly reducing or eliminating viable sperm to prevent fertilization of ova [85]. This is generally achieved by suppressing the appropriate endogenous male hormones that trigger spermatogonia, using a combination of androgens with progestins, occasionally with the addition of 5- α -reductase to prevent testosterone metabolism [85]. Because it appears that complete elimination of viable sperm will be unlikely, the failure rates with such male contraceptives are predicted to parallel ‘perfect use’ of female oral hormonal contraceptives, though implantable devices are also being developed for use by men [86,87].

4.2.2. Nonhormonal and surgical methods—The major approaches to nonhormonal but nonsurgical contraceptive methods for use by men do not disrupt the gonadal function

[85,88]. Instead, they rely on agents which interfere with Sertoli cell function, disrupt vitamin A or retinol function, optimize the use of calcium channel antagonists to reduce spermatozoa function, or mimic the effect of anti-epididymal protease inhibitor antibodies.

The main approach to surgical contraceptive methods for use by men has focused on reversibly blocking sperm passage in the vas deferens [85]. Compounds such as styrene maleic anhydride, silicone, or polyurethane ‘plugs’ are introduced in the vas deferens to occlude passage of sperm [89–91]. Small clinical trials have used these approaches but larger studies of efficacy and reversibility remain to be conducted.

4.3. Future use of MPTs for women living with HIV

MPTs which combine protection against pregnancy and STIs, particularly HIV, into one device are under development for HIV-negative women. For example, a vaginal ring which combines tenofovir and levonorgestrel has completed testing in a phase 1 clinical trial and several others combining antiretrovirals and hormonal contraceptives are in preclinical phases [92]. Given these devices often contain existing or new antiretrovirals for prevention of HIV, they may someday also be formulated for use by women living with HIV for the treatment of HIV and protection against pregnancy. For example, long-acting injectable antiretrovirals, rilpivirine and cabotegravir, have shown promising results for treatment of HIV in phase 2 clinical trials [93]. Implants embedded with long-acting antiretrovirals are also under development [94,95]. If successful, such long-acting antiretroviral formulations for HIV treatment could be combined with contraceptives for pregnancy prevention.

5. Conclusion

Adopting a rights-based approach helps ensure that women living with HIV and their partners are able to choose a contraceptive method that is best suited for their lives. To help facilitate the choice of contraceptive method for women, method mix should be optimized and reproductive health services should be fully integrated into HIV care, including the assessment of fertility intentions, with women being supported to either conceive or prevent pregnancies as desired. The overall effectiveness of contraceptive methods, alongside other factors, should guide method preference and counseling.

DDIs with hormonal contraceptives and antiretrovirals reducing contraceptive efficacy are one of the most important considerations in concomitant use of the two. The most notable interaction is efavirenz, concomitantly used with implants and progestin-containing oral contraceptives; data on nevirapine and concomitant progestin-containing oral contraceptives remains conflicting. The ethinyl estradiol exposure reductions for oral contraceptive used concomitantly with PIs is unlikely to be clinically significant for pregnancy prevention, since the exposure to the progestin contraceptive is maintained. The potential for hormonal contraceptives to negatively affect HIV disease progression, viral suppression, or potential for HIV transmission from women living with HIV to uninfected partners appears insignificant now with the use of universal ART.

While ways to optimize existing contraception options for women are underway, including possibly combining contraceptives with antiretrovirals for prevention or treatment of HIV,

greater innovation is occurring in the area of male contraceptive options. These male contraceptive options include both hormonal and nonhormonal or surgical methods with a primary goal of achieving timely reversibility. Such advances will greatly aid not only women living with HIV but all women in shifting the burden of family planning and contraceptive use to both or either partner.

6. Expert opinion

First and foremost, reproductive health decision-making, including for contraception use, must be woman-friendly and be grounded in a rights-based approach to reproductive health so that women living with HIV are best supported to achieve their goals [5]. Too often, women living with HIV have perceived lack of support for desiring children or difficulty discussing their fertility intentions at both the community and provider levels [96–99]. In general, these women should be better supported to realize their reproductive health goals, whether that is using safer conception options to conceive or effective contraception to prevent pregnancies [100].

As millions of women living with HIV are initiating or have initiated ART with anticipated life spans of their noninfected counterparts, use of family planning and concomitant management of chronic diseases will only increase worldwide. Therefore, greater research needs to occur and maintain pace with the growing needs of women living with HIV globally. For example, the issue of DDIs with hormonal contraceptives among women living with HIV on ART intersecting with the developing obesity epidemics in resource-limited settings [101] may have additional effects on contraceptive efficacy. Research to also determine ways of optimizing a contraceptive method when a DDI exists, by either increasing the exposure of the contraceptive method or decreasing the exposure of the culprit agent, is needed.

Generally, contraceptive methods available to all women and men should also be made available to people living with HIV. The WHO currently recommends all contraceptive methods as MEC 1 or 2 for women living with HIV, including on ART, except for the use of IUC in women with advanced HIV disease as MEC 3. Recent evidence suggests that the rates of post-IUC placement STIs and pelvic inflammatory disease are low and that disease status does not strongly influence the occurrence of these infectious complications [36,37,102]. In light of such evidence and the significant barriers that already exist to IUC use in resource-limited settings, the WHO MEC classification of 3 arguably is too cautious and a MEC 2 classification would be more appropriate.

Despite some DDIs between contraceptive methods and antiretrovirals, most contraceptive methods are still viable options for women living with HIV and generally rated as MEC 2 by the WHO. As the Kenyan cohort study demonstrated that despite pregnancy rates being higher in implant and efavirenz users than expected, the use of leading alternative contraceptive methods, such as injectables, with efavirenz actually resulted in even higher pregnancy rates, likely reflecting the typical use effectiveness of injectables in the setting [7]. Therefore, no contraceptive option, including implants with efavirenz use, should be

withheld from women living with HIV, and policy statements that urge withholding such methods potentially do harm by denying women an acceptable and desirable option [103].

Nonetheless, the aforementioned scenario with emerging data indicating significant DDIs between implant and efavirenz highlights the need for appropriate information sharing and counseling for women living with HIV. Women living with HIV who are considering implant placement or already have one in place should be informed about the possibility of the implant's decreased effectiveness with concomitant efavirenz use. Counseling on the potential risks of failure is essential to ensure that women can consider and preferably choose other equally or more effective methods, such as IUC. Ultimately, women should retain the right to make an informed decision and still choose a method after weighing the risks and benefits of available methods.

The significant DDIs between implants and efavirenz also underscore the importance of having a robust method mix, with a particular focus on LARCs, available to all women. For instance, hormonal or nonhormonal IUC could be an appropriate alternative to implants for most women living with HIV on efavirenz, maintaining high effectiveness for pregnancy prevention while not compromising treatment for the HIV. However, persistent challenges to optimizing method mix remain, for reasons including method cost, provider preferences, lack of trained staff, weak logistics and supply management, lack of demand for certain methods and misinformation. Efforts at programmatic and policy levels need to continue or intensify to help make a robust method mix a reality for all women, including women living with HIV.

Generally, to receive regulatory approval for marketing and distribution of drugs, such as by the US Food and Drug Administration, a single, crossover, PK study with short-term oral contraceptives in healthy subjects is currently required to characterize a new drug's impact on hormonal contraceptive exposure. Because of the numerous routes of administration, formulations, and doses of hormonal contraceptive options, such limited PK studies do not adequately assess a new drug's impact on many hormonal contraceptives. For example, the issue of a DDI with contraceptive implants and efavirenz could have been identified and addressed earlier if more comprehensive PK testing with several hormonal contraceptive methods had been done. Just as importantly, the field of antiretrovirals is moving rapidly, with new drugs within existing classes and new classes of therapeutics being developed. Therefore, more comprehensive but carefully planned PK studies, preferably with some pharmacodynamics outcomes, should be part of the development plan and regulatory approval for new antiretrovirals.

Lastly, as newer contraceptive technologies are being developed, women living with HIV as their potential users should be kept in mind. Ensuring the contraceptive technology does not interfere with HIV treatment and management, is not itself negatively impacted by HIV treatment, and can maximally fulfill these women's needs for family planning and HIV treatment is important. While the clear target for MPTs is HIV-negative women, to prevent both pregnancy and HIV acquisition, adding the focus of potential use by women living with HIV will only add value to MPTs, though admittedly the development requirements would be different for these two groups of women. The field of contraceptive technology should

welcome the development of greater male contraceptive options so as to help alleviate the current large burden of effective contraception on women.

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Highlights

- General principles for contraceptive provision to women living with HIV, including choice, method mix, relative effectiveness, and drug-drug interactions
- Current contraceptive options for women living with HIV, including discussion of drug-drug interactions with antiretroviral medications
- Future contraceptive options under development for women and men living with HIV
- Expert opinion on navigating contraceptive options for women living with HIV

This box summarizes key points contained in the article.

Figure 1. Typical-use median contraceptive failure rates within 12 months of use for select contraceptive methods world-wide (reproduced from Polis et al. [6])

Width of box is the interquartile range (IQR); whiskers are drawn to the lowest and highest values inside the area defined by $Q1 - 1.5(IQR)$ and $Q3 + 1.5(IQR)$; outliers beyond these ranges are depicted as individual dots.

Figure 2. Relative effectiveness of contraceptive methods (US Centers for Disease Control and Prevention Medical Eligibility Criteria 2016)

Reproduced with permission from Centers for Disease Control and Prevention (CDC).

Effectiveness of Family Planning Methods. Adapted from World Health Organization (WHO) Department of Reproductive Health and Research, Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP). Knowledge for health project. Family planning: a global handbook for providers (2011 update). Baltimore, MD; Geneva, Switzerland: CCP and WHO; 2011; and Trussell [11]. https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/pdf/contraceptive_methods_508.pdf

Table 1

Classes and generic names of current antiretrovirals most commonly used in resource-limited settings, such as sub-Saharan African settings.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)	Integrase inhibitors (INSTIs)
Tenofovir (TNF or TDF)	Nevirapine (NVP)	Lopinavir/ritonavir (LPV/r)	Raltegravir (RAL)
Abacavir (ABC)	Efavirenz (EFV)	Atazanavir/ritonavir (ATV/r)	Elvitegravir/cobicistat (EVG/c)
Zidovudine (AZT or ZDV)	Etravirine (ETR)	Darunavir/ritonavir (DRV/r)	Dolutegravir (DTG)
Emtricitabine (FTC)	Rilpivirine (RVP)		
Lamivudine (3TC)			

Table 2

Adapted WHO contraceptive use guidelines (based on WHO Medical Eligibility Criteria 2015).

Contraceptive method	MEC ^a recommendations by antiretrovirals			
	NRTIs (any)	NNRTIs (nevirapine or efavirenz)	PIs (any)	INSTIs
Surgical/permanent methods	Can be offered to all women or men living with HIV, but consider delaying in case of acute HIV-related infections (generally MEC 1)			
Intrauterine contraception (IUC) Initiation	<ul style="list-style-type: none"> MEC 2 for women with asymptomatic or mild HIV disease (WHO clinical stage 1 or 2, or any WHO stage once stable on ART) MEC 3 for women with symptomatic or advanced HIV disease (WHO clinical stage 3 or 4) until stable on ART 			
	Continuation Continue in all women regardless of HIV disease status (MEC 2)			
Implants	1	2	2	1
Injectables	1	1 (MEC 2 for NET-EN)	1 (MEC 2 for NET-EN)	1
Oral contraceptives ^b	1	2	2	1

WHO: World Health Organization; MEC: Medical Eligibility Criteria; NET-EN: norethisterone enanthate; NRTIs: nucleos(t)ide reverse transcriptase inhibitors; NNRTIs: non-nucleos(t)ide reverse transcriptase inhibitors; PIs: protease inhibitors; INSTIs: integrase strand transfer inhibitors; ART: antiretroviral therapy.

^aMEC categories: 1 – a condition for which there is no restriction for the use of the method; 2 – a condition where the advantages for using the method generally outweigh the theoretical or proven risks; 3 – a condition where the theoretical or proven risks outweigh the advantages of using the method; 4 – a condition which represents an unacceptable health risk if method is used.

^bGenerally, recommendations for vaginal rings or transdermal patches parallel those for oral contraceptives.