

Contraceptive challenges in adolescents living with or at risk of HIV

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Abstract

Many adolescents living with or without HIV are sexually active and in need of continuous free access to a variety of contraceptive methods. Dual contraception, condom use together with reversible effective contraception (hormonal contraception [HC] or intrauterine device), seems to be the most effective option for female adolescents for protection from unintended pregnancy and sexually transmitted infections. When counselling on specific contraceptive choice, healthcare providers should be aware about possible interactions of some types of HC with the immune system, with possible changes in infectivity, as well as about drug interactions between mainly efavirenz and some types of progestins. Adding HC to HIV-positive status and antiretroviral therapy could have additive effects on metabolism. At the same time, the possible disadvantages of using HC in women living with HIV should be balanced against the advantages of very reliable methods of preventing unintended pregnancies. To reach and deliver a contraceptive service to more young women, it has proven effective to organise adolescent-friendly clinics and/or integrate them with HIV services. Diverse approaches, including community-based contraceptive service provision and the use of modern technologies, can complement the effort of providing contraceptive services to this target group of female adolescents living with HIV or at risk of HIV.

Keywords: adolescents, HIV, contraceptive choice, contraceptive programmes

Introduction

This review gives an update on the challenges over the last 5 years related to contraceptive use by female adolescents who are living with, or at risk for, HIV and aged between 12 and 24 years of age. About one-third of perinatally HIV-infected children worldwide have reached adolescence [1,2] and half of them are female [1]. Additionally, about one-third of all new infections in sub-Saharan Africa, the region with the highest HIV prevalence in the world, are in young women 15–24 years of age [3,4]. Antiretroviral therapy (ART) gives young people with HIV a chance to live, grow up and enjoy life, including sex. Behaviourally infected, and in smaller numbers perinatally infected, HIV-positive adolescents are sexually active [2,5,6]. Many engage in unprotected sex and experience an unintended pregnancy [7–9]. In Thailand for instance, the median age of sexual debut in perinatally HIV-infected adolescents is 15 years, and about 20% of these sexually active female adolescents became pregnant [2]. Up to 80% of pregnancies in HIV-positive adolescents are reported as unintended [10].

Effective contraception (EC) can reduce the number of unintended pregnancies, and thus improve the quality of life of young women, socially and physically. Pregnancy in HIV-positive women is in general safe; however, adolescent pregnancy is usually viewed as more risky. Additionally, perinatally HIV-infected adolescents seem to be exposed to a higher risk of disease progression and death postpartum in comparison to those who are behaviourally infected [11] as a result of the complex inter-relation of reproductive health, adherence and mental health issues [8]. EC can also reduce vertical transmission of HIV from mother to child, by reducing the number of pregnancies. It might also reduce horizontal transmission as well, as HIV-negative pregnant women might have increased risk for HIV acquisition, while HIV-positive women may have increased infectivity [12].

Delaying the start of sexual life and using dual contraception thereafter, condom use together with reversible EC, seems to be

the most effective option for female adolescents for protection from unintended pregnancy and sexually transmitted infections (STI) [13]. Here, we focus on two areas of challenge related to the use of EC. The first area is related to the best choice of reversible EC for female adolescents living with or at risk of HIV; the second to the most effective ways to deliver EC to this target group.

Challenges related to the choice of reversible EC

The use of EC, has been widely promoted in HIV-positive women in the last few years [14,15]. Adolescents, due to their young age, can only be offered reversible methods of EC. The choice of reversible EC methods is limited to hormonal contraception (HC) or intrauterine device (IUD), which could be hormonal or non-hormonal, such as the copper IUD. HC can be progestin-only or combined progestin and oestrogen, and the hormones can be delivered in various ways to the body, including pills, injection, rings, patches and implants. Depending on the frequency with which reversible EC has to be re-administered, it is divided into short-acting (most HC) and long-acting reversible contraception (LARC), including the hormonal implant and the IUD, with re-administration every 3–10 years. Being independent of adherence issues, LARC is currently recommended as first-line contraception, especially for adolescents [16].

Hormonal contraception in adolescents living with HIV

The World Health Organization (WHO) states that there are no restrictions on the use of any hormonal contraceptive method for women living with HIV or at high risk of HIV [15]. Nevertheless, there are issues to be considered when offering HC to adolescents living with HIV, or at risk for HIV infection, related to disease progression and infectivity, pharmacokinetic (PK) interactions, as well as further metabolic changes.

Infectivity and disease progression with HC

The question of HC affecting immunity and thus influencing HIV infectivity and disease progression has been broadly discussed. A number of studies have looked at the topic,

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suggesting that the use of progestin-only HC, especially depot medroxyprogesterone acetate (DMPA) injection, can lead to increased genital viral shedding in HIV-positive women, and therefore increased infectivity [17–19], as well as to an increased risk of HIV acquisition, especially in young women below 24 years of age [20–22]. Pregnancy, a naturally high-progesterone state, has also been associated with an increased risk of HIV acquisition for HIV-negative women and increased infectivity of HIV-positive women [12,20]. Oestrogens and progesterone/progestins have an effect on the structure of the vaginal epithelial wall and microbiome, and they influence the immune system [23]. Progesterone can have a suppressive effect whereas oestrogens can have the reverse. The exact mechanisms are not clearly understood; however, some underlying reasons are starting to be found. A recent study found an association between DMPA use and higher pro-inflammatory and lower anti-inflammatory protein levels [20]. The genital tract microenvironment can also impact the effects of HC on cervical immunity [20,24]. HIV-uninfected women who used progestin-only contraceptives had an increase in the frequencies of cervical CCR5+CD4+ T cells that are targets for HIV [25]. Some authors have raised the question of whether there should be complete withdrawal of DMPA [19], or rather accept the more moderate approach of the WHO, which strongly advises to always use condoms and other preventive measures [15] together with an effective HC method.

If the use of HC can affect the immune system with possible clinical implications in HIV-positive adolescents, it is important to study and gain a good understanding of the underlying causes in order to maintain the balance between effectively preventing unintended pregnancies and causing no harm in relation to HIV, and possibly other diseases.

PK interactions between HC and ART

Sex steroid hormones (ethinyl oestradiol [EE2] and progestins) and some antiretrovirals (ARVs), have common metabolic pathways, mainly via the cytochrome P450 enzyme system (CYP450) [26,27]. As a result of using both at the same time, the levels of either can be reduced with possible compromises in effectiveness, or increased with possible enhanced toxicities. In addition, the activity of drug-metabolising enzymes in adolescents is influenced by physical and sexual development, with the greatest variability in puberty [28]. However, there are no published studies in adolescents, and potential effects are extrapolated from data gained in adult women.

Currently used ARVs that interact with sex steroid hormones leading to significant changes in drug concentrations include non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine and efavirenz, as well as protease inhibitors (PIs) such as lopinavir, atazanavir, darunavir and ritonavir (Table 1). Other ARVs such as nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs) a common backbone of combined ART, the newer NNRTIs etravirine and rilpivirine [29,30], maraviroc (a CCR5 receptor agonist) [31], and integrase inhibitors [32] do not seem to have clinically significant interactions, despite their metabolic pathways. There are no data yet on the outcome of interactions between cobicistat, a CYP450 inhibitor used as a booster for integrase inhibitors, and sex steroid hormones.

A number of PK studies, as well as several case reports and observational studies, have explored the topic, trying to understand its clinical significance.

PK interactions between nevirapine, efavirenz and sex steroid hormones

Nevirapine-based ART does not seem to reduce the effectiveness of HC [33–35] in observational and PK studies, in spite of significant changes in hormonal levels [33,36]. As a result of the PK interaction, ethinyl oestradiol (EE2) levels in the combined hormonal pills used dropped significantly; however, the progestin levels (the main suppressor of ovulation) fell insignificantly [37]. Serum progesterone, a marker for ovulation, also remained consistent with anovulation. Nevirapine levels were not affected [34].

In contrast to nevirapine, efavirenz-based ART seems to reduce the effectiveness of HC, regardless of the method of hormone delivery – combined contraceptive pill, ‘emergency’ pill or implant – due to significant reduction in progestin concentrations [33,34,38,39]. Furthermore, these findings are supported by case reports of contraceptive failure of the hormonal implant, Implanon, in HIV-positive women on efavirenz-based therapy [40,41]. Efavirenz effectiveness might also have been compromised, as efavirenz levels were below the targeted therapeutic threshold in approximately 20% of the participants [34]. Some recent large cohort studies have looked at HC use, or more specifically use of the hormonal implant, from a different perspective, in women on efavirenz-based therapy [35,42]. They reported that due to the high contraceptive efficacy of the hormonal implant as a LARC, there is still a lower real-life pregnancy rate among women on efavirenz-based therapy and implant in comparison to those using short-acting methods or no method. And this is true in spite of the reduced contraceptive efficacy as a result of the drug–drug interaction. However, we consider the findings of the PK studies with efavirenz to have a higher priority. Whenever possible, for women using efavirenz-based ART, we recommend the use of another LARC method, such as the copper IUD or DMPA injection, the only hormonal contraceptive so far without demonstrated interaction with efavirenz [43]. Alternatively, a switch from efavirenz may be considered, as it seems to be the only ARV that has clinically significant interactions with sex steroid hormones. Additionally, HC might compromise the efficacy of efavirenz [34].

PK interactions between PIs and sex steroid hormones

PIs, including the most commonly used today, lopinavir/ritonavir [44,45], atazanavir/ritonavir [46–48] and darunavir/ritonavir [49],

Table 1. Antiretrovirals/booster molecules entering into drug–drug interactions with sex steroid hormones, leading to significant changes in hormonal levels and having an impact on contraceptive and antiretroviral efficacy.

ARV	Ethinyl oestradiol changes	Progestin changes	Contraceptive efficacy	ARV efficacy
Non-nucleoside reverse transcriptase inhibitors				
Nevirapine	↓	Insignificant ↓	Not decreased	Not decreased
Efavirenz	↓	Significant ↓	Decreased	Decreased
Protease inhibitors				
Lopinavir	↓	Insignificant–significant ↑	Not decreased	Not decreased
Atazanavir	↑/↓	Significant ↑	Not decreased	No data
Darunavir	↓	Insignificant ↓	Not decreased	No data
Integrase inhibitor booster				
Cobicistat	No sufficient data	No sufficient data	No sufficient data	No data

have PK interactions with sex steroid hormones and, as a result, hormone levels change significantly. Oestrogen levels increase or decrease although progestin levels (delivered through combined contraceptive pills, patch or implant) increase significantly, often by up to 100%. As discussed, progestin is the hormone contributing mainly to the contraceptive effect of HC [37]. Whenever tested, serum progesterone level, a marker for ovulation, also remained low, consistent with suppressed ovulation. PI levels do not seem to be affected significantly as a result of the PK interaction. Therefore, the studies conclude that the contraceptive effect does not seem to be decreased when administering HC with PI-based ART.

We assessed the PK interaction between EE2/desogestrel in combined oral contraceptive (COC) and lopinavir/ritonavir-based ART in female adolescents living with HIV, and we had a comparable outcome [50]. Additionally, we found high variability of hormonal levels, which warrants close monitoring.

PK interactions between DMPA and ARVs

In contrast to the concerns of DMPA use in relation to HIV infectivity, DMPA does not seem to have clinically significant interactions with any of the studied ARVs, including nevirapine, efavirenz [43] and in recently published results for lopinavir/ritonavir [51].

The simultaneous use of condoms, together with the EC, should always be promoted, regardless of PK interactions, for prevention of STIs.

Metabolic changes with HC and ART

The use of HC in the general population has been associated to different degree of unfavourable changes in carbohydrate metabolism [52–55], lipid profile [55–57], bone turnover markers reflecting bone health [58,59], and marker of inflammation and coagulation [53,54]. These metabolic markers can already be affected by HIV infection alone and/or antiretroviral therapy, or may affect the course of HIV infection. Not much is known about the cumulative effect of HIV, ART and HC on metabolism and inflammation. We found two papers on these issues: the first was an older study from Womack *et al.* comparing carbohydrate and lipid changes between women living with and without HIV infection and using HC [60]; in the second one Beksinska *et al.* point to the importance of looking into bone changes in women living with HIV and using progestin-only contraception [61]. In a recently completed assessment in female adolescents living with HIV on ART and using HC, we have confirmed the high prevalence of metabolic changes in this target group and, additionally, found further deterioration with HC in some of metabolic markers (unpublished data). There is an urgent need for additional research in this field, especially because of the tendency to start prescription of HC very early in a woman's life, and promoting its use during the reproductive age [52,53].

Copper IUD in adolescents living with HIV

In a recent study offering and assessing the uptake and continuation of use of EC by sexually active female adolescents in several locations in Thailand, we found a significant increase in the EC users from 29% at screening visit (prior to study entry) to 74% at week 48 [62]. No participant chose an IUD. The IUD is the most effective LARC method; it is inexpensive, with no or minimal primary systemic side effects, in contrast to HC. It is safe for use in HIV-positive women, as well as in nulliparous and women below 20 years of age [63]. Studies from Africa found that the insertion of an IUD did not significantly alter the prevalence of cervical shedding of HIV-1-infected cells [64], and that IUDs in

HIV-positive women did not significantly increase the incidence of pelvic inflammatory disease, in comparison to women who chose to use hormonal contraception [65]. In women who used either the evonorgestrel IUD or the copper T380A IUD, the frequencies of CCR5+CD4+ T cells in the endometrium and cervix were diminished, suggesting that susceptibility to HIV infection would not be increased with IUD [66]. However, some healthcare providers are unnecessarily hesitant in using IUDs in young women [67]. Earlier reports showed higher incidence of adverse events such as dysmenorrhoea, expulsion and impaired restoration of fertility with prolonged use of IUDs in nulliparous and young women [68,69]. More recent studies have found that an IUD is a safe and effective long-term contraceptive method for the above-discussed population [67,70]. The continuation of use is also good – adolescents were six to 12 times more likely to have discontinued any short-acting contraceptive method in comparison to an IUD 6 months after initiation [71]. The main challenges related to IUD use in adolescents (and adult women), are related to acceptance of the method by healthcare providers and by users. Secondly, in contrast to HC, which is relatively easy to administer in any setting, IUD administration needs a clean and private setting with sterile instruments, in addition to a trained healthcare provider.

Challenges related to the strategies of delivery EC

In Thailand, about 80% of Thai women use modern contraception, among whom less than 1% chose a copper IUD [72], and in a cohort of HIV-positive Thai women, no one was using an IUD [73]. However, when the copper IUD was offered to women living with HIV free of charge at the HIV clinic, 44% of eligible women started using the method and more than 90% continued using it after the 6-month follow up visit [74].

Provision of knowledge on the advantages and disadvantages of the method by a trained and motivated healthcare provider, and access to the method in a setting linked with the HIV service delivery, seemed to be important factors that helped women to decide on IUD uptake [74]. Providing knowledge, not only to potential users but also to healthcare providers [75] and partners [76], might be beneficial for increasing IUD use. This approach can be applied to all other contraceptive methods as well. Linking reproductive health services with HIV care is considered to be effective, with no negative outcomes [77]. Although many international agencies, such as WHO and UNAIDS, have advocated for strong links between the two services, this is still rarely the case in practice in resource-limited settings [77]. Some even integrate family planning services for HIV-positive women with basic general gynaecological services [78,79]. These studies conclude that all aspects of sexual and reproductive healthcare in such centres had improved since the introduction of this integrated approach.

Similarly, health facilities should provide services for adolescent females in a youth-friendly manner and integrate HIV and contraceptive services [76]. WHO also recommends dedicated and integrated youth-friendly programmes, and in coordination with the specific health system context [80]. More specifically, in their '5S' approach they discuss the importance of supportive policies, strategic information, service delivery models that are youth friendly, sustainable resources and a cross-sectoral approach. It is important to build on what already exists – modifying existing facilities and building the competencies and attitudes of existing health service providers [80]. In a recently completed project with sexually active female adolescents living with HIV in five health centres in Thailand, we provided safe sex education on EC methods and dual contraception through an adolescent-friendly educational

movie, health brochures and individual counselling [62]. Individual counselling was the most appreciated method for delivering health messages compared to the educational movie and the brochures. We further offered and assessed the uptake and continuation of use of reversible EC, including COC pills, DMPA injection, hormonal implant and IUD. All activities were carried out at the HIV clinic of the paediatric department. There was a significant increase in the EC use from screening through to the last visit at 48 weeks, from 29% to 74%. However, fewer than one-third of the participants chose a LARC method by the end of the study. No one chose an IUD.

The uptake of contraceptives can be additionally improved by building community support for providing health education and contraception to adolescents outside the formal settings [81,82], through various outlets and well-trained social/healthcare workers. A Cochrane database review demonstrated that community-based interventions can improve the uptake even of copper IUD contraception [83]. Furthermore, adolescent-friendly clinics only are unlikely to attract all adolescents [81]. Outreach to adolescents in venues where they socialise can improve their access to contraceptive information and services – on the spot or through referral [84]. Use of modern technologies and social media could be additional ways of increasing contraceptive use among adolescents [81]. The authors emphasise the importance of further research in this area, particularly designing and testing programmes on how most effectively to deliver the service, especially to the most vulnerable individuals, as well as gaining the support of the community [81]. Additionally, a cost–benefit analysis may be required to ensure the applicability and continuity of such programmes [83].

Conclusions

Many adolescents living with or without HIV are sexually active and in need of continuous free access to a variety of contraceptive methods. Dual contraception, condom use together with reversible EC, seems to be the most effective option for female adolescents for protection against unintended pregnancy and sexually transmitted infections. When counselling on specific contraceptive choice, healthcare providers should be aware about possible interaction of some types of HC with the immune system, with possible changes in infectivity, as well as about drug interactions between mainly efavirenz and some types of progestins. Adding HC to HIV-positive status and ART could have additive effects on metabolism. At the same time, the possible disadvantages of using HC in women living with HIV should be balanced against the advantages of very reliable methods of preventing unintended pregnancies. To reach and deliver contraceptive services to more young women, it proves effective to organise adolescent-friendly clinics and/or integrate with HIV services. Diverse approaches, including community-based contraceptive service provision and the use of modern technologies, can complement the effort of providing contraceptive services to this target group of female adolescents living with or at risk from HIV.

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Conflict of interest

The authors state that there are no conflicts of interest.

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