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TECHNICAL ISSUE BRIEF

DRUG INTERACTIONS BETWEEN HORMONAL CONTRACEPTIVE METHODS AND ANTI-RETROVIRAL MEDICATIONS USED TO TREAT HIV

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BACKGROUND

This brief was produced in collaboration with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Office of Population and Reproductive Health at the U.S. Agency for International Development (USAID), with technical input from FHI 360.

What is the purpose of this brief?

This brief summarizes what is known on potential drug interactions between certain hormonal contraceptive methods and certain antiretrovirals (ARVs) used to treat HIV and to discuss recommendations and programmatic implications. This issue has been highlighted recently by the publication of a retrospective chart review that suggested a higher rate of pregnancy among women using levonorgestrel-releasing contraceptive implants (Jadelle) and efavirenz-based antiretroviral therapy (ART) compared with women taking non-efavirenz-based ART regimens.¹

What is a drug interaction?

A pharmacokinetic drug interaction occurs when a drug interferes (in a positive or negative way) with another drug, resulting in higher or lower levels of either drug in the body. Such changes in drug levels could have an impact on the effectiveness or side effects of either drug.

Why is this issue important for women living with HIV who use ART and a hormonal contraceptive method?

Certain hormonal contraceptive methods and certain ARVs have the potential to interact with each other and, in theory, to lead to decreases in efficacy of either medication or to increased side effects or toxicity. Any potential decrease in efficacy of a hormonal contraceptive method could increase risk of unintended pregnancy and associated negative health outcomes; any potential decrease in efficacy of ART could increase risk of treatment failure, development of viral resistance, and potential transmission to HIV-negative sex partners and infants. Increases in side effects can have an impact on the health and quality of life of the person living with HIV and may affect treatment adherence. Certain ARVs for which some concern about potential drug interaction exists, such as efavirenz, are becoming even more widely used following recent updates to WHO guidance on ART use.²

Who should read this brief?

- National policymakers responsible for HIV and/or family planning programming

- U.S. Government family planning and HIV program managers at headquarters and in the field
- HIV and family planning implementing partners, practitioners, researchers, and professional societies

TYPES OF HORMONAL CONTRACEPTIVES AND ART MEDICATIONS

What are some common hormonal contraceptive methods?

Common hormonal contraceptive methods include combined (estrogen/progestin) oral contraceptive pills (COCs, e.g., Microgynon*), progestin-only pills (POPs, e.g., Microlut*), injections (e.g., depot medroxyprogesterone acetate [DMPA] or Net-En), implants containing either levonorgestrel (e.g., Jadelle*) or etonogestrel (e.g., Implanon*), and levonorgestrel-releasing intrauterine devices (e.g., Mirena*). Emergency contraceptive pills (ECPs) may contain levonorgestrel (LNG ECPs), ulipristal acetate (UPA ECPs), or combined estrogen and progestin (Yuzpe regimen).

What types of ARVs exist?

Five basic classes of ARV drugs exist: (1) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs); (2) non-nucleoside reverse transcriptase inhibitors (NNRTIs); (3) protease inhibitors (PIs); (4) entry inhibitors; and (5) integrase inhibitors. Each class contains several different individual medications. In addition to individual medications, "fixed dose combination" drugs also exist; these combine two or more medications. A complete list of ARV medications approved by the U.S. Food and Drug Administration (FDA) is available at <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>.

Which ART regimens are commonly used?

The World Health Organization recommends that a first-line ART regimen for adults and adolescents should contain an NNRTI plus two NRTIs. The current recommended first-line regimen is efavirenz (EFV), tenofovir (TDF), and either lamivudine (3TC) or emtricitabine (FTC), provided in a fixed-dose combination.² If this regimen

* Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Government. In addition, this is not an exhaustive list of hormonal contraceptive methods but represents some commonly used methods in U.S. Government-supported foreign assistance programs.

is contraindicated or unavailable, other medications such as zidovudine (AZT) or nevirapine (NVP) may be incorporated (see WHO guidance for complete recommendations: <http://www.who.int/hiv/pub/guidelines/arv2013/download/en/>).² For adults or adolescents with treatment failure on a first-line regimen, WHO recommends that second-line regimens consisting of two NRTIs plus a ritonavir-boosted protease inhibitor (PI) be used, (e.g., ritonavir-boosted atazanavir [ATV/r] or ritonavir-boosted lopinavir [LPV/r]).²

Why does uncertainty exist around potential drug interactions between certain hormonal contraceptive methods and certain ARVs?

Identifying and predicting the impact of drug interactions can be difficult. Pharmacokinetic studies can evaluate changes in blood levels of contraceptive hormones and ARVs with simultaneous use, as compared to use of either drug alone. However, the clinical significance (e.g., actual increase in pregnancy risk due to decreased hormonal levels) can be difficult to determine without prospective studies that assess pregnancy (or less conclusively, ovulation) among HIV-positive women taking ART. For example, long-acting methods like implants are highly effective and require little action by the user, so slight reductions in contraceptive efficacy may not make these methods less effective than other, more user-dependent contraceptive methods like COCs (though contraceptive implant users should still be informed about such drug interactions). To assess ART efficacy, changes in ARV levels due to drug interactions with hormonal contraceptives can be compared to target levels; however, clinical studies such as those evaluating impacts on CD4 counts, viral load, drug resistance, and progression to AIDS or death are more informative. Currently, few pharmacokinetic studies and even fewer clinical studies have been published, examining effects of combinations of a hormonal contraceptive method and ART.

EVIDENCE**

ARVs most likely to interact with certain hormonal contraceptive methods (particularly COCs and possibly contraceptive implants) include some NNRTIs (particularly efavirenz), some PIs (particularly ritonavir-boosted PIs), and some integrase inhibitors (e.g., cobicistat-boosted elvitegravir). On the other hand, neither NRTIs nor some integrase inhibitors (e.g., raltegravir) are expected to have significant interactions with hormonal contraceptive methods studied to date.³⁻⁵

The table provides a summary of results from studies conducted to examine if specific ARVs affect the efficacy of specific hormonal contraceptive methods. Readers should also refer to the 2014 WHO guidance statement on hormonal contraception and HIV for complete information on all hormonal contraceptive methods (including contraceptive patches, rings, and estrogen/progestin combined contraceptive injections) and possible interactions with ARVs (http://www.who.int/reproductivehealth/publications/family_planning/HC_and_HIV_2014/en/).

Do specific ARVs reduce the efficacy of hormonal contraceptive methods?

Hormonal contraceptive method	Evidence
Combined oral contraceptives (COCs)	Efavirenz reduces blood progestin levels of COCs, ^{6,7} but no efficacy data are available, while other NNRTIs (e.g., nevirapine, etravirine, rilpivirine) do not appear to affect levels or efficacy. ^{5,8} Some PIs, particularly ritonavir boosted-PIs, also decrease progestin levels (which could potentially increase pregnancy risk) in COC users. ^{3,5} Conversely, cobicistat-boosted elvitegravir lowered ethinyl estradiol levels but increased norelgestromin levels (thus contraceptive efficacy is likely maintained).
Progestin-only pills (POPs)	Based on limited data, progestin levels with POPs do not appear to be reduced by some PIs ⁹ ; but no efficacy data are available; and data on POP levels when used with other ARVs (such as efavirenz or nevirapine) are not available. ⁵
Progestin-only injectables (e.g., DMPA or Net-En)	Levels of DMPA do not appear to be reduced by ARVs (including efavirenz, zidovudine, lamivudine, nevirapine, and nelfinavir). ¹⁰⁻¹² Studies on Net-En when used with ART are not available. ⁵
Contraceptive implants	A retrospective chart review suggests that efavirenz may decrease the efficacy of levonorgestrel implants (e.g., Jadelle), compared to use by women living with HIV not using efavirenz, though additional data are needed. ^{1,5} For the 16 women who became pregnant in this study, the mean time elapsed between implant insertion and pregnancy was 16.4 months. Several case reports and a pharmacokinetic study suggest that efavirenz (but not ritonavir-boosted lopinavir) ¹³ may decrease the efficacy of etonogestrel implants (e.g., Implanon), though additional data are needed. ^{5,14} In a Brazilian study, 79 women living with HIV received etonogestrel implants and were followed every 6 months for 3 years. Over the course of the study, between 60 percent and 71 percent of women were receiving various ART regimens; no pregnancies were reported. ¹⁴
Levonorgestrel-releasing intra-uterine devices (IUDs) (e.g., Mirena)	Limited evidence suggests that efficacy of the levonorgestrel-releasing IUD is unlikely to be affected by ART. ^{15,16}
Emergency contraceptive pills (ECPs)	Limited evidence suggests that levonorgestrel levels are significantly reduced among women using LNG ECPs and efavirenz, but no efficacy data are available. ¹⁷ Data for other types of ECPs (UPA ECPs or Yuzpe regimen) or other ARVs are not available.

Do hormonal contraceptive methods reduce the efficacy of ART?

While data are limited, ART efficacy does not appear to be impacted by use of hormonal contraceptive methods.^{5,15,18-20}

When hormonal contraceptive methods and ART are taken together, do side effects (from either hormonal contraception or ART) worsen?

Currently, very little data are available on this question. Pharmacokinetic data suggest that COCs, DMPA, and implants are unlikely to have an impact on ART toxicity.⁵

** More detailed information and references to specific studies are available in a systematic review conducted by Dr. Kavita Nanda of FHI 360 for the 2014 WHO technical consultation on the Medical Eligibility Criteria for Contraceptive Use. Please contact KNanda@fhi360.org for more information.

RECOMMENDATIONS

What are the medical eligibility criteria for contraceptive use (MEC)?

WHO produces evidence-based guidance called the *Medical eligibility criteria for contraceptive use*, often referred to as the MEC. Among many other issues, the MEC includes guidance on use of various hormonal contraceptive methods for women on ART.

Where can I find the most recent WHO medical eligibility criteria for use of hormonal contraception by women on ART?

WHO issued updated recommendations on use of hormonal contraceptives and ART in July 2014. The full WHO guidance statement including these recommendations and supporting annexes can be found here: http://www.who.int/reproductivehealth/publications/family_planning/HC_and_HIV_2014/en/.

Briefly, the guidance suggests that women taking ART are eligible for all hormonal contraceptive methods, but special consideration may be necessary for women using some hormonal methods (i.e., combined hormonal methods, progestogen-only pills, NET-EN or LNG and ETG implants) with certain ART regimens (specifically those containing efavirenz or nevirapine, as well as some protease inhibitors). These specific combinations are ranked as a MEC Category 2; the advantages of using the method generally outweigh the theoretical or proven risks (in this case, of potentially reduced contraceptive efficacy).

PROGRAMMATIC IMPLICATIONS

The U.S. Government remains committed to ensuring that all women have access to a full range of voluntary family planning methods and encourages sites to offer a comprehensive array of contraceptive methods within all HIV services. Several points should be considered when counseling HIV-infected women on ART about their contraceptive options.

- U.S. Government teams are encouraged to review the 2014 WHO recommendations on use of hormonal contraception for women using ART and to coordinate with Ministries of Health and implementing partners to strengthen voluntary and informed choice and comprehensive counseling to provide information on potential drug interactions for women using both ART and a hormonal contraceptive method.
- U.S. Government teams are encouraged to ensure comprehensive counseling on and access to a full range of contraceptive methods appropriate for people living with HIV, including enhanced counseling to help clients using ART assess risks for potential drug interactions and messages on the importance of dual method use.
- The U.S. Government continues to support access to a wide range of contraceptive methods, including hormonal contraception. Our guidance for procurement of hormonal contraceptive methods remains unchanged. We will notify USAID missions if any changes in hormonal contraceptive labeling occur, so clinical and counseling services can be updated accordingly.

- **Significant pharmacokinetic interactions occur between COCs and certain ARVs, particularly efavirenz, ritonavir-boosted protease inhibitors, and elvitegravir/cobicistat.** HIV-infected women using COCs and any of these ARVs should be informed about the possibility of decreased contraceptive efficacy (and therefore, increased risk of unintended pregnancy), counseled on dual contraceptive method use including correct and consistent use of male or female condoms (to provide back-up pregnancy protection in case of COC failure, in addition to reducing the risk of HIV transmission), and as always, informed about alternative contraceptive options. COCs are not expected to interact with NRTIs and some NNRTIs (e.g., etravirine and rilpivirine), or the integrase inhibitor raltegravir.
- **DMPA appears to be an effective contraceptive option for women using ART, including those on efavirenz- or protease inhibitor-based regimens, while more data are needed to assess for interactions between Net-En and ART.** While concerns have been raised about potential increased risk of HIV transmission from ART-naïve HIV-infected women using progestin-only injectables to HIV-uninfected male sexual partners,²¹ a recent study among women adherent to ART did not find significantly increased genital detection of HIV-1 RNA among women on DMPA compared to those not on a method of hormonal contraception.²²
- **The contraceptive efficacy of the levonorgestrel and etonogestrel implants may potentially be reduced among HIV-infected women on efavirenz-based antiretroviral regimens, though more definitive data are needed.** Implant users experience a normal decline in blood levels of contraceptive hormones over time; any additional decline in blood levels due to a drug interaction could be of concern, particularly in later years of use. However, even if drug interactions lead to slightly decreased efficacy for implants, overall efficacy might still be reasonably high compared to other contraceptive choices, such as COCs (which have higher failure rates than implants in general); more studies are needed. HIV-infected women using levonorgestrel implants or etonogestrel implants and efavirenz-based ART should be informed about the possibility of decreased contraceptive efficacy, counseled on dual contraceptive method use including correct and consistent use of male or female condoms (to provide back-up pregnancy protection in case of implant failure, in addition to reducing the risk of onward HIV transmission), and, as always, informed about alternative contraceptive options. If a woman living with HIV and using ART is informed of the possibility of decreased contraceptive efficacy but wishes to continue using the implant, removal is not needed. If she does wish to discontinue using the implant, help her to choose another method, if desired.
- **Levonorgestrel-releasing IUDs are not expected to have significant interactions with ART.** Levonorgestrel-releasing IUDs (or non-hormonal, copper-releasing IUDs – an additional contraceptive option that would not be affected by pharmacokinetic drug interactions) can be inserted or continued in women who do not have severe or advanced HIV clinical disease. Women with severe or advanced HIV clinical disease who already have an IUD do not need to have it removed but should be closely monitored for pelvic infection.

LOOKING FORWARD

- The U.S. Government supports research to improve knowledge of drug interactions between hormonal contraceptive methods and ARTs.
- Descriptions of ongoing studies assessing drug interactions can be found at www.clinicaltrials.gov.
- The Office of the U.S. Global AIDS Coordinator and USAID's Office of Population and Reproductive Health will keep you informed of any new developments in this area that may have an impact on your programming.

USEFUL RESOURCES

- See WHO Hormonal contraceptive methods for women at high risk of HIV and living with HIV: 2014 guidance statement: http://www.who.int/reproductivehealth/publications/family_planning/HC_and_HIV_2014/en/.
- For more information on the contents of this brief, contact Dr. Heather Watts at wattsdh@state.gov; Ms. Tabitha Sripipatana at tsripipatana@usaid.gov; or Dr. Amy Medley at igm8@cdc.gov.

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