



2016 UPDATE

Decreased Contraceptive Efficacy Reported in Women Living with HIV Who Use Implants While Taking the Antiretroviral Efavirenz

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Background

In October 2014, the U.S. Agency for International Development (USAID), U.S. Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services (HHS), and the Office of the Global AIDS Coordinator (OGAC) developed the technical brief, "Drug Interactions between Hormonal Contraceptive Methods and Antiretroviral Medications (ARVs) to Treat HIV." This earlier brief summarized the evidence of potential drug interactions between certain hormonal contraceptive methods and ARVs used to treat HIV and discussed recommendations and programmatic implications. For women living with HIV, drug interactions between hormonal contraceptives and ARVs could potentially lead to decreased efficacy of either medication or to increased side effects or toxicity. While data are limited, the efficacy of ARVs to treat HIV infection does not appear to be impacted by use of hormonal contraceptive methods.¹⁻⁴ However, evidence suggests certain ARVs reduce the effectiveness of some hormonal contraceptives to prevent pregnancy.⁵ Any potential decrease in effectiveness of a hormonal contraceptive method could increase the risk of unintended pregnancy and associated negative health outcomes including maternal mortality.

This technical update reviews recent evidence about the drug-drug interaction between the ARV efavirenz and the hormones found in contraceptive implants. This update also discusses the related programmatic implications of this new evidence. Efavirenz containing antiretroviral treatment (ART) is recommended by the World Health Organization (WHO) as part of first-line treatment, and millions of units of this medication are being provided annually in sub-Saharan Africa.

Hormonal contraceptive implants are very effective forms of long-acting reversible contraceptives (LARCs) and are increasingly available in many sub-Saharan African countries. Up to 14 percent of HIV-positive women in the region currently use implants and

that percentage continues to increase.⁶ There are distinctly different types of hormonal contraceptive implants available:

- Etonogestrel-releasing one rod implant (Implanon)
- Levonorgestrel-releasing two rod implant (Jadelle)

These implants differ in their hormonal formulations, probable mechanisms of action to prevent pregnancy, and the duration of their effectiveness to prevent pregnancy (3 versus 5 years, respectively). Expected failure rate is less than 1 percent for both implants.⁷

Evidence to date

Emerging evidence indicates that efavirenz reduces the blood levels of certain progestins by up to 50 percent for women using implants.⁸⁻¹² However, prospective data on pregnancy are quite limited.

Jadelle

In Swaziland and Uganda, recent studies have shown a reduced blood level of levonorgestrel and a higher than expected contraceptive failure rate among women using both an efavirenz-containing ART regimen and Jadelle.^{12,13} In Swaziland, a retrospective chart review found 15 pregnancies out of 121 women on efavirenz (12.4 percent), compared to no reported pregnancies for 208 women on nevirapine and 18 for women on lopinavir/ritonavir-containing ART.¹³ These pregnancies occurred on average 16 months after implant insertion. In Uganda, a small prospective study found a 15 percent contraceptive failure rate (3 pregnancies out of 20 women) among HIV-infected women on efavirenz-containing ART within 1 year of receiving Jadelle.¹² A recent unpublished study presented at the Conference on Retroviruses and Opportunistic Infections also found a 15 percent contraceptive failure rate (9 pregnancies out of 62 women) in Ugandan women using both efavirenz and Jadelle.¹⁴ Though the numbers of women in these studies are very small, this rate is higher than the expected less than 1 percent failure rate.

Implanon

The data for Implanon is limited but more reassuring. In a Brazilian study, 79 women living with HIV received Implanon 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 (25 women were using ARVs in the same class as efavirenz, and it is unclear how many were using efavirenz). No pregnancies were reported in this cohort.¹⁵ A

This technical update addresses increased pregnancy risk due to drug interactions between hormonal contraceptive implants and antiretroviral medications in HIV-positive women. For more information about the potential increased risk of HIV acquisition for HIV-negative women using hormonal contraception, please refer to the following site:

<https://www.usaid.gov/sites/default/files/documents/1864/HC-HIV-Brief-Update.pdf>

small study of 45 HIV-positive women using etonogestrel implants and on ART found that women on efavirenz-containing ART had a significant reduction in serum levels of etonogestrel, therefore, potentially interfering with the effectiveness of the implant.¹⁰

Compared to other methods

More pregnancies are seen than expected among women using both efavirenz and Jadelle. However, it is important to consider how implants perform in comparison to other contraceptive methods. A retrospective analysis was conducted of a longitudinal cohort of approximately 24,000 HIV-positive women in Kenya who were using different ART regimens and different contraceptive methods (including injectables [Depot medroxyprogesterone acetate or DMPA], Jadelle, and Implanon). Among this large cohort, there was an overall low rate of pregnancy among all women using implants (3.0 [95 percent CI, 2.3-3.6] per 100 person-years). Over the course of 3 years, women using efavirenz-based ART and implants had a lower incident pregnancy rate compared to women using other contraceptive methods such as pills or injectables. Only women using intra-uterine devices (IUDs) or permanent methods had a lower incident pregnancy rate. For example for women on efavirenz regimens, pregnancy rates were lower in Implanon (5.5 [95 percent CI 2.5-8.4] per 100 person-years) and Jadelle (7.1 [95 percent CI, 1.5-12.7] per 100 person-years) users when compared to DMPA users (9.4 [95 percent CI, 7.3-11.5] per 100 person-years), presumably due to a higher discontinuation rate among DMPA users.⁶

In a prospective cohort study of more than 5,153 HIV-positive women (843 on ART) from 7 different countries, implants were found to be the most effective contraceptive for women on any form of ART when compared to other methods including DMPA and oral contraceptives.¹⁶ However, all hormonal methods were shown to be less effective among efavirenz users, but this may be due to the small sample of women on efavirenz-containing ART in this study.

In conclusion

Four studies, specifically assessing pregnancy, show that HIV-positive women using both implants and efavirenz experience contraceptive failure at a rate of approximately 4 percent to 15 percent compared to expected failure rate of less than 1 percent.^{6,12,13,16}

The evidence to date for ARV-associated contraceptive failure leading to pregnancy has only been linked to drug interactions between efavirenz and the levonorgestrel-releasing Jadelle implant.^{12,13} However, decreased blood levels of hormone with Implanon use remains a concern and requires further monitoring. Currently, there is no evidence linking contraceptive method failure rates with non-efavirenz-containing ART regimens. There are data on other ARVs including nevirapine and lopinavir/ritonavir that are reassuring, but additional data are needed for other regimens.

Take home message

Despite an apparent decrease in contraceptive efficacy among women living with HIV using implants and an efavirenz-containing ART regimen, the effectiveness remains very high, especially in comparison with other shorter-acting hormonal methods. Data are still needed to support strategies for optimizing the effectiveness of contraceptive implants, including duration of effectiveness, when used with efavirenz-containing ART regimens.

What should USAID programs consider?

Women and couples have the right to make a voluntary informed decision about their contraceptive and reproductive health options, including women living with HIV who might wish to choose implants after weighing the risks and benefits of available methods.

- In support of the point above, use of implants by HIV-positive women who are also using certain ART regimens (specifically those containing efavirenz or nevirapine, as well as some protease inhibitors) is classified by the WHO medical eligibility criteria (MEC) guidance as category 2: the advantage of using the method generally outweighs the theoretical or proven risks (in this case, of potentially reduced contraceptive efficacy).⁵ USAID also does not endorse any changes to clinical guidance for the provision of implants; i.e., insertion of extra rods.
- Every effort should be made to ensure that women and couples have access to a variety of contraceptive methods and are able to select the method that best fits their individual needs and circumstances. Accurate and comprehensive information including counseling should be used to inform clients about the risks, benefits, and effectiveness of all available methods. Women living with HIV on efavirenz-containing regimens should be informed about the possibility of decreased contraceptive effectiveness and counseled on dual contraceptive method use, including correct and consistent use of male or female condoms.
- Providers must be trained on potential interactions and counseling approaches. Integrating family planning services into all HIV services (PMTCT, ART, Care and Support, and Prevention) provides important opportunities for providers to reach women and their partners with information about how their medications may interact.

What are some of the efforts that USAID is making in this area?

- USAID continues to support and monitor continuing research on the potential drug interactions between implants (both levonorgestrel-releasing and etonogestrel-releasing) and efavirenz that could result in unintended pregnancy.
- By sharing updated technical information with partners, USAID is striving to ensure that information on hormonal contraception and HIV is included in HIV and family planning guidance, service delivery protocols, training curricula, and counseling materials and is stressing the importance of key messages during counseling interactions.
- USAID supports integrating voluntary family planning services into all HIV services, including prevention and care and treatment platforms, because these platforms provide important opportunities for providers to reach women and their partners with information about how their medications may interact. The drug-drug interaction issue highlights the need for comprehensive care for HIV-positive women, who should receive tailored counseling messages that are relevant for their life situation.

Further resources

[WHO Medical Eligibility for Contraceptive Use Guidance](#)

[Drug Interactions between Hormonal Contraceptive Methods and Antiretroviral Medications \(ARVs\) to Treat HIV](#)

[WHO Hormonal Contraceptive Methods for Women at High Risk of HIV and Living with HIV: 2014 Guidance Statement](#)

Please send your questions/requests to HCHIVmailist@usaid.gov.

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