



## *Hormonal Contraception for HIV Positive Women*

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*Barrier methods such as condoms and diaphragms are the most commonly used forms of birth control among HIV positive women. Sterilization is the second most popular method and hormonal contraception is the third. Hormonal contraceptives, when used correctly and consistently, are highly effective in preventing unintended pregnancy and are also useful for treating health conditions such as painful menstruation.*

Despite their effectiveness and potential benefits beyond contraception, research indicates that HIV positive women use hormonal contraceptives less frequently than HIV negative women. Researchers estimate that in 2002, about 20% of HIV positive women used hormonal methods, compared with approximately 35% of HIV negative women. Usage rates vary widely, however, according to age, race/ethnicity, economic status, and other characteristics.

For all women, many factors must be considered in order to select the right type of contraception. A woman and her clinician should discuss the effectiveness, cost, ease of use, and side effects of various methods.

For HIV positive women, additional factors should be considered—some obvious, others less so—including preventing transmission of HIV and other sexually transmitted infections, interactions with antiretroviral drugs, risk of cardiovascular and other complications in the context of HIV and its treatment, and the desire to become pregnant in the future.

This article will describe the different types of available hormonal contraception and outline the facts every woman living with HIV should know when considering their use.

### *The Range of Hormonal Contraceptives*

In the United States, almost half of all pregnancies are unintended. Hormonal contraceptives containing estrogens (typically ethinyl estradiol), progestins (compounds similar to natural progesterone, e.g., norethindrone), or a combination of both are among the most effective methods for preventing unplanned pregnancy.

Hormonal contraceptives work by a variety of mecha-

nisms. Combination estrogen/progestin methods prevent ovulation (release of a mature egg) by interfering with triggering hormones produced by the hypothalamus and pituitary in the brain. Progestins suppress ovulation, impair the movement of sperm by thickening cervical mucous, and cause changes to the uterine lining that potentially prevent implantation of a fertilized egg.

Oral contraceptive pills (OCPs) are the most familiar example of hormonal contraceptives. OCPs have been one of the most popular forms of birth control since the early 1980s and are the type of hormonal contraception most commonly used by women between the ages of 15 and 44 in the United States. Several brands of estrogen/progestin combination pills and progestin-only pills are currently on the market.

Some hormonal contraceptives are injected or implanted in the body. Medroxyprogesterone depot injections (Depo-Provera) are administered every three months, while other injectables are given every one or two months. Contraceptive implants are inserted under the skin and slowly release progestins over a longer period. Implanon, which works for three years, was approved by the U.S. Food and Drug Administration (FDA) in 2006. Levonorgestrel implants (Norplant or Jadelle) are no longer available in the United States but are still used in resource-limited countries.

Other examples of hormonal contraceptives include the combination estrogen/progestin contraceptive patch (Ortho-Evra), a hormone-releasing contraceptive ring worn inside the vagina (NuvaRing), and intrauterine devices (IUDs) that gradually release hormones inside the uterus.

Finally, emergency contraception—commonly known as

the “morning-after pill”—can prevent pregnancy when taken within 72 (and possibly up to 120) hours after unprotected intercourse. Plan B contains levonorgestrel; higher doses of some standard oral contraceptive pills can also be used on an emergency basis, if indicated by the woman’s clinician.

### *Contraceptive Use by Women with HIV*

Women with HIV tend to use different forms of contraception than HIV negative women. In an analysis conducted within the Women’s Interagency HIV Study (WIHS), HIV positive women were less likely to use oral contraceptives, intrauterine devices, and the “rhythm method” (monitoring the menstrual cycle and avoiding sex when the likelihood of conception is greatest). Conversely, they were more likely to use male condoms for birth control, which also prevents transmission of HIV to their partners.

The proportion of HIV positive women using hormonal contraception has remained fairly stable between 16% and 21% from 1994 through 2002. Over time, there appears to be an increasing trend of HIV positive women using injectable progestin methods such as depot medroxyprogesterone or long-term implants.

### *Keeping HIV Positive Women Safe*

Safety concerns around hormonal contraception fall into three broad areas: HIV disease progression, adverse side effects, and preventing infection.

#### *HIV Disease Progression*

Some researchers are concerned that using hormonal contraception could increase the risk of progression of HIV disease. These fears are partially based on theories about HIV’s genes and the way hormones can regulate them, for example promoting faster viral replication. There have also been some studies suggesting that the presence of

extra progesterone could make HIV disease progress more rapidly in animals.

In contrast to animal studies, however, human studies have found that varying levels of female hormones that occur naturally during the menstrual cycle or pregnancy do not appear to accelerate disease progression or increase plasma HIV viral load.

Only a few studies have looked specifically at hormonal contraception and HIV disease progression in women. All of these were observational studies, not randomized controlled trials (considered the “gold standard” for biomedical testing). This research has produced conflicting data, and it is still not clear whether using hormonal contraceptive methods promotes more rapid progression.

Two studies analyzing a cohort of Kenyan women found that hormonal contraception use at the time of HIV infection was associated with a higher HIV viral load “set point,” a relatively stable level of virus in the body reached within months after infection. This finding was of interest because a higher viral set point has been linked to faster disease progression. However, two other studies—one looking at the WIHS cohort and another in Kenya—found no relationship between hormonal contraception and changes in viral load over time, and another study set in Uganda found no link between hormonal contraception and faster disease progression.

#### *Cardiovascular Disease and Cancer*

The second area of concern is whether HIV positive women are more susceptible to side effects or complications related to hormonal contraceptive use.

Research in HIV negative women has demonstrated an association between hormonal contraceptives and cardiovascular events, including myocardial infarction (heart attack), ischemic stroke, and pulmonary or deep vein thrombosis (blood clots). The increased risk was greatest with older oral contraceptive pills that

contained high hormone doses, and appears mainly attributable to estrogen in combination products rather than those that include only progestins.

This increase in cardiovascular problems is most pronounced in women with other risk factors, including abnormal blood lipid levels, diabetes, and smoking. HIV infection and its treatment have been linked to higher cardiovascular risk—some protease inhibitors, for example, can elevate blood cholesterol and glucose levels—raising the question of whether positive women might be particularly susceptible to the adverse effects of hormonal contraceptives.

Cancer presents a similar issue. While decades of research have produced conflicting findings, there is evidence that certain combinations of contraceptive hormones may slightly increase the risk of breast cancer, while lowering the chances of developing ovarian or endometrial cancer. Recent research has found that HIV positive people have a higher rate of cancer overall than HIV negative people, but there appears to be little or no difference in the risk for these specific types of cancer.

Further studies are needed to clarify the link between hormonal contraception and cardiovascular outcomes and cancer in women with HIV. In the meantime, women and their providers should consider the full range of risk factors when choosing a contraceptive method.

### *Preventing Disease Transmission*

Another concern for positive women—and one that may come to mind immediately—is whether using hormonal contraception, particularly in the absence of barrier methods, might increase the risk of transmitting HIV to their sexual partners.

Studying HIV transmission directly is very difficult. Instead, researchers typically look at biological markers that could be related to HIV transmission, such as levels of HIV in the genital tract or the number of HIV-infected cells be-

ing shed from the cervix (the neck of the uterus, located at the top of the vagina).

The idea behind examining these markers is that when more copies of HIV or infected cells are present in the female genital tract during sex, there is a greater risk that the virus will enter an HIV negative partner's body and cause infection.

Like studies of their potential effect on HIV disease progression, the few available studies looking at hormonal contraceptives and HIV transmission have produced conflicting results. A study of the WIHS cohort found an increased number of HIV-infected cells shed from the cervix in women using hormonal contraception, but no increase in genital virus levels. Another study, looking at women in Louisiana, found no relationship between hormonal methods and increased shedding of HIV in the genital tract.

As with disease progression, further studies are needed to fully understand the effect—if there is one—of hormonal contraception on HIV transmission. A growing body of evidence indicates that people who maintain a consistently undetectable viral load while on effective antiretroviral therapy have a low likelihood of transmitting the virus, but the risk is not eliminated (see “Is HIV Treatment HIV Prevention?” in the Summer/Fall 2009 issue of *BETA*). For this reason, HIV positive women are often encouraged to use condoms along with hormonal contraception to provide the greatest protection.

Adding condoms is potentially beneficial for positive women as well as their partners. If a woman's partner also has HIV, this can prevent superinfection with a new viral strain that might be more aggressive or drug resistant. Barrier methods also offer at least partial protection against other sexually transmitted infections, including syphilis, herpes, and human papillomavirus (the cause of cervical cancer).

### *Making Sure the Drugs Work*

For HIV positive women taking antiretroviral therapy, drug interactions are

always a concern. Many antiretroviral medications, especially non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), affect how the body metabolizes other drugs, including hormonal contraceptives.

Many types of drugs, including antiretrovirals and hormones, are processed by enzymes in the liver known as the CYP450 system. If a drug induces (speeds up) the action of these enzymes, they can process other drugs too rapidly, leading to low levels that are not effective. Conversely, if a drug inhibits (slows down) these enzymes, levels of other drugs can rise, potentially causing worse side effects or toxicities.

While hormonal contraceptives generally do not affect levels of antiretroviral drugs in the body, antiretrovirals may alter levels of hormonal contraceptives. Unfortunately, however, there is no simple rule about how specific antiretroviral classes will affect hormone levels.

Within the NNRTI class, most studies find that efavirenz (Sustiva) increases blood levels of ethinyl estradiol, the type of estrogen most often used in combination birth control pills; this also appears to be the case for etravirine (Intelence), though this newer drug has not been studied as extensively. Nevirapine (Viramune), in contrast, can lower estrogen levels. PIs typically reduce levels of ethinyl estradiol and norethindrone (a common oral progestin), but some studies have seen the opposite effect. Most research indicates that antiretroviral drugs have little or no effect on injected progestins like depo-medroxyprogesterone.

Pharmacokinetic studies, which examine how the body absorbs and processes drugs, use several different measurements to determine changes in drug levels due to interactions. One of the more common parameters is area under the curve (AUC), a measure of the body's overall exposure to a drug between two doses. When antiretrovirals and hormonal contraceptive agents are combined, drug interactions

may change the AUC of the hormonal contraceptives.

### *Non-Nucleoside Reverse Transcriptase Inhibitors*

*Efavirenz (Sustiva)*: One study found that adding 400 mg efavirenz to 50 mcg ethinyl estradiol daily resulted in a 37% higher AUC of ethinyl estradiol. (The medication doses used in this study were unusual, as most individuals who include efavirenz in their antiretroviral regimen take 600 mg daily; also, 50 mcg ethinyl estradiol is an older dose which is seldom used anymore.) Another study found no drug interactions when efavirenz was used with depo-medroxyprogesterone.

Another study examined the effect of 600 mg efavirenz on the pharmacokinetics of levonorgestrel (0.75 mg), and found that the antiretroviral drug significantly reduced blood levels of the emergency contraceptive. The study authors noted that, although the minimum effective dose of levonorgestrel is unknown, higher doses may be required for women taking efavirenz.

*Etravirine (Intelence)*: The second-generation NNRTI etravirine was studied in combination with 35 mcg ethinyl estradiol plus 1 mg norethindrone daily. A twice-daily dosage of 200 mg etravirine caused ethinyl estradiol AUC to increase by 22%.

*Nevirapine (Viramune)*: Twice-daily nevirapine doses of 200 mg, when administered with a daily combination oral contraceptive containing 35 mcg ethinyl estradiol plus 1 mg norethindrone, were shown to decrease ethinyl estradiol AUC by 22% and norethindrone AUC by 18%. Nevirapine appeared to have no effect on depo-medroxyprogesterone.

These studies suggest that it may be safe and effective to use efavirenz or etravirine with most oral hormonal contraceptives, but women and their clinicians should watch for side effects that might be related to increased estrogen levels, such as breast tenderness or vaginal bleeding outside of

menstrual periods. Women who are taking efavirenz and are considering using the emergency contraceptive Plan B should also consult their clinician about the correct dose.

Using oral contraceptive pills while taking nevirapine, on the other hand, may result in the contraceptive drug being less effective, potentially increasing the risk of unintended pregnancy. Depo-medroxyprogesterone appears safe when used in combination with NNRTIs. There is little information about drug interactions between the less widely used NNRTI delavirdine (Rescriptor) and hormonal contraceptives.

### Protease Inhibitors

*Atazanavir (Reyataz)*: A daily dose of 400 mg atazanavir was studied with a daily tricyclic oral contraceptive pill containing 35 mcg ethinyl estradiol plus 0.5, 0.75, or 1 mg norethindrone. Ethinyl estradiol AUC increased by 48% and norethindrone AUC increased by 110%.

*Darunavir/ritonavir (boosted Prezista)*. A 600-mg dose of darunavir taken with a 100-mg boosting dose of ritonavir twice daily lowered the AUC of ethinyl estradiol by 44% and the AUC of norethindrone by 14% when administered with a daily contraceptive containing 35 mcg ethinyl estradiol plus 1 mg norethindrone.

*Fosamprenavir (Lexiva)*: There are no formal drug interaction studies of fosamprenavir with hormonal contraceptives. However, fosamprenavir is a prodrug that is metabolized to amprenavir (Agenerase; withdrawn from the market in 2007). Amprenavir, used at its non-ritonavir-boosted dose of 1,200 mg twice daily, lowered ethinyl estradiol AUC by 29% when administered with 35 mcg ethinyl estradiol plus 1 mg norethindrone daily.

*Indinavir (Crixivan)*: When combined with 35 mcg ethinyl estradiol plus 1 mg norethindrone daily and used at a dose of 800 mg every eight hours, indinavir increased the AUC of ethinyl estradiol by 26% and norethindrone by 22%.

*Lopinavir/ritonavir (Kaletra)*: Lopinavir/ritonavir taken at a dose of 400/100 mg twice daily lowered ethinyl estradiol AUC by 42% and norethindrone AUC by 17% when combined with 35 mcg ethinyl estradiol plus 1 mg norethindrone daily.

*Nelfinavir (Viracept)*: A 750-mg dose of nelfinavir taken every six hours was studied in combination with 35 mcg ethinyl estradiol plus 0.4 mg norethindrone daily. The AUC of ethinyl estradiol decreased by 47% and norethindrone AUC decreased by 18%. (Doses of nelfinavir used in this study were unusually high; typical doses are 750 mg three times daily or 1,250 mg twice daily.) In another study, no clinically significant drug interaction was found between nelfinavir and depo-medroxyprogesterone. Hormone levels remained the same; nelfinavir AUC decreased by 16%, but its metabolite (a byproduct of the body's processing of the drug), which is active against HIV, increased by 6%.

*Ritonavir (Norvir)*: An unusual single-dose study found that 500 mg twice-daily ritonavir plus 50 mcg ethinyl estradiol resulted in a 40% reduction in ethinyl estradiol AUC. The hormonal contraceptive used in this study contained higher levels of estrogen than typically used today, and the dose of ritonavir was higher than the low boosting doses (100–200 mg) used in modern antiretroviral regimens (though lower than the usual 600-mg twice-daily dose when ritonavir is used as the sole PI).

*Saquinavir (Invirase)*: There is little formal data from interaction studies evaluating the effect of saquinavir on hormonal contraception, though one analysis did find that hormonal contraceptives did not affect saquinavir levels.

Tipranavir/ritonavir (boosted Aptivus). Tipranavir boosted with ritonavir (500 mg/100 mg) taken twice daily lowered ethinyl estradiol AUC by 48% in a single-dose study using 35 mcg ethinyl estradiol plus 1 mg norethindrone daily. (Again, the antiretroviral drug dose was unusual; the typical

boosting dose of ritonavir when used with tipranavir is 200 mg twice daily.)

Based on these studies, it appears that most PIs—including those boosted with low doses of ritonavir—lower blood concentrations of ethinyl estradiol and norethindrone in oral contraceptive pills. There are no studies evaluating the effects of atazanavir/ritonavir, indinavir/ritonavir, or saquinavir/ritonavir on hormonal contraceptive levels. Hormonal contraceptives may be used with caution by HIV positive women taking atazanavir or indinavir as their only PI (without ritonavir). These women should select a contraceptive pill that contains the lowest dose of ethinyl estradiol and watch for any side effects of excess estrogen.

### Other Antiretroviral Classes

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are not expected to interact with hormonal contraceptives because hormones and NRTIs are metabolized in the body through different physiological pathways. To date, tenofovir (Viread, also in Truvada and Atripla), is the only NRTI to be formally studied with hormonal contraceptives. Tenofovir had no interactions with a tricyclic hormonal contraceptive pill containing 35 mcg ethinyl estradiol plus either 0.18 mg, 0.215 mg, or 0.25 mg norgestimate (another progestin).

The CCR5 antagonist maraviroc (Selzentry) demonstrated no interactions when studied with 30 mcg ethinyl estradiol plus 150 mcg levonorgestrel. There are no data from formal interaction studies of the integrase inhibitor raltegravir (Isentress) or the entry inhibitor enfuvirtide (Fuzeon). However, based on their effects on hormone metabolism, no interactions are expected.

### Questions Remain

While data from studies of interactions between antiretroviral drugs and hormonal contraceptives can be helpful, the information is imperfect. For example, the studies described here

varied greatly in their design, making the results difficult to compare. Some lasted for several months, while others were single-dose studies. Some took blood samples after a single day, while others took blood samples after several days. The length of a study and the time at which blood is sampled are important because researchers must ensure that drugs have had adequate time to reach steady levels in the bloodstream.

There are many unknowns with regard to hormonal contraception and HIV itself, as well as with antiretroviral interactions. Many of the interaction studies included small numbers (fewer than 20) of HIV negative volunteers. Larger sample sizes would make the studies more statistically powerful. There is no reason to believe the drugs might act differently in HIV positive women, but we do not know for certain.

In addition, as noted, several of the studies employed unusual drug doses not typically used in modern antiretroviral therapy or in today's hormonal contraceptives. It is not known whether similar interactions would occur using modern antiretroviral regimens and the newer low-dose estrogen-containing contraceptive pills.

The available drug interaction studies primarily looked at only two types of progestin: norgestimate and norethindrone. It is uncertain, for example, how antiretrovirals other than efavirenz might impact the efficacy of the Plan B emergency contraceptive pill containing levonorgestrel.

Likewise, there are no studies concerning HIV medications and the contraceptive patch or contraceptive ring. These formulations are thought to be better than oral forms with regard to interactions because they avoid the body's "first pass" metabolism in the gut and liver; however, there is still a potential for drug interactions.

Finally, drug interaction studies can show how much hormonal contra-

ceptive levels drop in the presence of antiretrovirals, but they do not indicate how much of a decrease in AUC is required to allow conception. Even after decades of use, the exact threshold for efficacy of hormonal contraceptives is still unclear. There are still many questions to answer and many studies that need to be performed.

### *Weighing In: Hormonal Contraceptives for HIV Positive Women*

Any HIV positive woman who is thinking about hormonal contraception should first have a clear discussion with her clinician about why she wants to use it. Some women use hormonal contraceptive agents for reasons other than birth control, including regulation of the menstrual cycle, treating dysmenorrhea (painful menstruation), or preventing severe acne. In these cases, decreases in hormone levels due to antiretroviral drug interactions may be less critical.

If a woman with HIV wishes to use hormonal contraception primarily for birth control, she should be aware that it might be less effective if she is taking antiretroviral therapy. She must also consider the risk of HIV transmission to her sex partners. For both of these reasons, many positive women choose to use both hormonal contraception and a barrier method, such as male or female condoms.

Whatever the reason for seeking a hormonal contraception method, the woman and her provider should consider any coexisting conditions or risk factors that might increase the likelihood of complications such as cardiovascular events.

Much has been learned about hormonal contraception and HIV over the last decade. The studies that have been performed have helped forward our understanding of women's health and HIV, yet there are still many unknowns. Positive women can advocate

for future studies that may help them select the best hormonal contraceptive methods that are effective at preventing pregnancy and have the least impact on HIV transmission and disease progression.

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