

# Outlook

## Hormonal contraception and HIV: new findings, but policies remain unchanged

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Used by more than 100 million women worldwide, hormonal contraceptive methods are among the most widely used contraceptives.<sup>1</sup> In recent years, however, the reproductive health community has become concerned about the possibility that hormonal contraception might increase a woman's susceptibility to HIV. Researchers have theorized that hormonal contraception might have an impact on HIV acquisition by previously uninfected women, on disease progression in women living with HIV, or on the likelihood that HIV-positive women might pass the virus on to their partners. If any of these possible effects were confirmed, it would be a matter of grave significance, particularly given that hormonal contraception is a popular form of family planning in many countries, including some with high HIV prevalence rates. In addition, the percentage of recent mothers in many African countries whose last birth was not wanted or wanted later is relatively high (see Table 1).<sup>2</sup>

Although efforts to determine whether there is a relationship between hormonal

contraception and HIV acquisition, transmission, or progression have been inconclusive, new research findings are shedding light on these and related issues. This issue of *Outlook* explores the potential association and discusses the effects that hormonal contraception has on women living with HIV and AIDS. The issue also discusses how reproductive health programs can respond to emerging information.

### A 2005 review

After conducting a systematic review of the evidence base on hormonal contraception and HIV in 2005, the World Health Organization (WHO) concluded that available research does not justify modifying current *Medical Eligibility Criteria for Contraceptive Use* guidelines. WHO therefore does not recommend restricting use of combined oral contraceptives or depot medroxyprogesterone acetate (DMPA) by women at high risk of acquiring a sexually transmitted infection (STI).<sup>3</sup> This position was reiterated at an Africa Regional meeting held by WHO, the University of Witwatersrand's Reproductive Health and HIV Research Unit, International Planned Parenthood Federation Africa Region, and Family Health International in September 2005. However, participants suggested that at its next meeting the WHO Family Planning Working Group review the classification regarding women at high individual risk of HIV infection to assess whether some caution on use of these methods may be appropriate (although the participants acknowledged that the benefits of using combined oral contraceptives or DMPA to prevent unintended pregnancy would offset any excess risk of acquiring HIV infection in the majority of cases). In addition, participants agreed that women and their partners should be strongly encouraged to protect themselves against unintended pregnancy, STIs, and HIV, through use of condoms alone or in addition to another contraceptive method.<sup>4</sup>

### Research challenges

Determining whether there is an association between hormonal contraception and

**Table 1. Contraceptive use among women who are married or in union in countries with the highest HIV prevalence rates**

Country	% of population aged 15–49 with HIV (2003–2004)	% of women aged 15–49 using contraception (1990s and 2000s)	% of women aged 15–49 using hormonal contraception* (1990s and 2000)	% of recent mothers whose last birth was wanted later or not wanted (1990s and 2000)
Swaziland	39	28	N/A	N/A
Botswana	37	40	22	N/A
Lesotho	29	41	23	N/A
Zimbabwe	25	54	44	37
South Africa	22	56	34	N/A
Namibia	21	44	16	34
Zambia	17	34	8	36
Malawi	14	31	19	40
Central African Republic	14	28	2	23
Mozambique	12	17	4	24

\*Pills or injectables. N/A = not available.  
Source: Population Reference Bureau.<sup>1,2</sup>

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HIV is a complex research effort. Issues such as sexual behavior and practices are inherently difficult to measure, and self-reporting may be unreliable. Numerous confounding factors—that is, external elements that may affect research outcomes—can complicate analysis or comparison of results. Other limitations, such as varying study designs and small sample sizes, make it difficult to generalize study findings. Despite researchers’ best efforts, these limitations make it difficult to accurately identify the risk that hormonal contraception presents in different contexts.

**Confounding factors**

Women who are at risk of contracting or transmitting HIV while using hormonal contraception may have other behavioral characteristics that are strongly associated with HIV acquisition. These confounding factors—which may include inconsistent condom use, high numbers of partners, anal sex, pre-existing STIs, or, in some contexts, drug use and sharing of needles and syringes—are a major obstacle to interpreting results.<sup>5–8</sup>

**Observational studies versus randomized, controlled trials**

Randomized, controlled clinical trials are among the most rigorous approaches to research. If used to assess the effects of hormonal contraception, however, they would entail significant ethical challenges, particularly if women in a control group were randomized to a less effective contraceptive method or no contraceptive method at all.<sup>9</sup> For this reason, randomized, controlled trials may not be a feasible approach to researching this topic. None, in fact, have been conducted to date.

Unlike randomized trials, prospective observational studies allow women or couples to choose their method of contraception. The main challenge with observational studies, however, is that the group of women who choose to use hormonal contraception may be different—perhaps in an immeasurable or difficult-to-measure way—from women choosing not to use hormonal contraception. In addition, the measurement of exposure to contraception at the time of HIV infection is imprecise, since the timing of infection often remains unknown. Many of

the prospective studies conducted to date have encountered these or other limitations such as low numbers of hormonal contraceptive users, limited assessment of the comparability of study groups, and inadequate follow-up. These factors make it difficult for investigators from each study to formulate generalizable conclusions.<sup>9,10</sup>

**Association with HIV acquisition**

Researchers are exploring the effects that reproductive hormones may have on a woman’s susceptibility to HIV infection.

**Theoretical physiological effects**

Since both estrogen and progesterone affect women’s cell-mediated immune response (possibly to allow for fertilization or implantation to occur), researchers have theorized that hormonal changes due to menstruation or hormonal contraception might increase a woman’s risk of HIV infection by depressing her normal immune response.<sup>6</sup>

Other mechanisms also may have an effect. For example, some researchers suggest that progesterone-linked

thickening of cervical mucus might prevent HIV infection and that high levels of estrogen may strengthen the vaginal microenvironment (for example, by thickening the vaginal wall), increasing its resistance to infection. Other research has suggested that progestin-only injectable contraceptives may increase the risk of HIV infection in women by inhibiting production of estrogen and causing the vaginal wall to become thinner and more vulnerable to abrasions during intercourse.<sup>9,11–13</sup> These theories are largely speculative, however, and require further study.

### Studies among users

Studies assessing whether these mechanisms actually increase a woman's risk of HIV infection have come to varying conclusions (see Table 2). A study undertaken with sex workers in Thailand, for example, detected an association between the use of injectable contraceptives (type not specified) and an increased risk of HIV acquisition.<sup>14</sup> Another study conducted among Kenyan sex workers detected an association between the use of DMPA or oral hormonal contraceptives and an increased risk of HIV acquisition.<sup>6,15</sup> Other studies, however, including those carried out among clients of family planning clinics, (who are not identified as high risk), have not revealed an association.<sup>16–18</sup>

A systematic review of studies on hormonal contraception and HIV found that only 5 of 32 relevant studies were specifically designed to analyze the relationship between a range of types of hormonal contraceptives and HIV transmission, and even these studies yielded inconsistent results. Of the 22 cross-sectional and retrospective studies, most reported a statistically insignificant increased risk of HIV acquisition. Studies that reported a significantly increased risk generally took place among higher-risk populations (for example, sex workers and women attending STI clinics), while those that adjusted more thoroughly for confounding factors tended to report a lower risk of HIV acquisition.<sup>11</sup>

## An overview of hormonal contraceptives

Hormonal contraceptives prevent pregnancy by interfering with the release and/or fertilization of human eggs.<sup>20</sup> Combination hormonal contraceptives—such as combined oral contraceptive pills, contraceptive patches, injectable estrogen and progestin combinations, and vaginal rings—contain estrogen and progestin that work together to impede ovulation. Hormonal contraceptives that contain only progestin (which is synthetic progesterone) include progestin-only injectables such as DMPA, progestin-releasing IUDs, progestin-only pills, and progestin-only implants. These methods thicken cervical mucus, thereby inhibiting the entry of sperm and stop ovulation in about half of menstrual cycles.<sup>20</sup>

When used correctly and consistently, hormonal contraceptive methods are more than 99 percent effective at preventing pregnancy.<sup>21,22</sup> Equally important, women can control the use of these methods, which offers them an important way to protect themselves from the risks of unintended pregnancy. *Outlook* issues 20(2) and 21(1) provide more information on these and other contraceptive methods.

**Progestin-only injectables.** Studies carried out in Africa, Asia, Latin America, and North America have come to varying conclusions about a possible association between the use of progestin-only injectables and HIV acquisition. Those conducted among sex workers tend to find a significant association,<sup>6,15</sup> while studies undertaken with populations of women attending family planning clinics, who presumably are at a lower risk of acquiring HIV than sex workers, generally have not shown a statistically meaningful association.<sup>5,7,16,17</sup>

**Oral contraceptives.** Researchers who examined 28 studies on oral contraception (type not specified) and the probability of HIV infection found a small but statistically significant association between the use of oral contraceptives and the incidence of HIV infection (relative risk of 1.19, or about a 20 percent higher probability of acquiring HIV).<sup>9</sup> As with studies focusing on injectable contraceptives, however, research conducted among sex workers tends to detect an association,<sup>6,15,19</sup> while most research undertaken with women attending family planning clinics, including a study conducted in rural Uganda among more than 5,000 women, does not.<sup>16,17</sup>

### Effect on acquisition of other STIs

The presence of other STIs dramatically increases the risk of HIV infection. This is particularly true of bacterial STIs such as chlamydia and gonorrhea, which cause inflammation of the cervix,<sup>23</sup> and viral infections that cause genital ulcers, such as the herpes simplex virus.<sup>24</sup> The biological probability of HIV transmission is greater for ulcerative diseases, but the population risk attributable to infections such as chlamydia and gonorrhea may be larger, due to their much higher prevalence.<sup>25</sup>

Some researchers have concluded that hormonal contraception may increase the risk of acquiring some STIs, which in turn would increase women's risk of acquiring HIV. One study conducted in the United States detected a correlation between hormonal contraceptives (unspecified types of oral contraceptive pills, levonorgestrel implants, and DMPA) and the number of inflammatory cells in the cervicovaginal fluid,<sup>26</sup> while another study found a correlation between the use of DMPA and a higher acquisition rate of chlamydia and gonorrhea; oral contraceptives (type not specified) were not correlated with these infections, however.<sup>27</sup>

## Researchers gather to investigate potential association

In May 2005, Gynuity Health Projects, a health research and advocacy organization, convened a meeting entitled “Hormonal Contraception and HIV Transmission: Links? Mechanisms? Implications?” in New York. The meeting brought together researchers from universities, nongovernmental organizations, WHO, and other groups. Participants presented results from the most up-to-date animal, laboratory, and population-based research; examined the limitations of this research and appropriate caveats for interpretation; and discussed whether the research warrants changes in the ways family planning and HIV services are delivered—especially given that unwanted pregnancy is itself a health risk in countries where maternal morbidity and mortality are high. Detailed summaries of the meeting and its findings, as well as a list of frequently asked questions on hormonal contraception and HIV, are available at [www.gynuity.org](http://www.gynuity.org).

In September 2005, WHO headquarters and the WHO Regional Office for Africa convened a meeting on “Hormonal Contraception and HIV: Science and Policy.” The participants reviewed published studies and preliminary data from two new studies conducted in Uganda, Thailand, Zimbabwe, and South Africa that found no overall increase in the risk of HIV infection in women who use hormonal contraception. A statement issued after the meeting included numerous recommendations, including continuing to uphold the *WHO Medical Eligibility Criteria for Contraceptive Use* guidelines,<sup>28</sup> strongly encouraging women and their partners to use condoms alone or in addition to another contraceptive method, involving men and HIV-positive people in HIV prevention activities and services, ensuring strong family planning programs, and committing further resources to HIV prevention and care efforts.<sup>4</sup> Complete study results are expected soon.

A study conducted among sex workers in Kenya found that, compared to women using no contraception, women using oral contraceptives (type not specified) had an increased risk of chlamydia and vaginal candidiasis but a decreased risk for bacterial vaginosis. Women using DMPA were at a significantly increased risk for chlamydia but at a significantly decreased risk of bacterial vaginosis, trichomoniasis, and pelvic inflammatory disease. Women who used condoms consistently had a significantly decreased risk of acquiring any of these infections compared to women who did not use condoms consistently.<sup>29</sup>

### Association with HIV transmission

There is a theoretical concern that the use of hormonal contraception among HIV-positive women may increase shedding of HIV in the female genital tract, which in turn would increase

the likelihood of HIV transmission to sexual partners.<sup>30</sup> Research conducted among 242 HIV-positive sex workers in Mombasa found that women using injectable or oral contraceptives (type not specified) had a higher risk of acquiring cervicitis than non-users; injectable contraceptive users also were more likely to acquire chlamydia than were women not using hormonal contraception. This is notable because both cervicitis and chlamydia may increase shedding of HIV-1 cells in the genital tract, which likely results in increased infectivity to sexual partners.<sup>31</sup> Research is required to confirm the potential association, however.

### Effect on the progression of HIV infection

Researchers also have begun to investigate whether hormonal contraception influences the progression of HIV infection and the advent of AIDS. A related

issue is whether use of hormonal contraception at the time of HIV infection predisposes women to acquiring multiple variants of HIV, which have been associated with faster disease progression.

A study conducted among 161 HIV-positive sex workers in Mombasa, Kenya, found that women who used either injectable contraceptives or had a genital ulcer disease at the time of HIV infection were 2.7 times more likely to acquire multiple variants of HIV. They also experienced a higher viral setpoint than women using no contraceptive method. (The “viral setpoint” is the balance between viral replication of HIV and the body’s host control, which results in steady virus levels in the plasma. Higher viral setpoints are a strong predictor of progression to AIDS.)<sup>32</sup>

Other studies that have investigated the impact of hormonal contraception on clinical disease progression—including a cross-sectional analysis of available data on 1,721 HIV-positive women enrolled in the Women’s Inter-agency HIV Study<sup>33</sup>—have not detected an association between hormonal contraception and the progression of disease in women living with HIV or AIDS.<sup>32–34</sup>

## The prevalence of STIs, including HIV

As of 2004, nearly 40 million people were living with HIV or AIDS; nearly 5 million HIV infections occur annually and 20 million people have died from the infection since the pandemic began.<sup>35,36,37</sup>

In 1999, WHO estimated that approximately 340 million curable STIs (including gonorrhea, chlamydia, and trichomoniasis) occur worldwide each year. Currently, condoms are the only available contraceptive method that provides women with effective protection from both pregnancy and STIs, including HIV.

**Table 2. Key studies on hormonal contraception and HIV acquisition**

First author (year)	Country	Study population	Findings	Limitations
Criniti (2003) <sup>38</sup>	Kenya	5,301 women attending family planning clinics	Use of oral progestin-only contraceptives was associated with lower HIV prevalence (odds ratio of 0.5) than was the use of depot medroxyprogesterone acetate (DMPA).	Factors such as breastfeeding status, history of previous contraceptive methods, date of last delivery, and past and current sexual behaviors may have influenced results.
Kapiga (1998) <sup>16</sup>	Tanzania	2,471 women attending family planning clinics	There was no significant increase in risk of HIV infection for users of low-dose combined oral contraception, intrauterine devices (IUDs), or DMPA. Women under age 20 who reported multiple sex partners and consumed alcohol during the follow-up period had a higher risk of HIV infection.	Participants may not have been representative of all women of reproductive age in the study population; many women lost to follow-up.
Kiddugavu (2003) <sup>17</sup>	Uganda	Community-based survey of 5,117 rural women	Use of DMPA or oral contraception (type not specified) was not associated with HIV acquisition.	Possible confounding factors include marital disruption, multiple sex partners, and genital ulcer disease; findings based on self-assessment. Measurements occurred only at 10-month intervals, so precision of results may be low.
Martin (1998) <sup>6</sup> and Lavreys (2004) <sup>15</sup>	Kenya	Sex workers attending an STI clinic (779 in 1998 study; 1,272 in 2004 study)	Women who used DMPA or high-dose combined contraceptives (1998 study) or DMPA or oral contraceptives (type not specified, 2004 study) had an increased risk of HIV infection.	Possible confounding factors include underreporting of sexual exposure and high prevalence of other STIs.
Tovanabutra (2002) <sup>8</sup>	Thailand	493 female partners of HIV-positive men	Long-term users of oral contraceptives (type not specified), DMPA, or levonorgestrel implants were at higher risk of acquiring HIV than were short-term users (odds ratio of 1.9 for hormonal contraceptive use lasting 8–26 months and 2.4 for more than 26 months, compared to women using hormonal contraception for less than 8 months).	Possible confounding factors include HIV status of women's partners, possible high rates of chronic inflammation in the vaginal epithelium, cross-sectional design of the study, and status of couples who enrolled in the study (which may have been different from those who did not).
Ungchusak (1996) <sup>14</sup>	Thailand	489 sex workers	Use of injectable contraceptives (type not specified) was associated with a significant risk of HIV infection.	Possible confounding factors include prevalence of other STIs, especially syphilis; many women lost to follow-up.

### Interaction with antiretroviral drugs

Antiretroviral drugs are an important component of treating HIV infection. Combinations of antiretroviral drugs—known as highly active antiretroviral therapy (HAART)—can significantly reduce HIV replication. Findings from the Women's Interagency HIV Study suggest that the use of hormonal contraception does not influence the effectiveness of HAART regimens.<sup>39</sup>

The effect of HAART on hormonal contraception is less clear, however, as studies of clinical outcomes (such as

pregnancy rates or ovulation indicators) have not been completed. Pharmacokinetic research shows that some HAART drugs decrease the contraceptive hormone levels in the blood, while others increase the hormone levels.<sup>40</sup> Concurrent use of a second form of contraception is recommended for women who use a HAART regimen and wish to avoid pregnancy.<sup>41</sup>

### Applying research to programs

WHO has not changed its recommendations regarding hormonal contracep-

tive use and, after reviewing emerging data in 2005, continues to recommend hormonal contraception as a key contraceptive method.<sup>3</sup>

### Advising women who seek hormonal contraception

The latest research findings confirm that existing guidelines on hormonal contraception are sound.<sup>3</sup> Family planning providers therefore should continue to include hormonal contraception in their mix of available methods. For sex workers and other women at extremely high risk of HIV expo-

sure, some concern may be warranted and a barrier method of protection is advised. As with any method, providers should present complete information about risks and benefits. It is essential that family planning providers and providers of HIV testing and counseling services have the skills and training needed to promote use of contraceptives, improve usage skills, and encourage discussion between clients and their partners.<sup>9,17,29,31</sup>

Encouraging the use of dual methods to obtain dual protection—such as hormonal contraception to protect against pregnancy and condoms to protect against both pregnancy and STIs—is appropriate, particularly in areas with high HIV prevalence rates. Dual-method use also is important for women who are already living with HIV, as condoms can prevent them from acquiring other STIs and transmitting HIV to their sexual partners, and hormonal contraception offers added pregnancy protection, should the condom fail. Despite the effectiveness of this method, however, a range of obstacles—such as added cost or inconvenience, lack of product availability, or the difficulty of negotiating

contraceptive use with a partner—may lead some women to use only one method.<sup>16</sup> In addition, couples who use highly effective contraceptive methods such as sterilization, IUDs, or hormonal contraception may be less likely to use condoms consistently.<sup>42</sup> These realities

couples are referred to prevention-of-mother-to-child-transmission (PMTCT) programs. If a couple is HIV discordant or does not know their HIV status but lives in a high-prevalence area, counselors should advise unprotected intercourse only around the time of ovulation and consistent condom use during other times.

### The role of voluntary counseling and testing

Health care providers can support women at risk of HIV by offering voluntary counseling and testing or referrals to family planning services. If a woman is HIV-positive, the provider can encourage her to obtain immediate health care to

lessen the impact of HIV, use effective contraception if she wishes to avoid pregnancy, and use condoms to protect against HIV transmission and coinfection with other STIs. If the woman is HIV-negative, the provider can emphasize monogamy (although this will only be effective if her partner also is monogamous and HIV-negative) or encourage her to reduce the number of sexual partners and use dual methods. If she is HIV-negative but her partner is infected, counseling messages should

Experts agree that current evidence does not support making changes to current family planning recommendations regarding use of hormonal contraceptives among HIV-negative women.<sup>3,4</sup>

highlight the need for family planning providers to guarantee access to an array of contraceptive choices.

### When pregnancy is wanted

Some couples may desire a pregnancy even if one or both partners is HIV positive. Although advances in the development of and access to antiretroviral therapy can help reduce the risk of transmitting HIV to infants at or shortly after birth, family planning service providers must ensure that

**Table 3. Contraceptive and reproductive health counseling messages\***

If the woman is HIV-negative, options include:	If the woman is HIV-positive and wishes to avoid pregnancy, options include:	If the woman is HIV-positive and wishes to become pregnant, options include:
<ul style="list-style-type: none"> <li>• Counseling regarding the benefits of monogamy for her and her partner, or partner reduction if monogamy is not possible.</li> <li>• Access to contraceptive method of choice.</li> <li>• Counseling about and access to condoms; emphasis on dual protection.</li> </ul>	<ul style="list-style-type: none"> <li>• Referral for counseling to sustain health and mitigate the impact of HIV infection.</li> <li>• Access to contraceptive method of choice.</li> <li>• Counseling about and access to condoms; emphasis on dual protection.</li> </ul>	<ul style="list-style-type: none"> <li>• Referral for counseling to sustain health and mitigate impact of HIV infection.</li> <li>• Referral to services that can help prevent mother-to-child transmission of HIV.</li> <li>• Counseling regarding optimal times for conception.</li> </ul>

\*While awaiting more conclusive findings on potential associations between hormonal contraception and the risk of HIV acquisition or transmission, individuals and communities must make their own informed decisions about what is best for them. However, at this time, WHO has not changed its recommendations regarding hormonal contraception. WHO places no restrictions on these methods, including for women at risk of acquiring HIV.

include using condoms and seeking effective contraception (see Table 3).

## Future research

The results of two studies seeking to clarify the potential association between hormonal contraceptive use and HIV will be published imminently. One study being conducted in Uganda, Thailand, and Zimbabwe is particularly important because it has been conducted among family planning clients, who are considered to be at lower risk of HIV infection than groups such as sex workers. Yet many medical, policy, and service questions about the possible effect of hormonal contraception on HIV acquisition and transmission remain.

Animal models could help researchers examine how viruses penetrate the vaginal epithelium and how hormones affect the mucosal immunology of the vagina and cervix. Researchers also could examine defense mechanisms inherent to the female genital tract, physiological changes that occur during menstruation, and how hormones affect these elements. Since large-scale randomized trials on humans are unlikely, prospective studies on HIV-negative women with HIV-positive partners that include specific information about risk factors and contraceptive use prior to HIV infection could provide more conclusive evidence. Such studies would need to counsel women about consistent condom use to help prevent HIV transmission.<sup>11</sup>

Additional topics for future research include:

- The effect of hormones on women living with HIV, including disease progression, HIV acquisition among partners, and the interaction with antiretroviral drugs.
- The difference in HIV transmission rates between HIV-positive women using hormonal contraception and other HIV-positive women.<sup>43</sup>
- The link between hormonal contraception and HIV among populations of HIV-positive women other than sex workers.

## The promise of microbicides

Vaginal microbicides offer the potential for a woman-initiated form of pregnancy and STI prevention. Currently under development, microbicides will be substances that are applied in the vagina to protect against HIV transmission; some also may protect against other STIs as well as pregnancy. They may be produced in many forms, including gels, creams, suppositories, films, lubricants, sponges, or vaginal rings. While no microbicides are commercially available, 18 products that have been proven safe and effective in animals are now being evaluated in human trials. Among them, five candidates—BufferGel™, Pro-2000, Savvy™ C-31G, cellulose sulphate, and Carraguard™—are in late-stage clinical trials.

If one or more of these candidates prove successful, and if sufficient investment is made, a successful microbicide could be available in developing countries by 2010. Although new microbicides would be unlikely to provide complete protection against HIV, other STIs, or pregnancy, the fact that microbicides will be women-initiated will help fill an important preventive gap for women and expand women's options for dual protection.<sup>44</sup>

- The effects of prior hormonal contraceptive use on ensuing disease in HIV-positive women.
- The development of female-controlled microbicides, which could offer protection against both pregnancy and STIs (see box, this page).

## Conclusion

To date, no major health body has limited its provision of hormonal contraception, even to women at risk of HIV. Until more conclusive evidence clarifies the potential linkages between hormonal contraception and HIV, the greatest service that health care providers can offer is ensuring that women and couples have complete information, broad access to contraceptive options (particularly condoms), and the freedom to make choices that meet their needs.

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