Hormonal Contraception and HIV Transmission: Links? Mechanisms? Implications

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Summary of Meeting

"Hormonal Contraception and HIV Transmission: Links? Mechanisms? Implications?"
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Background and Introduction

Concern about a possible association between hormonal contraceptive (HC) use and increased risk of HIV infection has been mounting in recent years. A series of laboratory, clinical and epidemiological studies have contributed to a growing body of evidence that suggests such an association may exist. As of now, however, the association remains speculative, and a causal relationship between HC use and changes in HIV risk has not been established. Given the enormity of the AIDS epidemic, especially among women, and the popularity of HC use in many settings, any evidence that HC use may increase the risk of HIV transmission or contribute to disease progression would have significant implications for policy, programs, and individual women's decisionmaking.

With the support of the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, and the Rockefeller Foundation, Gynuity Health Projects convened a two-day meeting bringing together scientists, reproductive health programmers, researchers, policymakers and activists to:

- examine the evidence for any effect of HC use on transmission of HIV to and from women and/or on disease progression in already-infected women;
- debate and address the methodological challenges in researching this topic;
- discuss the implications of our current state of knowledge for policy and practice in providing contraception and family planning services; and
- identify further research that may be needed to answer outstanding questions.

Given the uncertainty, complexity and nuance of the topic, participants also debated appropriate strategies for presenting it to the public in a manner that is clear, comprehensible, and maximizes sound policy and practice, while preserving women's ability to make informed choices about contraceptive use and HIV risk. Due to the sometimes contradictory nature of the data and the lack of firm evidence of causality, the meeting was characterized by debate and discussion. No clear consensus emerged.

The meeting began with an overview of geographic patterns of HC use and HIV infection drawing on data from the Demographic and Health Surveys. These data show that while there are many settings with high rates of both HC use and HIV prevalence, there are also areas where the two variables do not correspond. Given the diversity of these settings in terms of culture, religion, sexual practices, and a host of other risk factors, it is not possible to tease out from this data what contribution, if any, HC use may make to overall rates of HIV infection. However, given that there are many countries where high HIV prevalence coincides with high use of HC, the data do suggest that if a causal relationship between HC use and increased HIV risk is ultimately established, it would have significant implications for women and for reproductive health programs.

Another important background presentation reviewed the composition and mechanism of action of various types of hormonal contraception. Put simply, there are two basic formulations of these medications: one containing both progestin and estrogen (for example, combined oral contraceptive pills), and one containing only progestin (for example, DMPA ("Depo-provera") and the "mini-pill"). Many of the possible effects of HC on HIV (discussed in detail below) appear to be driven by progestin; estrogen may, in fact, have a somewhat protective effect. Nevertheless, even those methods of HC which

contain both progestin and estrogen are "progestin-dominant" – that is, the effects of progestin outweigh those of estrogen. The result appears to be that, although the possible effects of HC on HIV are more strongly associated with progestin-only methods, they may be linked to combined methods, as well.

Evidence from the laboratory

Use of hormonal contraception may give rise to systemic and genital-tract changes, some of which could influence women's risk of contracting and transmitting HIV as well as the progression of HIV disease in infected women. Several presentations examined evidence on this topic from laboratory studies of animals and humans.

Widespread alarm about the possibility of HC use contributing to HIV infection was first raised by studies of Simian Immunodeficiency Virus (SIV), a virus closely related to HIV, in rhesus macaque monkeys. In these studies, macaques treated with progestin-only hormonal contraceptives experienced a dramatic thinning of the vaginal lining, or epithelium, and were much more susceptible than untreated macaques to infection with the SIV virus. Researchers concluded that thinning of the vaginal epithelium had reduced the monkeys' natural barrier to SIV, thus allowing for greater uptake of the virus.

Later experiments using low-dose progestin-only contraceptives in humans failed to find the kind of marked epithelial thinning among HC-treated women as was found in monkeys. Nevertheless, changes in the vaginal epithelium (less dramatic thinning; decrease in number of cell layers; changes in the relative number of mature cells) appear to be one mechanism by which HC use might increase susceptibility to HIV among humans.

Beyond this, research in humans has established at least six other plausible mechanisms by which HC use might have an impact on HIV infection and disease progression:

- HC use may increase women's susceptibility to acquiring RTIs/STIs (Chlamydia; cervicitis; candidiasis) and/or to expressing STIs with which they may already be infected (*Herpes simplex*). Presence of an active RTI or STI could then, in turn, increase women's susceptibility to HIV;
- HC use may increase cervical ectopy (the number of cells normally within the cervical canal which are exposed to the vagina), giving rise to increased uptake of HIV via these cells;
- HC use may disrupt populations of lactobacilli and other microorganisms which in the normal vaginal environment provide protection from certain pathogens, possibly including HIV;
- HC use may change the vagina's immunologic environment so as to affect receptor cells (macrophages, T cells and dendritic cells) and co-receptor expression;
- HC use may increase the viral variety, set point, and expression of HIV in infected women;
- HC use may promote shedding of HIV into the vaginas of infected women, thus increasing their ability to transmit the virus to others.

These mechanisms appear to be activated primarily by progestin. They may be most strongly associated with use of progestin-only contraceptives (including DMPA), but may also operate in users of combined methods, such as oral contraceptive pills (OCs). Some evidence suggests that estrogen may have a protective effect: in macaques, estrogen gel applied vaginally has had a significant effect on preventing SIV transmission. However, the levels of estrogen in methods such as combined OCs may not be high enough to counter any negative effects which may arise from progestins.

The effects of both endogenous and exogenous hormones on HIV acquisition, disease progression, and transmission in women were presented in a comprehensive review of laboratory studies. In sum, these studies suggest that there may be some reason for concern about the effects of exogenous hormones

(such as HC), although with important differences from what has been observed in animal models. Effects that have been noted differ somewhat by type of HC, as summarized in the following table.

Table 1: Summary of effects of HC on HIV suggested by research to date[1]

Effect	Oral Contraceptive Pills	Injectable Progestins
Overall thickness, number of cell layers, and thickness of the glycogen layer of the vaginal epithelium	-	↓?
Cervical ectopy	↑	↑?
Chlamydia infection	↑	↑
Vaginal candidiasis	↑	?
Vaginal lactobacillus population	?	↓
Reactivation of existing *Herpes simplex* infection	↑?	↑?
Genital inflammation	↑	↑
Local immune effect (HIV-1 co-receptor expression)	↑	↑
Systemic immune effect	?	?
Effect on HIV viral variety, set point and/or expression	↑?	↑?
Increased vaginal shedding of HIV in infected women	↑	↑

Key: - no net effect ● ↑ increases listed item or effect ● ↓ decreases listed item or effect ● ? effect unknown
A symbol followed by a question mark (?) indicates that the listed effect appears to function but remains questionable

Finally, very little is known about the effect of HC use on progression of HIV disease in women. Similarly, there is little information about any effect that HC use may have on the efficacy and side effects of high active anti-retroviral therapy (HAART). The scant evidence that does exist suggests that there may be some effects but they are likely to be subtle. More research in this area will be needed before any definitive conclusions can be drawn.

Evidence from population-based studies:

The population-based studies of this topic conducted to date have used observational designs – no randomized controlled trials (RTCs) have been conducted (see discussion below). These studies have sometimes – but not always – shown a clear association between hormonal contraceptive use and HIV incidence, transmission, and/or disease progression.[2]

Comparing these studies is difficult as they have differed in many important ways, including location, study population and design, and frequency of follow-up. Studies that have found no association include those among general populations and sero-discordant couples in Uganda, Zambia, and Rwanda. On the other hand, studies among sex workers in Thailand and Kenya have demonstrated an association. Data from the Uganda and Kenya studies were presented in depth at the meeting.

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[1] This table is largely based on a presentation made at the meeting by Dr. Jared Baeten of Massachusetts General Hospital.

[2] Unfortunately, data from a large, new study by Charles Morrison of Family Health International and colleagues had not been released at the time of the Gynuity Health Projects meeting. It is not known whether this new data, also from an observational study, will convincingly shift the weight of evidence in either direction. It is not likely, however, that the evidence will be significantly stronger or more unequivocal than that of previous observational studies.

A study conducted among sex workers in Mombassa, Kenya suggests that the use of hormonal contraception is associated with increased risk of HIV-1 acquisition and a higher viral set point in infected women, which may lead to faster disease progression. This study also showed an association between HC use and Chlamydia acquisition, and an increase in vaginal HIV shedding among HIV+ women using HC. The study, begun in 1993, followed 1,650 sex workers from an existing cohort to measure HIV sero-conversions by HC use (DMPA and OC) as compared with non-use. It included monthly follow-up measurements of HIV-1 sero-status, STI infection, contraceptive use and sexual behavior. This data has been analyzed and presented for several time periods, and has remained consistent. For the overall period 1993-2003 the hazard ratios for DMPA and OCs were 1.8 (95% CI 1.4-2.4, p<.001) and 1.5 (95% CI 1.0-2.1, p=.04), respectively. Using data from the more recent period 1997-2003 the respective HRs were 1.9 (95% CI 1.2-2.9) and 1.8 (95% CI 1.0-3.1). An additional study in this cohort showed an association between DMPA use and acquisition of varied virus types: HIV-1 viral diversity during primary infection was associated with use of DMPA at the time of HIV-1 acquisition (OR 3.0, 95% CI 1.3-6.9, p=0.005). Viral diversity, in turn, was associated with a higher plasma viral load and a faster decline in CD4 count.

The study in Rakai, Uganda, which involved secondary analysis of data gathered in a larger study of HIV incidence, measured HIV incidence among HC users (OC, injectable, or both) and non-users to ascertain the relative incidence rate ratio (IRR) between the two groups. Participants were interviewed every 10 months, and the study included data from sexually active, originally HIV negative females aged 15-49 years who completed at least 2 study clinic visits. Data were collected on a variety of risk factors, including marital status, number of sex partners, condom use and presence of genital ulcer disease (GUD). When data were adjusted for age, marital status, education status, number of sex partners, condom use, and presence of genital ulcer disease (GUD) there was no statistically significant increase in HIV risk recorded in either study population. The study showed an overall (non-significant) adjusted IRR of .98 for HC users (1.12 for pill users; .84 for injectible users) as compared with non-users. The most significant cofactors were number of sex partners and reported GUD. Especially given that GUD might, itself, be a consequence of HC use (since HCs may increase the likelihood of contracting certain STIs), and therefore possibly a variable that should *not* be adjusted for, these results underscore the critical importance that confounding and other sources of bias can play in the analysis of observational data.

Bias and Confounders:

A primary concern in interpreting these observational, population-based studies is the possible role of sources of bias, including confounding. This issue was discussed at length at several different points during the meeting. The concern is that women who use HC may differ from non-HC users in ways that condition their risk of HIV acquisition. Confounders can affect both exposure and outcome variables. The history of medical research makes it clear that unmeasured or improperly measured confounders can have a profound effect on the outcomes of a study. Small mistakes can sometimes significantly distort results and conclusions, as well as resulting program and policy actions. These caveats were explored eloquently and in depth in a discussion that touched on, among other examples, early (and subsequently discredited) "findings" of associations between OCs and breast cancer and vasectomy and prostate cancer. While randomization is considered to be the "gold standard" for combating confounding, it is not clear that randomized controlled trials are feasible when studying HC and HIV (see below).

Both known and unknown variables can confound study results. In any study, accurately determining, modeling and measuring even known confounders is challenging. In studies of HC and HIV, many of the potential confounders – for example, sexual behavior, sexual practices, number of partners, and condom use – can be especially tricky to research. These private and sometimes stigmatized matters present difficulties both to researchers and to participants: researchers are not certain how to elicit valid data, and recall and reporting on the part of participants is not always full, truthful, and/or accurate. Additionally,

there may be a significant "courtesy bias" associated with questions on, for example, condom use: after years of condom promotion programs, study participants are likely to be well aware that using condoms at each sex act is the "correct" way to behave, and may be inclined to report such behavior to authorities (including study personnel) whether or not these reports are accurate. Measurement challenges like these, of particular relevance to researching HC and HIV, exacerbate the concerns about confounding which apply to any study. The meeting included a presentation on ACASI (Audio Computer-Assisted Self Interview), a novel approach to gathering information on sensitive subjects which may hold promise for improving the accuracy of data collection in future studies of a possible HC/HIV interaction.

Future Research:

Given the inconclusive and somewhat contradictory evidence to date, participants engaged in a lively discussion about what additional data would be desirable, and what types of research would be feasible, to help strengthen the base of evidence on a possible HC/HIV interaction. Participants suggested areas for additional work, including studies designed to yield a greater understanding of:

- The risk of infection with HIV and other STIs faced by women during the luteal phase of the normal menstrual cycle, a time when the vaginal epithelium naturally thins somewhat
- Differences in hormone effects on primary infection vs. disease progression vs. transmission of the disease from women to others
- The relevance of animal models, particularly the macaque/SIV model, to HIV acquisition in women
- Possible effects of HC use on highly active anti-retroviral therapy (HAART)
- The possible value of vaginally applied estradiol cream in strengthening the barrier offered by the vaginal epithelium and thus in protecting women from HIV
- Subtler aspects of the HC/HIV relationship, such as whether or not differences in length of use of HC modify any effects on HIV, or what the actual levels of various hormones are at the time a woman becomes infected with the virus
- The effects of HC on specific immunological processes or elements (Toll-like receptors, CCR-5 coreceptors, and CXCR-4 co-receptors, for example)
- Other specific mechanisms (such as cervical ectopy, increased viral replication, and greater viral diversity) whereby HC might have effect on HIV
- How to best measure the immunologic environment of the vagina

There was also considerable interest in devising and exploring creative approaches to improving the identification and measurement of confounding factors and other sources of bias in HC/HIV studies.

Participants actively debated the feasibility and desirability of conducting randomized controlled trials (RTCs) to address the central questions of whether HC use increases HIV incidence, infectivity, or disease progression. While there was a range of views, in general participants thought that RTCs on this topic might not be practical or even necessary, and might present considerable ethical challenges. A major practical concern would be participants' willingness and ability to continue using a contraceptive method they had been randomly assigned rather than one they had chosen. Presentations from the Rakai and Mombasa studies both underscored the methodological challenge presented by study participants switching among different HC methods; this would likely be an even greater obstacle in an RTC. Some attendees questioned whether random assignment would even be ethical, since it might involve assigning participants to a contraceptive method that could *increase* their risk of acquiring or transmitting HIV and/or developing HIV disease, and/or could result in women who seek highly effective contraception being randomized to a less-effective method.

Given the difficulties of conducting an RTC on this topic, and the challenges and costs of mounting large population-based studies in general, participants agreed it would be useful to explore opportunities to collect data on HC and HIV in the context of other large ongoing studies (for example, trials of vaginal microbicides or of diaphragm use). Such an approach would also present many challenges, but it might be able to make important contributions to the evidence base on the topic with a minimum of cost and logistical difficulty. Another similar approach that was suggested was to examine already-existing data sets gathered for other purposes to see if any of them could be re-analyzed to shed light on the HC/HIV nexus.

Implications for policies and programs

Some of the data presented at the meeting supports an association between HC use and HIV infection, transmission, and disease progression; as of now, however, an association of any kind, to say nothing of a causal association, cannot be said to have been proved. We therefore must approach the topic – and, in particular, recommendations for policy and programmatic changes – with caution. There was considerable debate at the meeting on the implications of current knowledge for policy, programs, and individual women's decisions.

Several presenters and participants underscored the important contribution to women's health and rights that HC use has made by reducing pregnancy-associated morbidity and mortality, as well as by affording women more reproductive autonomy and choice. The significance of these benefits is even greater in low-resource settings where the risk of death or disability from pregnancy- or abortion-related causes is high. Against this backdrop, a number of participants felt strongly that no change in policy or practice is currently warranted. Any change in policy or an individual's contraceptive practice geared toward avoiding a possible increased risk of HIV by reducing HC use would need to carefully weigh other benefits and risks, as well, including those associated with pregnancy and, especially, unwanted pregnancy.

In contrast, a number of meeting participants found the laboratory and population-based evidence suggesting an association between HC and HIV compelling, and felt that policy and programmatic changes may be warranted in certain settings and populations. Many women who are at high or unknown risk of HIV infection have few options for decreasing this risk, and providing them with information that might help decrease this risk even slightly could be significant for individual women and for the course of the epidemic, particularly in high-HIV-prevalence areas or groups.

The principle most clearly highlighted by the discussion was the importance of *context* – of considering any increased risk of HIV that HC use may present within a host of other population and individual factors. These include:

- the magnitude of any relative risks for HIV infection, progression, and/or transmission which may eventually be established in HC users;
- the HIV incidence and prevalence in a given community or group;
- the risk of maternal mortality and morbidity in a given locale;
- a woman's individual risk of HIV and maternal mortality;
- the feasibility of other risk-reduction and contraceptive options

The importance of context was underscored by presentation at the meeting of a model suggesting that even if HCs are shown to increase HIV risk, in many settings, especially those with high pregnancy-associated morbidity and mortality, they may still bring enough benefits to warrant continued and possibly even increased use. Although the model presented was very simple, incorporating only four variables, it is an excellent example of the kind of multifaceted thinking that will need to take place if an intelligent response to a possible HC/HIV link is to be developed.

Unfortunately, this sort of complex and nuanced thinking will be difficult to maintain in the "real-world" situation of understaffed and ill-equipped health systems. Discussion therefore also focused on the importance of striving for a service delivery model that integrates family planning, reproductive health, voluntary counseling and testing for HIV, and treatment and care for people living with HIV/AIDS. Ideally, these services would equip providers and clients with the skills and information necessary to assess HIV risk and would tailor risk reduction strategies and contraceptive information and services to each specific situation.

If further evidence suggests a strong association between HC and HIV, policymakers will need to consider a range of critical questions. Is excess risk associated with HC fuelling the HIV/AIDS epidemic? Would discouraging HC use reverse or have a substantial impact on the epidemic? It is not at all clear that either of these questions can be answered in the affirmative. An extreme policy decision of, for example, taking HC off the market in settings with high HIV incidence and high HC prevalence would likely have a small impact on reducing HIV relative to the impact of reduced sexual risk and increased condom use, while it would deprive women of an effective and beneficial contraceptive. To address questions of this nature, WHO will shortly convene a regional meeting in Africa to promote evidence-based discussion and decisionmaking on hormonal contraceptive use in the context of the HIV epidemic. This meeting will consider a wide range of evidence, including anticipated results from the study by Morrison et al. (see note 1, above).[3]

Finally, there was a lively discussion about how best to convey information about HC and HIV to the public in a manner that is clear, nuanced and comprehensible, and that promotes appropriate decisionmaking, discourages sensational reporting, and does not lead to ill-considered responses. Institutions associated with the Morrison, et al., study are developing a strategy for presenting their findings; they and others anticipate an increase in attention and interest in this area when these results are released. The findings and attendant messages are likely to be subtle and complex, emphasizing that different actions and approaches are warranted in different settings and for different women. Acknowledging the limitations of traditional scientific presentation to convey such messages and the tendency of the media to simplify and sensationalize scientific findings, a number of participants suggested working together on a strategic and coordinated effort (perhaps making use of public- and press-relations professionals) which might include varied materials for diverse audiences and seminars for journalists and key opinion leaders.

[3] This meeting – which had the benefit of some initial findings of the Morrison study, though not the full, final results – has since occurred (September 19-21, 2005, Nairobi, Kenya). At it, WHO reaffirmed that there is not enough evidence to change current practice with regard to hormonal contraceptive use, although there may be some reason to revisit this conclusion for women who are at high individual risk for acquiring the virus. The meeting's final statement of recommendations reads: "There should be no restrictions on the use of COCs and DMPA by women at risk of acquiring HIV, consistent with the current *WHO Medical Eligibility Criteria for Contraceptive Use* guidelines. However, participants suggested that the WHO Family Planning Working Group at its next meeting 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, though the participants acknowledged that the benefits of using COCs or DMPA to prevent unintended pregnancy would in the majority of cases offset any excess risk of acquiring HIV infection." For the full meeting statement, see http://www.who.int/reproductive-health/rtis/statement.html.

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