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Hormonal Contraception and HIV Disease Acquisition: A Limited Review and Reassessment of Findings

A discussion paper
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Table of Contents

Summary

This paper reviews some of the key studies within the epidemiological literature that examine the relationship between hormonal contraception (HC) use, primarily depot-medroxyprogesterone acetate (DMPA) injectables, and HIV acquisition. The primary objective is to reassess the findings rather than reinterpret them; consequently, it synthesizes the findings and implications published in peer-reviewed scientific journals, and it discusses their translation into preventive actions. Recent publication of findings raises lingering questions about the role of DMPA injectables, administered once in three months, in the transmission of the virus. The vulnerability of young females to infection in the epidemic, a phenomenon as yet not fully understood, and of the women engaged in sex work makes it critical to re-examine and reassess the findings that "overall" there is no association between hormonal contraception (HC) use and HIV disease acquisition.

Emerging and persistent questions about hormonal contraception's role in disease progression and infectivity (transmission) have also increased the urgency of gaining a fuller and more nuanced understanding of the potential hormonal contraception-HIV relationship, especially because investigators and commentators have noted limitations of their findings. The 2005 WHO Nairobi statement left the Medical Eligibility Criteria for Contraceptive Use (MEC guidelines) unchanged and appears to have sanctioned the continuing use of these contraceptives by all women living in areas where the HIV epidemic is widespread. The WHO statement has been reinforced by reassurance on the website of Family Health International (FHI), a contraceptive research and service agency, that hormonal contraception does not increase the risk of contracting HIV. In scientific publications, FHI researchers acknowledge that age could be a modifier of the association and more research is needed. The researchers' recommendations for further research and for hormonal contraceptive users to use dual protection, however, are less likely to be mentioned when the principal finding of no "overall" association is cited.

Through synthesis of the findings from two groups of studies that each followed a cohort of women and measured changes in their status over a period of time, the paper highlights important insights and information that have to be disseminated alongside the finding of "no overall association." It discusses the shortcomings in the HC-HIV study that precipitated the WHO statement, and their implications, and recommends that revised guidelines are instituted to protect, inform and educate all women and particularly the subgroups of women at risk when using hormonal contraception.

1 Background & Introduction

Hormonal contraception is widely used around the world as a safe and effective form of women-controlled family planning method. In the sub-Saharan African region, which has high rates of maternal mortality and where 90 percent of deaths in urban African women of reproductive age are caused by HIV infection, hormonal contraception is expected to prevent pregnancy-related deaths of women and the vertical transmission of HIV to infants. Having a very low failure rate, this form of contraception provides the best protection against pregnancy, compared to the more failure-prone male condom. Female condoms are slowly gaining acceptance, but still not found widely in use. Consequently, male condoms remain the most effective barrier to the acquisition of sexually transmitted infections (STI's) such as HIV.

Among countries in the region, South Africa has been extensively affected by the epidemic. Here, both oral contraceptives (combined and progestin alone) and injectable progestin (progestogen) only contraceptives such as *depot-medroxyprogesterone acetate* (DMPA) and *norethisterone enanthate* (Net-En) are highly popular. Reviews of clinical literature do not distinguish greatly between these two injectable progestin-only contraceptives in terms of efficacy and side effects, although it appears that cost differences determine the choice made by health systems [Draper, 2008]. Hormonal contraception is used by 43 percent of sexually active South African women in the reproductive age range of 15 to 49 years [Morrison, 2007b, p.1]. At the start of the epidemic the use of barrier methods in the region was rare; however, the discreet nature of injectables afforded women the privacy they needed to subvert pronatal norms and enabled DMPA to emerge as the most popular method of choice [Allen, 2003a]. Women make quarterly visits to receive injectables at the neighborhood family planning clinic. DMPA users are required to have the shots quarterly, while those on Net-En receive them more frequently – once in two months. In contrast to these two hormonal contraceptive products, user-independent methods such as bilateral tubal ligation (BTL), intra-uterine device (IUD) and *levonorgestrel* implants (Norplant) are rarely recorded in the region. The low usage is attributed to the dearth of nurses trained to insert IUDs and implants as well as the limited awareness on the part of women about these options (Allen, 2003b).

Married couples form the largest subgroup in the population that is at risk for both HIV and unintended pregnancy. The HIV status of both partners determines the method best suited to preventing both HIV transmission and unwanted pregnancy. When both partners are positive, counselors focus on prevention of unplanned pregnancy. When the couple is HIV-discordant, one partner positive and the other negative, the main recommended approach is a dual method that uses condoms to prevent HIV transmission and an effective long-acting contraceptive to protect the woman from pregnancy.

In its 2004 Medical Eligibility Criteria for Contraceptive Use (MEC) guidelines for combined oral contraceptives (COC), injectable contraceptives and progestogen (progestin) only contraceptives (POCs), the World Health Organization (WHO) cautions that "*POCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV*." (Italics added) What is not clear, however, is the rigor with which providers and counselors are enforcing the WHO guidelines in the family planning clinical centers in urban and rural areas of sub-Saharan Africa. The absence of integrated services for family planning and HIV

testing/counseling makes it less likely that women who choose DMPA, a progestin only contraceptive, are counseled to use the dual method when they are at risk of acquiring or transmitting the virus. Without such counseling, women on DMPA may be uninformed about the urgency of using a dual protection method to guard against sexually transmitted infections (STIs), particularly HIV, when partners are serodiscordant or uncertain about their status.

Vulnerable Groups in the HIV Epidemic

In the early years of the HIV/AIDS epidemic, men were the principal viral carriers and outnumbered women. Gradually, as the epidemic spread widely, its predominantly heterosexual nature resulted in women constituting half of all adults living with the disease in 1995. In its 2008 Report on the global AIDS epidemic, UNAIDS states that "heterosexual intercourse is still driving the epidemic in sub-Saharan Africa, which shouldered two-thirds of the global AIDS burden and three-quarters of all AIDS-related deaths in 2007."[1] Based on their biology (reproductive physiology), women are two to eight times more likely to contract HIV during vaginal intercourse. This grim reality is reflected in the UNAIDS data for sub-Saharan Africa, where approximately 60 percent of adults (15+ years) living with HIV/AIDS were female in 2007. The corresponding figure, globally, is 50 percent. [2] Over the last decade, according to the agency, "the proportion of women among people living with HIV has remained stable globally, but has increased in many regions." (This balance could grow even more disproportionate if circumcision that is protective only for men should result in inadequate protections for women.[3])

During 2005-2007, among individuals 15-24 years old, HIV prevalence was consistently higher among females in sub-Saharan African countries, with the exception of the Democratic Republic of the Congo where the rate for men was higher. Prevalence in females was highest in Swaziland (23%), followed by South Africa (17%) and Zimbabwe (12 %) approximately.[4] Among youth and young adults (15-24 years) worldwide, women are 1.6 times more likely than men to be positive.[5] UNAIDS data for Lesotho in 2006 showed that less than 10 percent of girls aged 18 and 19 were positive and projected that by age 24 almost 40 percent would be positive.[6]

UNAIDS reports that approximately 40 percent of males and 38 percent of females (15-24 years) responded correctly to all five questions in a survey that tested their knowledge of HIV.[7] These results raise concerns about the informedness of an incipient sexually active population of youth and young adults. Women, particularly young women, are likely to be more sexually active and at higher risk for contracting HIV even as they are exposed to the possibility of pregnancy. High maternal mortality rates in the region, due largely to inadequate and inaccessible health services, have created serious risks for girls and women. Those who want to avoid pregnancy have to ensure dual protection against conception and infection. The demographic and epidemiological literature often project young heterosexual women, entering their reproductive phase, as a vulnerable group biologically susceptible to the virus and needing to be shielded from both HIV and unwanted pregnancy. A less recognized risk is that of anal intercourse among heterosexual couples, where research is of more recent origin.[8]

Methodology

A preliminary search of the literature was conducted on PubMed using the keywords "hormonal contraception" and "HIV." The research articles that were generated were scanned and those without relevance to the focus of the review were excluded. In addition, a Google search was used to generate literature about the hormonal contraception-HIV association that was in the public domain. The two groups of studies reviewed in this paper were selected to represent the two conflicting findings on

the relationship between hormonal contraception and HIV acquisition. They were chosen with due consideration for the integrity of their research design, the size of their study population and the strength or significance of their findings. Three articles published in 2008 that revived the debate were brought to the writer's attention and initiated this discussion paper.[9]

To provide an overview of the studies and their findings for readers with varied exposure to epidemiological terms and concepts, we created a matrix in Appendix I, titled Select Principal Studies on the Association between Hormonal Contraception (DMPA) and HIV Infection. Data are presented in a detailed tabular form that makes comparisons easy and highlights important similarities and differences. The matrix provides an easy reference check for studies discussed in Part II. The principal findings are listed, followed by a column dedicated to discussing features of the study design that include the type of study, the size of study population and its characteristics, the date of initiation and/or duration, the nature of measurements taken and their frequency. In the next column, the strengths and weaknesses of the study design are recorded, both from the perspective of the researchers and from that of the writer of this paper. The final column on recommendations uses excerpted statements from the researchers; these quotations include important caveats and cover the continuing gaps in knowledge, as well as areas for further study.

DMPA, Fertility Control and HIV Transmission

The growing popularity of Depo (as DMPA is commonly known) for birth control, worldwide, started in the early 1980's long before a response to the HIV epidemic was mounted. Depo is one option among a number of hormonal contraceptives available to women. Broadly divided, these formulations are either oral contraceptive pills containing estrogen and progestin or those containing only progestin (DMPA). The availability of the latter in the form of quarterly injections appears to suit the personal, social and cultural needs of women in sub-Saharan Africa, providing them the best contraceptive option in terms of adherence, invisibility or inconspicuous usage.[10]

It is known that estrogen thickens the walls of the vaginal epithelium during the follicular phase and provides more resistance to viral penetration. Progestin spikes during the luteal period and is associated with the thinning of the vaginal epithelium, decreasing the resistance to viral and bacterial (STI) penetration. The danger of progestin-based hormonal contraception to women at risk of contracting the HIV virus can be linked to the role of these steroids in women's reproductive cycle.

During the 1990's studies of the biological factors that modified the transmission and acquisition of the HIV virus in men and women focused on sexually transmitted infections (STI's), genital ulcers and male circumcision [Martin, 2005]. A potential role for hormonal contraception in the acquisition of HIV started to emerge during this period in study findings. In 1993, researchers initiated a prospective study that followed a cohort of sex workers in the city of Mombasa, Kenya who attended an STI clinic. This study was designed to be methodologically rigorous through frequent interviews and testing (monthly) of the women to record their usage of contraceptives and any changes, as well as their HIV serostatus. The first publication of their findings in 1995 [Martin et al., 1995] showed a significant positive association between hormonal contraception use and the risk of acquiring HIV for this group of high risk women. In the case of oral contraceptive users, a trend was also noticeable. In later date analysis of data from the open cohort of women, subgroups were followed and assessed; findings on the association between hormonal contraception and HIV-1 seroconversion were reinforced with data gathered ten years after the cohort was initiated [Lavreys, 2004].

Data from the Mombasa cohort of sex workers show a consistent association between hormonal

contraception and the risk of HIV-1 acquisition, when the women were followed up over a 10-year period. The consistent findings from this study, run by researchers from the University of Washington, Seattle raised troubling questions about the safety of hormonal contraception for women in the HIV epidemic. However, results from cross-sectional studies were mixed and did not provide a strong base of evidence to discontinue hormonal contraception.

Plausible mechanisms linking HC use with HIV acquisition, progression and transmission:

1. HC use may increase women's susceptibility to acquiring RTIs/STIs (Chlamydia; cervicitis; candidiasis) and /or to expressing STI's with which they may already be infected (Herpes simplex). Presence of an RTI or STI could then, in turn, increase women's susceptibility to HIV
2. 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
3. HC use may disrupt populations of lactobacilli and other microorganisms which in the normal vaginal environment provide protection from certain pathogens, possibly including HIV
4. 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
5. HC use may increase the viral variety, set point, and expression of HIV in infected women
6. HC use may promote shedding of HIV into the vaginas of infected women, thus increasing their ability to transmit the virus to others.

(Gynuity meeting summary; Page 2, 2005)

The Gynuity Meeting

In 2005, Gynuity, a New York-based women's health organization, convened a meeting of scientists, policy makers, activists and other stakeholders to discuss the conflicting findings from the studies and to determine the need for policy change on the use of hormonal contraception by women living in areas where the epidemic was widespread and therefore at greater risk for HIV-1.

{*The Summary report of the meeting of family planning and HIV researchers, scientists and policymakers provides a comprehensive overview of the issues at the heart of the debate and outlines the principal mechanisms by which long-acting progestin contraceptives like DMPA can affect the acquisition and transmission of the HIV virus, as well as the progression of the disease.*}[11]

On page two of the summary report, there is a list of six mechanisms that could account for the association between the use of hormonal contraception such as DMPA and women's elevated risk for HIV infection. According to the summary document, the mechanisms listed below are "activated primarily by progestin. They may be most strongly associated with use of progestin-only contraceptives (including DMPA), but they may also operate in users of combined methods, such as oral contraceptives (OCs)."

It was noted that estrogen could exert a protective effect, but the amount used in a combined oral contraceptive would not necessarily be enough to "counter the negative effects which may arise from progestins." Evidence from laboratory studies and human studies were examined at the meeting to look

at the effects of exogenous and endogenous hormones on HIV acquisition, progression and transmission. The evidence currently available is suggestive but not conclusive.

Studies that found a strong association between hormonal contraceptive use and HIV acquisition as well as those that failed to show an association were discussed; however, the inconclusive and contradictory findings merely underscored the need for more research.

The meeting listed areas for future research, which are reproduced in the box above. Some of these areas are in consonance with the interests of women's health advocates. Remarkably, this list is more comprehensive than the recommendations for research inquiry that are found in the 2005 WHO statement released in Nairobi.

The Gynuity meeting was held in May, 2005. Proceedings of the meeting were made available on the organization's website in a summary format.

Topics for future research on Hormonal Contraception & HIV Relationship

1. 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
2. Differences in hormone effects on primary infection vs. disease progression vs. transmission of the disease from women to others
3. The relevance of animal models, particularly the macaque/SIV model, to HIV acquisition in women
4. Possible effects of HC use on highly active anti-retroviral therapy (HART)
5. The possible value of vaginally applied estradiol cream in strengthening the barrier offered by vaginal epithelium and thus in protecting women from HIV
6. 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
7. The effects of HC on specific immunological processes or elements (Toll-like receptors, CCR-5 co-receptors, and CXCR-4 co-receptors, for example)
8. Other specific mechanisms (such as cervical ectopy, increased viral replication, and greater viral diversity) whereby HC might have effect on HIV
9. How to best measure the immunologic environment of the vagina.

(*Gynuity meeting summary*, Page 5, 2005)

Collaborating with PATH, Gynuity published a special issue of *Outlook* dedicated to the topic. Following the conference convened by Gynuity, in September 2005, WHO's Special Programme of Research, Development and Research Training in Human Reproduction released a statement at a regional meeting in Nairobi.[12]

The foregoing list of topics for future research covers multiple aspects of a potential association between hormonal contraception and HIV acquisition. However, it should be noted that all topics treat women as an undifferentiated category, disregarding demographic variables such as age, marital status and occupation that can interact with biological factors.

The 2005 WHO Nairobi Statement

The WHO statement was issued jointly with the Reproductive Health and HIV Research Unit of the University of Witwatersrand in South Africa at a meeting of 72 representatives from 17 francophone, lusophone and anglophone sub-Saharan African countries on "Hormonal Contraception and HIV: Science and Policy." Participants were drawn from a wide field of stakeholders including policymakers and program mangers working in family planning, sexual and reproductive health, and HIV/AIDS, women's health advocates, positive people, and scientists and clinicians, and representatives from NGOs and the donor communities. After reviewing the scientific data and study findings, including forthcoming study findings, the group issued a statement wherein they clarify that, "***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***." {Emphasis added}

The statement urged women and their partners to use male and female condoms to prevent STIs, including HIV. It emphasized the critical role of effective hormonal contraception in family planning interventions that were essential "to reduce maternal and infant morbidity and mortality, HIV infection in infants, and poverty, and to promote sustainable development." The recommendations suggested future research focused on the "interaction between hormonal contraception and HIV in specific subgroups, particularly adolescents who are already very vulnerable to HIV infection." It also listed hormonal contraception interaction with HIV disease progression and antiretroviral treatments as important topics for future research. And it urged countries to "facilitate the integration of family planning and HIV service delivery and policies." While many of these recommendations are left to countries in the region to implement, there is a growing body of research, on many of the topics listed for more scientific exploration, whose findings call for a re-examination of the guidelines.

Evidence to Support Statement

The decision of the WHO to move forward with its statement in 2005, soon after the Gynuity meeting that recorded inconclusive evidence on the hormonal contraception and HIV acquisition relationship, was based on the early release of findings from a multi-center prospective study taking place in Uganda, Zimbabwe and Thailand, where a large cohort of family planning clients, 18-35 years old, were closely followed. The exclusion of Thailand from the final analysis reduced the cohort size to 4439 women. At baseline measurement approximately 34 percent of women were on oral contraceptives, and approximately 33 percent were on DMPA. The remaining group of women used non-hormonal methods. In this clinic population, which is viewed as representative of the general population unlike a subgroup such as sex workers, no association was found between hormonal contraception and HIV acquisition overall.

Morrison et al. in their January 2007 publication of this prospective study's findings, in the journal *AIDS,* discuss the shortcomings of their study that included: lack of randomization for ethical reasons, primarily to allow women to choose their methods; selection and confounding bias that followed from the failure to randomize; and limited power for subgroup analysis. The authors acknowledge that the accuracy of self-reported sexual behaviors can be an issue. It must also be emphasized that family planning clients are not representative of the general population of women of reproductive age, and the profile of the clientele can vary by location. In countries, where there is community-based distribution of contraceptive injectables such as Uganda, there are clients using hormonal contraception, who are not seen at the centers where recruitment has taken place [Stanback, 2007]. The study adhered to rigorous ethical

standards and participants were informed of the risks and received counseling on the prevention of HIV transmission.

Finally, the lead investigator, Charles Morrison, who is at FHI, disclosed that he owns stock in Pfizer, the manufacturer of Depo Provera. FHI also appears to have a contract for the community-based distribution of injectable contraceptives in the region.[13] In view of the significance the WHO has attached to the findings of this study, these potentially conflicting interests must be duly noted.

FHI dedicated its fall 2007 newsletter, *Network* (now ceased publication), to documenting the complex associations between hormonal contraception and HIV acquisition, progression and transmission, antiretroviral (ARV) therapy, STIs and other related topics. The researchers and scientists who have contributed to this issue discuss the lack of conclusive evidence (overall no association) in the HC-HIV study; however, they emphasize that condoms are the only effective barrier against HIV transmission and users of hormonal contraception should use condoms to protect against STIs, particularly HIV [Morrison and Cates, 2007].

2 Disscussion of Key Studies

In this section we examine the relationship between contraceptive method, sexually transmitted infection and human immunodeficiency virus type 1 (HIV-1) disease acquisition. Principally, we analyze the findings and commentaries from two groups of studies and briefly touch on related studies whose conclusions have added to the cumulative evidence that sustains the debate on that relationship. Although the WHO Nairobi 2005 statement appears to have been accepted as the authoritative word on the lack of an association between hormonal contraceptive use and an increased risk for HIV infection, it is critical to reassess the status of current knowledge based on ongoing scientific research findings and reanalysis of the data. This paper will be confined to a brief account of the related studies that were published just before and after the statement and which raise concerns about the need for more focused evidence on the association. It will discuss in greater length the findings about the hormonal contraception-HIV association from the two groups of studies, the Mombasa (Kenya) prospective cohort of sex workers followed for 10 years and the multicenter prospective cohort study of hormonal contraception and HIV (HC-HIV study), whose preliminary findings provided the basis for the 2005 WHO Nairobi statement. The translation and dissemination of the HC-HIV study findings have set policy and influenced scientific understanding with implications for the health and lives of sexually active women in the sub-Saharan African region. It is therefore justifiable to survey the full scope of the findings and explore their implications.

Mombasa Study

The Mombasa cohort studies are the first four studies listed in the matrix. Chronologically, the first two studies pre-date the WHO Nairobi Statement and were the earliest notable studies to support a relationship between hormonal contraception and HIV using data from a large cohort of sex workers, who had been enrolled in a STI clinic in the port city of Mombasa, Kenya and followed up through monthly clinic visits. This prospective, observational study of a large cohort (n=779) of sex workers attending a municipal STD clinic began in 1993 and gathered comprehensive data from physical and pelvic exams, STD screening, serological testing for HIV, sexual behavior inventory taking and the recording of changes in contraceptive use. The practice of switching contraceptive methods, non-adherence to the oral pill regimen and substitution of one method for another, particularly before the prescribed time, have made the tracking and documentation of such changes critical to measure in assessing the association of hormonal contraception with HIV disease acquisition. Researchers from the University of Washington, the University of Nairobi and Coast Provincial General Hospital published their findings in a 1998 article in the *Journal of Infectious Diseases* showing a significant increase in HIV incidence for women receiving DMPA [Martin et al. 1998]. A trend for oral contraceptives was noted but the association was weaker. In the multivariate analysis, when sexual behavior, condom use and STD were controlled, women on hormonal contraception appeared to have twice the risk of contracting HIV compared to women not on hormonal contraception.

From the epidemiological standpoint, the Mombasa cohort study was well designed and carefully executed, raising the credibility of its findings. However, the participants were from a high risk population (group at most risk for contracting the virus) and therefore the applicability of its findings to the general population of women contraceptive users (generalizability) would be limited. Hormonal contraception can be considered a biological risk factor, based on the changes it can induce in the vaginal epithelium; nevertheless, the

participants' increased exposure to sexual intercourse created an occupational hazard that set them apart from women in the general population.

Ten years after the Mombasa cohort was initiated and followed up, researchers conducted a study that updated the analysis using data from the Kenyan sex workers who enrolled between 1993 and 2003 [Lavreys et al., 2004]. Once again, their principal finding showed that use of both DMPA injectables and oral contraceptives was likely to increase the women's risk for contracting the HIV virus. This association held up regardless of STD status and type of sexual behavior.

In 2007, further analysis of the Mombasa cohort data (1206 HIV-1 seronegative women) showed that both hormonal contraception and Herpes Simplex Virus – subtype 2, were associated with an increased risk of HIV-1 infection [Baeten, et al., 2007]. The results were statistically significant and reinforced the consistency of the findings from this 10-year prospective study of the Mombasa cohort.

In their recommendations, the researchers emphasize that condoms are the only known protection against HIV-1 transmission and they should be used in conjunction with all forms of contraception, including hormonal contraception. They have stressed that women at high risk for HIV-1 should use condoms consistently. In effect, these researchers strongly recommend a dual protection approach for hormonal contraception users, especially those at high risk. (See Appendix I for recommendations excerpted from articles).

The strong methodological grounding of the Mombasa cohort study raises questions about actions taken by policy makers and health practitioners, particularly family planning counselors and health workers who administer the hormonal contraceptive injectables, to translate these findings for female sex workers and ensure the women know that they must use condoms when they are on hormonal contraception. The key question here would be: "Are sex workers who receive hormonal contraception told about the critical need to use condoms for dual protection?"

During the period when findings from the Mombasa cohort emerged, other studies in the region that examined the observed association between hormonal contraception and HIV released their findings. The lack of association found in some of these studies created an inconsistency in the findings. In urban Tanzania a study conducted in three large family planning clinics showed no significant association between HIV infection and the use of different contraceptives [Kapiga et al.,1998]. While this is a prospective study that included a large subgroup of young women, it had several drawbacks including loss to follow up that raised questions about the findings.[14] In the rural Uganda study (Rakai), no association was detected; however, the study's long intervals between follow-up visits could make contraceptive measurements less reliable [Kiddugavu et al., 2003].

HC-HIV Study / Uganda, Zimbabwe and Thailand Multi-Center Study

The WHO decision not to modify its contraceptive counseling guidelines to address a possible association between hormonal contraception and HIV acquisition was based on the HC-HIV study findings. As a consequence of its determinative role, this review critically examines the published findings and commentary by the lead researchers for a fuller explication of the nuances inherent in an observational study.

Under the sponsorship of the National Institute of Child Health and Development, a team of researchers based in the US, Uganda, Zimbabwe and Thailand launched a multi-center study to investigate the hormonal contraception-HIV association at sites in Uganda (3), Zimbabwe (4) and Thailand (7). Women seeking reproductive and general health

care services were recruited and followed between November 1999 and January 2004. After screening and enrollment, women were tested for HIV, HSV and STIs and followed up every 12 weeks (3 months) for 15 to 24 months. Follow up visits conducted the same tests done initially for HIV, HSV and other STIs. Preliminary findings from this study showing no association between hormonal contraception and HIV precipitated the WHO 2005 statement; however, the first publication of the study findings appeared only in January 2007 in the journal *AIDS* and was followed by a commentary in the *International Journal of Epidemiology* [Morrison et al. 2007a; Morrison, 2007b]. For the study's analysis, Thailand was excluded, reducing the total number of sites from 14 to 7 and leaving the two African sites with a combined total of 4439 women, in the age range of 18-35 years.

The participant characteristics at enrolment depict some biases in age and hormonal contraception usage that may well have contributed to the findings. There were equal numbers of participants in Uganda and Zimbabwe. The median age was 25 years and median number of years of education was 10 years. Not only did most participants live with a partner, there were only a few who

> "…reported multiple sex partners, commercial sex or sex while using alcohol or drugs, and less than half reported recent condom use….Compared with the non-HC participants, *more participants using hormonal contraceptives were older (25-35 years),* lived with a partner, and had two or more previous pregnancies." (Italics added) [Morrison, 2007a; p. 88]

The study found no association between hormonal contraception and HIV acquisition overall. The use of the word "overall" emphasizes that the result refers to the entire study population of women recruited in Uganda and Zimbabwe. At the same time, the researchers suggest that for a subgroup of young women the finding could be to the contrary.

"Young age (18-24) was a covariate significantly associated with HIV acquisition." [Ibid; p. 90]

The researchers admit that the study had limited statistical power for subgroup analyses, unlike that for the entire study population, which restricted them from assessing the risk for young women in the age range of 18-24 years. Women in this age range have been shown to be at greater risk for HIV acquisition than men of the same age, so this restricted analysis is a critical shortcoming that needs to be addressed in future studies. Moreover, with more of the hormonal contraception participants being older (25-34 years), the probability of finding an association was decreased. Writing in the *International Journal of Epidemiology* that year, Morrison acknowledges that age can and does play a role in modifying the effects of hormonal contraception on HIV acquisition.[15]

> "Finally, other characteristics such as age that vary across study populations could modify the effect of hormonal contraception on HIV risk. Young women tend to use progestin-only injectable contraception disproportionately. For example, injectable use (and particularly NET-EN use) is especially high among young women and adolescents in South Africa where about half of all sexually active women aged 15-24 years use them. Notably young women acquire HIV rapidly in South Africa: 17% of 15- to 24-year-old women are infected and HIV prevalence among young women is approximately four times that for young men of the same age group.
>
> "Hormonal contraception may affect young women differently (through changes in the vaginal epithelium or local immunological effects) than older women. These differences could be associated with

> HIV acquisition risk. For example in the HC-HIV study, among women 18-24 years, COC and especially DMPA use was significantly associated with an increased HIV risk compared with no hormonal contraceptive use. In contrast, among women 25-35 years of age, hormonal contraceptive use was associated with a statistically significant decreased risk of HIV acquisition…" (p. 2)

Evidence from other studies support the role of age as a modifier in HIV acquisition by women using hormonal contraception [Leclerc et al. 2008]. Women over 35 years appear to be at lesser risk, which suggests that endogenous hormonal changes with increasing age could play a role. Commenting on their statistical results, Morrison and co-investigators acknowledge that their results were not "inconsistent with a modest increase in HIV risk associated with hormonal contraceptive use, particularly for DMPA" [Morrison et al. 2007a; p. 92]. It is not clear how the term "modest risk" is to be interpreted in terms of exposure and demographic characteristics. Consequently, the "overall" absence of an association between hormonal use and HIV acquisition found in this study may be masking significantly different outcomes for subgroups in the study population.

Additionally, small subgroups of high risk women in the study did not register a higher risk for HIV associated with hormonal contraception use. The increased risk for HIV acquisition among HSV-2 negative women was an anomalous finding that has not been replicated in later studies. In his commentary, Morrison lists the questions that remain unanswered and the areas where more data are needed for clarifying the relationship between hormonal contraception and HIV acquisition [Appendix 1]. In an edition of *Network*, a FHI periodical dedicated to contraception news, researchers Cates and Morrison present a condensed report of the HC-HIV study meant for a wide readership. They state categorically that based on "current knowledge of HIV acquisition risks, hormonal contraception users who are HIV-negative need not switch to another contraceptive method." Later, they warn HIV-negative hormonal contraception users that if they are at risk for infection they should, "if possible, reduce their number of sex partners and also use condoms consistently and correctly." [Cates W. and Morrison CS, 2007, p. 3]

The report of the HC-HIV study presents data on condom use that clearly indicate that dual protection is not being widely used among the participants.

> "However, more non-HC than hormonal users reported consistent condom use (63% versus 5%; P<0.0001) during the previous 3 months." [Morrison et al. 2007; p. 89]

It is also important to note here that the Thailand data were excluded because there were far too few seroconversions to permit statistical analysis. There is a high prevalence of condom use in Thailand, which could contribute to the more widespread adoption of the dual protection method by couples. The country has had remarkable success in reducing HIV spread and increasing condom use, especially among vulnerable groups like sex workers. The HC-HIV study documents this low prevalence rate through screening for infected women before recruitment: Thailand (2.1%); Uganda (16.4 %) and Zimbabwe (38.1%) [Morrison et al. 2007; p. 88].

The lower level of condom use in the sub-Saharan region does distinguish family planning clients in this region from clients in other regions and challenges the notion that they are "similar to most women worldwide who use hormonal contraception."[16]

Recent Studies

Two other studies conducted in South Africa and published in 2007 found no increased risk of HIV acquisition for the hormonal contraception users. The

first recruited women from a cervical cancer screening study, aged 35-49 years, and followed them for 24 months [Myer L. et al., 2007]. The second study had a far smaller cohort of HIV-negative women (n=551), who were followed for a short period [Kleinschmidt et al. 2007]. It included users of the injectable Net-En about which there is little data and more research is needed.

In her secondary analysis of data from the Demographic and Health Survey (DHS) for Kenya, Lesotho, Malawi and Zimbabwe, Leclerc examined a representative sample of 4549 women, aged 15-24 years, and estimated the HIV risk attributable to DMPA at 6% for the combined data for four countries. (Leclerc's analysis of data for women aged 25-49 years did not show an effect for hormonal contraception; Myer's study population was in a parallel age range). The investigators see this as a "small" risk. However, in these countries of high HIV prevalence, the "small" percentage could translate to several hundred or thousand women – a situation that would be untenable in the western world. These robust findings from secondary analysis of survey data need to be followed up by a focused study on young women who are choosing hormonal contraception for protection against pregnancy. Leclerc and colleagues state this categorically, "Since numerous studies show that age is a crucial factor for HIV acquisition, future investigations should take it into account, and focus on very young women" [Leclerc et al., p. 375].

The vulnerability of young women to HIV infection is widely known; however, Leclerc's findings and the observations of the HC-HIV study on this subgroup emphasize the urgency of investigating the role of DMPA and other hormonal contraceptives in elevating this risk. Although sexual behavior patterns and sexual partnering within social networks could explain some of the observed association, there still remains a gap in our understanding of the hormonal role in increasing the susceptibility of adolescent girls and young women. [17] A survey conducted in Kisumu, Kenya and Ndola, Zambia to examine sexual partnerships states that the male-female discrepancy in HIV prevalence could not be explained by behavioral factors alone and the female susceptibility could be driving the epidemic [Glynn JR et al. 2001].

Related Issues

An early draft of this paper discusses the role of hormonal contraception in elevating the viral load of infected women and progressing more rapidly to full blown AIDS [Kumwenda et al., 2008]. In addition it brought up early stage research on a possible role played by hormonal contraception in increasing the infectivity of HIV positive women and consequently posing a greater risk to their sex partners [Stringer and Antonsen, 2008]. Following suggestions from a preliminary review we excluded them from this discussion paper.

We also touched upon the role of unclean needles in the spread of the epidemic. There is consensus on the potential for unclean/unhygienic needles to spread infection, but there is little agreement on the extent to which unclean needles at clinical centers are contributing to the spread of HIV infection.

Contraceptive Counseling and Dual Protection Method

Family planning proponents use a cost-benefit calculus in order to justify the funding of contraception programs as prevention. A recent publication by an FHI scientist estimates that contraceptive usage in PEPFAR countries has resulted in potential cost savings as high as $2.2 million in South Africa by the prevention of unwanted and unintended HIV-positive births [Reynolds, et al., 2008]. We noted earlier that contraception had a major role in the prevention of vertical transmission of HIV from infected mothers to newborns. By quantifying the savings in the cost of therapeutics (antiretroviral regimens), the family

planning researchers justify the need for expanding contraceptive availability for HIV infected women in the region to save on Prevention of Mother-to-Child Transmission (PMTCT) services. They see contraception as a major HIV prevention strategy in reducing the number of infant HIV positive infections with enormous potential for savings over the cost of *nevirapine* to prevent mother-to-child transmission [Reynolds, 2008; Wilcher, 2008].

The use of such cost-benefit calculus for the numbers of women and girls infected by HIV through the use of hormonal contraception, in order to prevent pregnancy with its attendant risks, is both complicated and problematic to generate. Leclerc's six percent increased risk may be a conservative projection, depending on the country and the current prevalence rates. The limited access to antiretrovirals (ARVs) in this region would not bode well for the infected women.[18] For three decades the high risk for maternal mortality in the same region has justified the benefits of contraception, often with attendant costs for the women. It is not in their interest to trade one mortality risk for another; consequently, the use of a barrier method along with hormonal contraception is absolutely critical for women in areas of high HIV prevalence.

The "dual protection" method is strongly advocated by the WHO and the investigators who support the use of hormonal contraception in this population. [Appendix 1] Under the circumstances just described, the larger issue to be raised here is the implementation of the dual protection safeguard through counseling hormonal contraception users. Are family planning clinics counseling clients who receive DMPA injections to use condoms for non-monogamous sexual activity? The low use rates for condoms in the region suggest otherwise.

The South African Demographic and Health Survey 2003 reports increased use of condoms over a five-year period; however, young males register a much higher use rate than females of the same age.[19] Only 49.3 percent of women aged 15-19 years who engaged in high risk sex reported using (male) condoms, compared with 73.3 percent of men in the same age group. Only a small percentage of women reported ever using the female condom (3%), with almost negligible usage by women in the lowest age group (.5%). These statistics raise questions about the effectiveness of the dual protection method in areas where there has been longstanding resistance to barrier methods. They suggest that there is need for extensive outreach and intensive education to ensure women on hormonal contraception are effectively and consistently protecting themselves.

The WHO's recommendations are not mandatory for national governments. Consequently, the family planning clinics, where hormonal contraception is provided, by default, are the sites where counseling must be done for the dual protection method. In many of the countries where the epidemic rages family planning and HIV services are separately funded and implemented [Wilcher, 2008]. Some efforts have been made in Kenya to integrate the services, but others have yet to follow. Integration can also bring hierarchical challenges for clinical workers accustomed to treatment environments and divert valuable funding away from life-saving treatment based on the cost-saving effectiveness of contraception. There is strong evidence to support the role of contraception in preventing the vertical transmission of HIV from mother to infant; however, the evidence that hormonal contraception is safe for all age groups and high risk populations is still debatable and requires more dedicated research.

Critical Areas for Follow-up and Action

The table (Appendix 1) summarizes the principal features of the studies on hormonal contraception and HIV acquisition and displays the recommendations that investigators have made. Irrespective of their findings, the majority of researchers have

emphasized the need for women using hormonal contraception to adopt dual protection, by using male or female condoms to prevent HIV acquisition. The recommendations also highlight the consistent findings of an association between HIV acquisition and young age of contraceptors (15-24 years) as well as with the high risk group of sex workers. These two subgroups in the population must use dual protection if they choose DMPA or oral contraceptives. Until scientists fully elucidate the association between hormonal contraception and HIV acquisition, progression and transmission, we need integrated services for family planning counseling and HIV counseling so that clients receive comprehensive information about the potential risks of hormonal contraception and the urgency for adopting a dual protection approach. To do this there should be vertical integration of family planning and HIV counseling centers and an expansion of educational efforts to get communities fully informed about the risks and benefits of hormonal contraception.

Scientists and researchers examining the association between hormonal contraception and HIV acquisition have accepted the findings of no association "overall" without addressing the shortcomings of the HC-HIV study [Morrison et al., 2007a] or the limits of its generalizability. The WHO and FHI website statements promote the consensus that women at risk for HIV can use "all available contraceptive methods," including hormonal contraception [Heikinheimo and Lahteenmaki, 2008]. Few commentators note the accompanying restrictions; an exceptional review and commentary brought up observations made in this paper:

> "Detailed virological studies among commercial sex workers in Kenya suggested that hormone use predisposes them to the acquisition of a diverse HIV-1 virus population, which leads to higher levels of viral replication and more rapid HIV disease progression [16-18]. It is possible that these biological effects are more pronounced in young women and adolescent girls, who have been shown to be at disproportionately high risk of acquiring HIV-1 infection in sub-Saharan Africa [19]." [Bultreys et al., 2007].

It is critical that the implications of the research findings for subgroups of women in the population such as sex workers, teenage girls and young women are reviewed, reassessed and disseminated so that preventive actions can be taken to save lives while research goes on. From our standpoint, the current state of knowledge on this potential association warrants the activation of the precautionary principle, which is a preventive mechanism when definitive scientific knowledge is unavailable.[20]

3 Recommendations for Discussion

We need modifications in WHO's policy guidelines for clinicians and health workers who counsel women seeking contraception in all regions of high HIV prevalence. Although there appears to be no "overall" association between hormonal contraception use and HIV acquisition, there is a consistent trend in the findings that support a higher level of risk for women engaged in sex work and for very young women, in the age range 15-24 years. While research for greater scientific understanding of these associations must continue, we expect safeguards to be instituted until more permanent measures can be taken. When hormonal contraception is used, particularly by young women, then a barrier method like the condom (male or female) should also be used to prevent STIs and HIV. Counseling at the family planning clinics should promote the dual protection method and community education campaigns must form groups and tap networks to discuss and spread the message [Cleland and Watkins, 2006].

We prioritize issues for policy development based on their level of urgency for the vulnerable subgroups of women in the sub-Saharan African region that were discussed in this paper:

A. Policy formulation for immediate action: Development of guidelines for hormonal contraceptive providers and the initiation of educational campaigns in communities.

1) We need policy guidelines that will ensure that women engaged in sex work and those having greater exposure to sexual activity are fully informed and educated about the increased risk for HIV if they choose hormonal methods of contraception, wherever it may be dispensed. (Rationale: The findings of a hormonal contraceptive and HIV acquisition association in the Mombasa study have been explained in terms of the greater sexual exposure to which the women are occupationally subjected, compared to women in the general population. Because this is a biological phenomenon, the findings could have implications for sex workers in other regions of the world.)

2) Providers and counselors must follow a protocol that informs their clients about the need to use a dual protection method when they provide DMPA injectables. (The WHO statement did stress the need for dual protection, "The use of male or female condoms is recommended whenever there is any possibility of exposure to STIs, including HIV. Programmes to promote dual protection should be actively supported.") While there has been an increase in condom use within the region, it is not clear what is being done in different local contexts.[21]

3) Adolescent girls and young women (15 – 24 years) should be counseled to adopt dual protection methods if they choose hormonal contraception. They should be educated and supported in the use of the female condom.[22]

B. Policy to identify issues for continuing research: Expansion of current research agenda for understanding the hormonal contraception and HIV association.

1) There should be expanded research on the association between hormonal contraception and HIV disease acquisition, progression and transmissibility in the general population of women. The research agenda framed at the 2005 meeting hosted by Gynuity (p. 5) broadly documents areas to address.

2) The research design should incorporate purposive sampling to include large enough samples from subgroups like teenage girls and young women who show marked susceptibility, in order that statistical tests can be performed for this subgroup.

3) We need more studies to explicate the relationship between hormonal contraception and the acquisition of HIV by young women, with attention to changes in the vaginal epithelium and immunity response mechanism.

C. Policies to emphasize the importance of translation research: Creation of regional scientist-lay committees to review and prioritize the scientific findings that have implications for women's health.

1) The tendency for mass mediated communications to simplify and summarize complex and nuanced scientific findings is a pervasive problem in the translation of new knowledge and its application in clinical settings. In this instance, there seems to be a gap between the nuanced presentation of the findings in a scientific forum and its simplified interpretation in the research literature. We need to examine the diffusion of findings and the threats to the integrity of the information that is relayed both in the mass media and in scientific publications.

2) There is need to set up mechanisms for ensuring that findings with serious implications for women's health are followed up and public education programs initiated with little loss of time.

Endnotes

1. http://data.unaids.org/pub/GlobalReport/2008/jc1510_2008_global_report_pp11_28_en.pdf , accessed November 13, 2008.
2. UNAIDS 2008 Epidemiology Slides, accessed November 13, 2008. http://www.unaids.org/en/KnowledgeCentre/HIVData/Epidemiology/epidemiologySlidesAuto.asp, Figure 2.4.
3. Personal communication from Robert Reinhard, January 7, 2009.
4. *2008 report on the global AIDS epidemic* (UNAIDS, July 2008), Figure 2.10, http://www.unaids.org/en/KnowledgeCentre/HIVData/Epidemiology/epislides.asp, accessed November 13, 2008.
5. IPPF/UNFPA/Young Positives, "Change, Choice and Power: Young Women, Livelihoods and HIV Prevention," 2007, p.2.
6. UNAIDS, 2006 AIDS Epidemic Update, December 2006.
7. *UNAIDS 2008 Epidemiology Slides*, ibid. See Figure 4.4.
8. This risk was underscored by Robert Reinhard. Received January 7, 2009.
9. To keep the paper focused on the discussion of the association between hormonal contraception and HIV acquisition, two papers on hormonal contraception and disease progression, included in an earlier draft, have been removed both from the discussion and from the analysis presented in the matrix (Kumwenda et al., 2008; Stringer and Antonsen, 2008).
10. Female -controlled methods have received little emphasis in the family planning programs of sub-Saharan Africa and condoms are generally associated with less trusted partners. For a discussion of these issues see Richey, Lisa (2008) *Population Politics and Development: From the Policies to the Clinics.* New York; Palgrave MacMillan. On the perceptions of injections as symbols of healing, see Birungi, Harriet. Injections and Self-Help: Risk and Trust in Ugandan Health Care. *Soc. Sci. Med*. 1998; 47(10): 1455-1462.
11. http://gynuity.org/downloads/MtgSummaryHIV-HormonalContraception.pdf, accessed November 9, 2008.
12. *WHO Hormonal Contraception and HIV: Science and Policy*, Africa Regional Meeting. Nairobi 19-21 September 2005. http://www.who.int/reproductive-health/stis/hc_hiv/nairobi_statement.html, accessed November 15, 2008.
13. On its website, FHI notes that it is providing community-based distribution of injectable contraceptives (DMPA) in Kenya, working with the MOH. It states, "There is substantial unmet need for family planning in Uganda. FHI and the Uganda Ministry of Health are working to meet this need by revitalizing long-acting and permanent contraceptive methods and promoting the provision of DMPA by community-based health care workers. To improve access to and client continuation of contraception, FHI also is surveying drug shops to see whether they would be suitable outlets for providing injectable contraception." Source: www.fhi.org; accessed December 3, 2008.
14. Barbra Richardson, a statistician at the University of Washington, Seattle, points out: "This study had a major flaw in that OCP users were included in the comparison group when assessing the effects of DMPA and DMPA users were included in the comparison group when assessing the effects of OCPs." [March 31, 2009]
15. Morrison, Charles S. Commentary: Hormonal contraception and HIV acquisition---current evidence and ongoing research needs. *Int. J. Epidemiol.* Advance Access published January 24, 2007.
16. Best, Kim Hormonal Contraception and HIV: more Research Needed: No Changes in Family Planning Practices Currently Warranted. *Global Health Technical Brief*. Family Health International / CRTU Program. March 30, 2007.

17. Personal communication from Marge Berer to Betsy Hartmann, January 8, 2009: "As for levels of risk among young women, sexual networking issues come in, and the evidence as I understand it is that young women protect themselves less than young men, young women are more worried about pregnancy than HIV, young women have partners older than themselves and therefore the levels of HIV are lower in young men than young women of the same ages, while levels are higher in men in the age group 24-34, and they are the ones infecting women aged 15-24. Men have more female sexual partners than women have male partners, and so the proportion of women infected has increased over time where the epidemic is primarily heterosexual."
18. Marion Stevens argues that in the HIV-AIDS care context the dominance of the maternal-health paradigm has deflected attention from women's sexual and reproductive health and rights. Stevens M. From HIV prevention to reproductive health choices: HIV/AIDS treatment guidelines for women of reproductive age. *African Journal of AIDS Research* 2008 7(3) 353-359.
19. The South African Demographic and Health Survey (SADHS) 2003. See Table 9.4. http://70.84.171.10/~etools/doh/sadhs/chapter9.pdf, accessed December 8, 2008.
20. The principle and the main components of its implementation are stated this way in the 1998 Wingspread Statement on the Precautionary Principle: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof. The process of applying the precautionary principle must be open, informed and democratic and must include potentially affected parties. It must also involve an examination of the full range of alternatives, including no action." - Wingspread Statement on the Precautionary Principle, Jan. 1998 (The Science and Environmental Health Network) http://www.sehn.org/precaution.html, accessed December 8, 2008.
21. WHO expects its general global guidance to be "made relevant to the context of the individual user/client." It has no role in enforcement. It recognizes the need for more research in this area but lacks the funding to proceed. Personal communication with Tim Farley, February 18 and February 24, 2009.
22. The 2005 WHO Statement on Hormonal Contraception and HIV: Science and Policy acknowledged the need for further research to follow up data trends and included this focus in its recommendations for research: "Interaction between hormonal contraception and HIV in specific subgroups, particularly adolescents who are already very vulnerable to HIV infection."

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APPENDIX: Select Principal Studies on the Association between Hormonal Contraception (DMPA) and HIV Infection

Study	Findings	Design	Strengths / Weaknesses	Recommendations
##Martin et al. *J Infect Dis.,* **1998** Oct	Women who used DMPA had an increased incidence of HIV-1 infection. [HR 2.2; 95% CI]; multivariate model **[HR 2.0; CI 1.3-3.1].** Trend for OCP use and HIV-1 acquisition [HR, 2.6; CI, .8-8.5] ***Women on HC have a twofold increased risk of contracting HIV than women not on HC, when sexual behavior, condom use and STD are held constant***.	Prospective, observational study of cohort (n= 779) of prostitutes / sex workers attending a municipal STD clinic, **Mombasa, Kenya** initiated in 1993. Monthly follow-up visits included physical exam, pelvic exam, STD screening, and HIV-1 serologic testing and measurement of contraceptive use and sexual behavior	#(+/-) Study population a high risk group of sex workers; (+)Monthly follow-up enhances precision in estimating date of HIV seroconversion (+)Sound methodology with frequent follow up and measurement to establish causal path. Robust findings. [# occupation-based group / limited generalizability]	Caveat: Findings were observed in a population of women with high rates of sexual exposure and STDs and may not be generalizable. ***"Until a research consensus is reached, the message to sexually active women is straightforward. Only condoms are known to protect against HIV-1 transmission, and their use should be advocated for HIV and STD prevention in conjunction with all methods of contraception."*** **[page 1059]**
##Lavreys et al *AIDS*, **2004**	***Use of both injectables and OC may increase the risk of HIV-1 acquisition, independent of sexual behavior and STD exposure.*** DMPA use was associated with a significantly increased risk of HIV-1 acquisition [HR 1.8, 95% CI 1.4-2.4], similar to finding Martin et al. 1998. The use of oral contraceptive pills was also associated with a significantly increased HIV-1 risk [HR 1.5, 95% CI 1.0-2.1]	10-year follow-up of **Mombasa** cohort of Kenyan prostitutes enrolled between 1993 and 2003. (n=1272). **Median age 26 years.** Updated analysis of data first reported in 1998. Relatively low level of sexual activity, because majority of participants (74%) had primary employment as barmaids and supplemented their income with commercial sex work. None reported injection drug use and only 3 (<1%) practiced anal sex, making heterosexual vaginal intercourse the principal HIV-1 risk factor for virtually all **.**	(-) High rate partner change* (+) Sexual intercourse frequency similar to general population (+) Monthly measurement of HIV-1 status, contraceptive use, sexual behavior, and STD – minimizing the potential for bias caused by the misclassification of either outcomes or exposures. [* "…average sexual frequency was similar to that reported in surveys among general population of African women." page 697]	"Given the widespread use of HC in areas of high HIV-1 prevalence, our findings are concerning. ***Regardless of the method women choose for pregnancy prevention, healthcare providers must emphasize that condoms are the only method proved to prevent HIV-1 transmission***. ***Women who use HC, especially those at high risk of HIV-1, should be especially encouraged to use condoms consistently."*** **[page 697]**
##Martin et al *J Acquir Immune Defic Syndr* **2005**, March	Presentation of Mombasa cohort findings. Discussion of results of meta analysis for OC and HIV acquisition studies. [Studies conducted in Africa had an OR of 1.45 (CI 1.15-1.83), and the highest quality African studies calculated OR of 1.65 (CI 1.09-2.52)]	Re-presentation. See above	See above.	Further studies to understand the differences in results between different populations. ***Any fertility regulation counseling must include education about HIV and STI & condom promotion.*** [page **S14]**

Study	Findings	Design	Strengths / Weaknesses	Recommendations
##Baeten JM et al. *AIDS,* **2007** August	Re-analysis of Mombasa cohort data (high risk African women) showed that HC and HSV-2 infection were both associated with increased risk for HIV-1 acquisition, HIV-1 risk associated with HC use was not related to HSV-2 serostatus (Morrison finding) (+) **HIV-1 and OC** [HR **1.46;** 95% CI 1.00-2.13] (+) **HIV-1 and DMPA** [HR **1.73**; 95% CI 1.28-2.34] (+) **HIV-1 and HSV-2** [HR **3.58;** 95% CI, 1.64-7.82]	Reanalysis of data from prospective cohort study of 1206 HIV-1 seronegative sex workers from Mombasa, Kenya followed monthly.	See above	***"Debate regarding the true risk that use of hormonal contraception poses for women at-risk for HIV-1 will continue. Nonetheless, it is clear that hormonal contraceptives are not protective against HIV-1 acquisition, and the public health message must be that dual protection with condoms should be the goal for women using hormonal contraception."*** **[page 1776]**
Kiddugavu et al *AIDS* **2003**	***Use of hormonal contraception is not associated with HIV acquisition, after adjustments for behavioral counseling.***	Observational study of on-going rural community-based cohort, from **November 1994 to December 1999 (5 years). Adults (n=5117**) who consented, **aged 15-59 years**, resident in **56 communities** of **Rakai** district, Uganda, were enrolled and followed at **10-month intervals. Six surveys were conducted during the 5-year period.** Analysis: women attending two or more study visits in order to ascertain HIV serostatus. Contraceptive change counted as 5-month exposure during the interval.	(+) Large-sized cohort of family planning clientele (+) Large age subgroups (+) Condom users did not seroconvert increasing self-report reliability. (-) Observational study; limitations of self-selection (-)Self-reported exposure to HC use not verifiable. (-) Potential carry over effect of the HC after cessation of use, leading to possible under-estimation of HC effect. (-) Long interval between follow-up visits	**Family planning providers should be trained to provide HIV/AIDS counseling to clients and should consider promotion of both hormonal methods in conjunction with condoms**.* Also, HIV counselors should be encouraged to provide family planning services or referrals. [**page 239]**

Study	Findings	Design	Strengths / Weaknesses	Recommendations
!!Morrison CS et al. *AIDS,* **2007** Jan	***No association found between HC and HIV acquisition overall [DMPA HR 1.25; 95% CI, 0.89-1.78; OCP HR 0.99, 95% CI 0.69-1.42]. HC users, who were HSV-2 seronegative showed increased risk of HIV acquisition.*** [**Young age (18-24) was a covariate significantly associated with HIV acquisition** (page 90) as were 'not living with partner', 'Zimbabwe site,' 'Uganda high risk referral group', 'primary partner risk', and 'behavioral risk' among others.]	Multicenter (**Uganda, Zimbabwe** & Thailand) prospective, observational cohort study of HIV- women, **18-35 years** and followed at **12-week** intervals for **15-24 months.** Thailand data excluded from analysis. African participants included in analysis were **4439** women, with 34.7% using OCs and 34.2 % using DMPA and the rest methods that were non HC at baseline measurement.	(+)Study participants drawn from clients at family planning centers and followed closely. (?) (+) Women continued chosen method (-) Selection and confounding bias, since groups not randomized. (-)Self-reported sexual behavior data's accuracy questionable (-)Limited power for subgroup analyses. (-)3-month intervals between clinic visits	Additional research needed to confirm and interpret HSV-2 negative findings. "…***Therefore, our study results are not inconsistent with a modest increase in HIV risk associated with hormonal contraceptive use, particularly for DMPA***. [**page 92]** Nevertheless, we found no evidence of higher HIV risk associated with hormonal contraception among high-risk subgroups in our study, including among participants with STI." **[p. 92]**
!!Morrison CS *Int. J. Epidemiol.* **2007** January		Descriptive review: Commentary on HC and HIV acquisition-- current evidence and ongoing research needs		1) We await results of studies evaluating modifying effects of HSV-2 seronegative (status). 2) ***We need studies to more fully explore modifying effects of age.*** 3) We need data on whether other forms of HC (progestin-only implants *Jadelle* and *Implanon* (different progestin) affect HIV acquisition risk. 4) ***Need to know - Risks and benefits of HC use among HIV+ women in terms of their infectivity, disease progression and treatment effects.*** **[page 2]**
!!Cates W and Morrison CS *Network* **2007**	-"In sum, on the basis of current knowledge about HIV acquisition risks, hormonal contraceptive users who are HIV-negative need not switch to another contraceptive method." (page 3)	Condensed report of the HC-HIV study for FHI periodical meant for a wide readership.	Strives for balanced presentation. States research on HC users and HIV disease progression as well as infectivity to male partners continue without conclusive findings	"While hormonal contraception is highly effective against pregnancy, it does not protect against HIV. Thus HIV-negative hormonal contraceptive users at any risk of infection should, if possible, reduce their number of sex partners and also use condoms consistently and correctly." (**page 3)**

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Myer L et al. *Int. J Epidemiol.* 2**007** Feb	HC use not associated with increased risk of HIV acquisition. No association between increased duration of DMPA use and HIV incidence (P-value for trend, .51)	Prospective cohort cervical cancer screening study of women, in **South Africa,** using combined oral contraceptives (COC), Net-En and DMPA. Participants were 4200 HIV- women, aged **35-49 years**. Followed for **24 months.**	(+) Study drew from general population and was large (n=4200) (+)Included 3 types of HC (DMPA, Net-En, COC) (-) Study population confined to older woman with lower risk (-) Large time intervals between study visits (-) Measurements for cohort staggered – weakening infection timing determination.	***"…dual method use (combined use of condoms with a non-barrier method) should be actively promoted by family planning services in populations where HIV is prevalent."*** **[page. 173]** ***"While further research is required, there is no indication that the benefits of hormonal contraception for sexually active women should be qualified by concerns regarding increased risk of HIV infection."*** **[page 173]**
Kleinschmidt et al. *Contraception* **2007** June	No evidence of an association between injectable contraceptives DMPA and Net-En and HIV infection.	Prospective study. Cohort of HIV seronegative women were followed up for a total of 491 person-years in **South Africa**, to investigate HIV incidence in women using either DMPA or Net-En.	(+) Includes Net-En users. (-)The study population was small (n=551) and lacked the power for sub-group analysis. Follow up period was short.	"…it is therefore important that research-based evidence is produced that can reassure users and health providers of the safety of NET-EN with regard to HIV risks." **[page 466]**

Study	Findings	Design	Strengths / Weaknesses	Recommendations
Leclerc PM et al *Contraception* **2008**	-DMPA users have a significantly higher seroprevalence than nonusers (and users of OC and traditional methods). Multivariate analysis using as controls age, duration since first intercourse (exposure), urban residence, education, # sexual partners and marital status yielded an OR of 1.34[95% CI 1.10-1.63] -Finding of no impact for pill deviates from other studies. -Analysis for women 25-49 years found no effect of hc (p=.170), suggesting **age is a modifier**. - The increased risk of DMPA was present in 3/4 countries and significant in Lesotho and Zimbabwe, the countries with highest seroprevalence.	**Secondary analysis** of Demographic and Health Survey **(DHS**) data for **Kenya, Lesotho, Malawi and Zimbabwe** gathered between 2003 and 2006 on a representative sample of **4549** women, aged **15-24 years**.	(-) Secondary analysis of survey (observational) data rather than a randomized controlled trial or intervention. (+) Robust results without selection bias and controlled for confounders	-Age was rarely taken into account in previous epidemiological studies. ***Since numerous studies show that age is a crucial factor for HIV acquisition, future investigations should take it into account, and focus on very young women.*** **[p375**] - Leclerc sees the risk as small: "The increased risk of DMPA was present in three of the four countries investigated, and significant in Zimbabwe and Lesotho, the countries with the highest seroprevalence. HIV risk attributable to DMPA remained small altogether and was estimated at 6 % in the four countries combined." [**p 371**] NB: In countries with high HIV prevalence, 6% could amount to thousands of women]

Key:

*	Emphasis added to highlight theme
##	Studies of the Mombasa (or Kenyan) cohort or a subgroup within the cohort
!!	Multicenter (Uganda and Zimbabwe only) prospective cohort study that finds no association between HC and HIV acquisition overall and forms the basis for the WHO 2005 Nairobi statement.
CI	Confidence Interval
COC	Combined Oral Contraceptives
HC	Hormonal Contraception
HIV-1	Strain of HIV virus first discovered and found around the world; it is virulent and easily transmitted
HR	Hazard Ratio
HSV	Herpes Simplex Virus has two subtypes: HSV-1 is associated with oral infections (cold sores); and HSV-2 with genital infections.
PMTCT	Prevention of mother-to-child transmission
RR	Relative Risk (Risk Ratio)

Morrison CS, Richardson B A, Mmiro F et al. Hormonal contraception and the risk of HIV Acquisition. *AIDS* 2007; 21:85-95.

"Our finding of no overall association between hormonal contraceptive use and HIV acquisition suggests that the inconsistent results of previous studies would not support a strong association between hormonal contraception and HIV. Previous studies had important methodological shortcomings: few hormonal contraceptive users and low study power, poor measurement of hormonal contraceptive use and potential confounding variables, lack of adjusted analyses, and poor follow-up. **Nevertheless, one methodologically strong study conducted among Kenyan sex workers found an association between both DMPA and COC use and HIV acquisition [15,17]. As our study participants were seeking family planning services, our study cannot rule out the possibility that hormonal contraception might increase HIV susceptibility among some highly exposed subpopulations. Also, the upper bound of the CI values around our risk estimates were very close to the risk estimates from the Kenyan study (HR values of 1.5 for COC, 1.8 for DMPA)**. **Therefore, our study results are not inconsistent with a modest increase in HIV risk associated with hormonal contraceptive use, particularly DMPA.*** Nevertheless, we found no evidence of higher HIV risk associated with hormonal contraception among high-risk subgroups in our study, including among participants with STI." (page 92)