



Hormonal contraception and HIV

Technical statement

16 February 2012

Executive summary

Following new findings from recently published epidemiological studies, the World Health Organization (WHO) convened a technical consultation regarding hormonal contraception and HIV acquisition, progression and transmission. It was recognized that this issue was likely to be of particular concern in countries where women have a high lifetime risk of acquiring HIV, where hormonal contraceptives (especially progestogen-only injectable methods) constitute a large proportion of all modern methods used and where maternal mortality rates remain high. The meeting was held in Geneva between 31 January and 1 February 2012, and involved 75 individuals representing a wide range of stakeholders. Specifically, the group considered whether the guideline *Medical eligibility criteria for contraceptive use, Fourth edition 2009* (MEC) should be changed in light of the accumulating evidence.

After detailed, prolonged deliberation, informed by systematic reviews of the available evidence and presentations on biological and animal data, GRADE profile summaries on the strength of the epidemiological evidence, and analysis of risks and benefits to country programmes, the group concluded that the World Health Organization should continue to recommend that there are no restrictions (MEC Category 1) on the use of any hormonal contraceptive method for women living with HIV or at high risk of HIV. However, the group recommended that a new clarification (under Category 1) be added to the MEC for women using progestogen-only injectable contraception at high risk of HIV as follows:

Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition, other studies do not show this association. A WHO expert group reviewed all the available evidence and agreed that the data were not sufficiently conclusive to change current guidance. However, because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to *also always use condoms, male or female, and other HIV preventive measures*. Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential. These recommendations will be continually reviewed in light of new evidence.

The group further wished to draw the attention of policy-makers and programme managers to the potential seriousness of the issue and the complex balance of risks and benefits. The group noted the importance of hormonal contraceptives and of HIV prevention for public health and emphasized the need for individuals living with or at risk of HIV to also always use condoms, male or female, as hormonal contraceptives are not protective against HIV transmission or acquisition.

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Background

Hormonal contraceptives – oral contraceptive pills (OCPs), injectables, patches, rings, or implants – are highly effective methods of pregnancy prevention. Besides preventing unintended pregnancies these family planning methods offer additional important health benefits. Family planning plays a crucial role in contributing towards achieving important global public health targets such as reducing maternal mortality and pregnancy-related morbidity, preventing mother-to-child-transmission of HIV, reducing poverty and hunger, promoting women's empowerment, achievement of universal primary schooling, and long-term environmental sustainability. For women at high risk of HIV, or living with HIV, consideration must be given to the interaction between HIV-related-risks and the use of contraceptive methods.

The Department of Reproductive Health and Research of the World Health Organization (WHO) produces evidence-based guidance on contraceptive use. One of its guidelines, *Medical eligibility criteria for contraceptive use, Fourth edition 2009* (MEC), provides recommendations on the use of various contraceptive methods by women and men, particularly on *who* can safely use the methods. As such, the MEC provides guidance regarding the safety of using hormonal contraceptives for women at high risk of HIV infection and women who are living with HIV. The Department carefully monitors the publication of new research evidence in order to keep these guidelines up to date with the state of knowledge in the field.

New data have recently been published about the use of some hormonal contraceptive methods and risk of HIV. The need arose to evaluate the published evidence on hormonal contraceptive use and HIV-infection acquisition among women at high risk of HIV, disease progression among women living with HIV, and transmission of HIV from women living with HIV to non-infected male partners. Guidance on contraception was developed to inform Member States, policy-makers, programme officials, and key stakeholders in service delivery.

Method of work

WHO and a group of experts and partners analysed all published data on the subject, and resolved to convene a technical consultation which brought together 75 participants from 18 countries; 18 agencies were represented. The multidisciplinary group comprised experts in international family planning and HIV, including clinicians, epidemiologists, researchers, programme managers, policy-makers, guideline methodologists, reproductive biologists and pharmacologists, and HIV and women's health advocates. All participants were asked to declare any conflict of interest; 13 declared an academic conflict of interest relevant to the subject matter of the meeting (for details see: http://www.who.int/reproductivehealth/topics/family_planning/hc_hiv/en/index.html). No one was asked to withdraw from the deliberations or recommendation development.

Existing WHO recommendations on use of specific hormonal contraceptive methods for women at high risk of HIV or living with HIV were reviewed in accordance with procedures outlined by the WHO Guidelines Review Committee and the Grading Recommendations, Assessment, Development and Evaluation (GRADE) approach to evidence review. Three systematic reviews of the epidemiological evidence were conducted: hormonal contraception and acquisition in HIV-negative women; hormonal contraception and transmission from HIV-positive women to HIV-negative men; and hormonal contraception and disease progression in HIV-positive women. *PubMed* and *EMBASE* databases were searched for studies published in any language in a peer-reviewed journal up to 15 December 2011. Reference lists and contact with experts in the field were also used to identify other studies, including those in press. Grey literature and conference abstracts were not considered. GRADE evidence profiles were prepared to assess the quality of the summarized evidence. The three systematic reviews were peer-reviewed by an Advisory Committee prior to the meeting and final drafts provided to all meeting participants several weeks prior to the meeting. Particular attention was paid to studies published since the last meeting to update the MEC, held in 2008. The systematic reviews, along with presentations given on possible biological mechanisms for any epidemiological associations, and on balancing risks and benefits for women using hormonal contraceptives in different parts of the world, served as the basis for the group's deliberations during the meeting.

During the meeting, all evidence was subjected to careful review and extensive discussion. The group considered the overall quality of the evidence, paying particular attention to the strength and consistency of the data, according to the GRADE approach to evidence review. Input from all stakeholders was valued equally. The group arrived at its recommendations through consensus.

The process and recommendations of the expert group were subsequently reviewed by the WHO Guidelines Review Committee on 15 February 2012. The Guidelines Review Committee approved the recommendations. The Guidelines Review Committee is the body responsible for ensuring that all WHO recommendations are based on the best available scientific evidence and have been developed in a transparent, unbiased and clearly reported manner.

Summary of the evidence

Biological studies

Biological data pertaining to the plausibility of an effect of individual methods of hormonal contraception on HIV acquisition, progression in women living with HIV, and transmission to non-infected male partners were reviewed. Several biological mechanisms by which individual methods of hormonal contraception could theoretically increase the risk of HIV acquisition, progression, or transmission have been postulated, but it is unclear which (if any) are clinically relevant. Potential mechanisms

include alteration of the systemic and local immune response or changes in the genital tract environment. It was noted that different forms of hormonal contraception may change these factors in different ways. Combined contraceptives such as combined oral contraceptives (COCs), which contain estrogen as well as progestogen, may have a different effect than progestogen-only methods. Additionally, various progestogen-only methods, such as depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN), may change immune function variably. Some findings suggest a harmful effect of progestogen, and others suggest no effect, leading to inconsistency in findings. The extent to which data from animal and laboratory studies, including doses used, can be applied to clinical outcomes in humans remains uncertain.

Epidemiological studies

In general, most available epidemiological evidence has assessed COCs or progestogen-only injectable contraceptives (including DMPA and NET-EN); little evidence is available on the potential relationship between HIV risks and other hormonal contraceptive methods such as implants, vaginal rings, patches, or intrauterine devices.

1. Acquisition in HIV-negative women

In total, 20 prospective studies assessed the risk of HIV acquisition among HIV-negative women using different hormonal contraceptives; the group focused largely upon a subset of studies considered to be of higher methodological quality.

Most higher-quality studies found no statistically significant association between oral contraceptive pill use and HIV acquisition, although point estimates varied and several had limited statistical power (indicated by wide 95% confidence intervals). No currently available studies report a statistically significant association between use of NET-EN and HIV-acquisition risk. Evidence on injectables was mixed; some higher quality observational studies reported a significant increase in risk (ranging from a 48% to 100%) of HIV acquisition, other higher-quality observational studies did not report such an association.

All studies had limitations that affected data interpretation. Inconsistencies between point estimates related to injectable contraception were not explained by differences in overall HIV incidence in the study population, primary study objective, study size, number of seroconverters, or the statistical methods used. Other methodological factors, including manner of controlling for potential differences in condom use, length of time between study visits, and analysis of serodiscordant couples could explain part, if not all, of the differences in results from the various studies. These factors merit additional consideration in future analyses. Owing to serious limitations and inconsistency in the data, the quality of the body of evidence on hormonal contraception and HIV acquisition in women was given a GRADE rating of “low”.

2. Transmission from HIV-positive women to HIV-negative men

One recent observational study provided direct evidence on the relationship between oral contraceptive pills or injectable contraception and female-to-male HIV transmission. It suggested a two- to three-fold increased risk (depending on statistical method) with use of injectable contraceptives, but not for oral contraceptive pills. This study had several strengths, including statistical adjustment for multiple potential confounders, low loss to follow-up and frequent follow-up visits, large size of the population studied, genetic linkage of HIV transmissions, and measurement of genital viral shedding. However, limitations included the potential for residual confounding in observational data, uncertainty regarding whether the genital shedding data bolster the main findings, and the limited statistical power given small numbers of new HIV infections in men.

Indirect evidence on two possible mechanisms by which hormonal contraception may impact female-to-male HIV transmission, namely increased genital HIV viral shedding or altered plasma viral load, was also assessed. Findings from studies assessing hormonal contraceptive use and genital HIV viral shedding were inconsistent, but studies assessing hormonal contraceptive use and plasma viral load or viral load setpoint largely indicated no adverse effects. Owing to serious limitations of the data and serious imprecision in the study results, the GRADE rating for the quality of the body of evidence on injectable contraception and female-to-male HIV transmission was “low” and the rating for oral contraceptives and female-to-male transmission was “very low”.

3. Disease progression in HIV-positive women

None of the 10 observational studies examining use of various hormonal contraceptives and HIV disease progression (as measured by mortality, time to CD4+ cell count below 200 cells/mm³, initiation of antiretroviral therapy (ART), increased HIV-RNA viral load, or decreased CD4+ cell count) found a statistically significant association. An increased risk of a combined outcome of progression to AIDS, ART initiation or death was reported in one randomized controlled trial that compared hormonal contraceptive users with copper intrauterine device users; however, interpretation of this association is difficult due to high rates of method switching and loss to follow-up. Due to serious limitations of the data and the imprecision of study results, the GRADE rating for the quality of the body of evidence on hormonal contraception and HIV disease progression was “low”.

Recommendations

All evidence was reviewed carefully, and there was extensive discussion of the interpretation and implications of the results. The group considered the strength of the epidemiological and biological data, possible implications for country programmes, taking into account the need for HIV prevention, and the risk of unintended pregnancy on maternal mortality and pregnancy-related morbidity. Most concern focused on the relationship between progestogen-only injectable contraception and risk of HIV acquisition in women. In considering the totality of available evidence, the group determined that currently available data neither establish a clear causal association with injectables and HIV acquisition, nor definitively rule out the possibility of an effect. The group agreed that use of hormonal contraceptives should remain unrestricted if a strong clarification was added to the MEC, which reflected the difficulties the group had with the data, the need for an enhanced message about condom use, for both male and female condoms, and other HIV prevention measures, and the need for couples to have access to as wide a range of contraceptive methods as possible. A clear recommendation was also made on the need for further research on this issue and an undertaking to keep emerging evidence under close review.

Thus, the expert group determined that women at high risk of HIV or living with HIV, can continue to use all existing hormonal contraceptive methods (Category 1) (oral contraceptive pills, contraceptive injectables, patches, rings, and implants), but that a strong clarification (as detailed above) relating to the use of progestogen-only injectables be added for women at high risk of HIV.

Overall, women should receive correct and full information from their health-care providers so that they are in a position to make informed choices.

Recommendations for women at high risk of HIV infection

- Women at high risk of HIV can continue to use all existing hormonal contraceptive methods without restriction.
- It is critically important that women at risk of HIV infection have access to and use condoms, male or female, and where appropriate, other measures to prevent and reduce their risk of HIV infection and sexually transmitted infections (STIs).
- Because of the inconclusive nature of the body of evidence on progestogen-only injectable contraception and risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to also always use condoms, male or female, and other preventive measures. Condoms must be used consistently and correctly to prevent infection.

Recommendations for women living with HIV infection

- Women living with HIV can continue to use all existing hormonal contraceptive methods without restriction.
- Consistent and correct use of condoms, male or female, is critical for prevention of HIV transmission to non-infected sexual partners.
- Voluntary use of contraception by HIV-positive women who wish to prevent pregnancy continues to be an important strategy for the reduction of mother-to-child HIV transmission.

More information and related documents

The technical consultation list of participants and agenda, the summary of declarations of interest, and GRADE profiles for: (i) hormonal contraception and acquisition in HIV-negative women; (ii) hormonal contraception and transmission from women living with HIV to HIV-negative men; and (iii) hormonal contraception and disease progression in women living with HIV:

http://www.who.int/reproductivehealth/topics/family_planning/hc_hiv/en/index.html

The *Medical eligibility criteria for contraceptive use, fourth edition, 2009* (in English, French and Spanish) is available to download from:

http://www.who.int/reproductivehealth/publications/family_planning/9789241563888/en/index.html

Further information on WHO's work on family planning:

http://www.who.int/reproductivehealth/topics/family_planning/en/index.html

Further information on WHO's Guidelines Review Committee:

http://www.who.int/kms/guidelines_review_committee/en/index.html

Annex 1. Summary of recommendations for contraceptive use for women at high risk of HIV and living with HIV with clarification†

COCs, P, R, CICs, POP, D/NE, LNG/ETG 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, male or female, is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.

CONDITION	CATEGORY							CLARIFICATIONS/EVIDENCE
	COC	P	R	CIC	POP	D/NE	LNG/ETG	
COC = combined oral contraceptives P = combined contraceptive patch R = combined contraceptive vaginal ring CIC = combined injectable contraceptives POP = progestogen-only pills LNG/ETG = levonorgestrel and etonogestrel implants D/NE = depot medroxyprogesterone acetate (DMPA) / norethisterone enantate (NET-EN)								
HIGH RISK OF HIV	1	1	1	1	1	1†	1	<p>Clarification: Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition, other studies do not report this association. A WHO expert group reviewed all the available evidence and agreed that the data were not sufficiently conclusive to change current guidance. However, because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to also always use condoms, male or female, and other HIV preventive measures. Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential. These recommendations will be continually reviewed in the light of new evidence.</p> <p>Evidence: Prospective studies have assessed the risk of HIV acquisition among HIV-negative women using different hormonal contraceptives. Most found no statistically significant association between use of oral contraceptive pills and HIV acquisition, except one study among sex workers in Kenya, which just reached statistical significance. None of the three studies assessing NET-EN injectables reported a statistically significant association with HIV acquisition. Studies evaluating an association between use of DMPA or non-specified injectables and HIV acquisition showed inconsistent results, and are limited by methodological problems. Due to the inconsistency of the body of evidence, available data do not establish a clear causal association with HIV acquisition, nor is the possibility of an association definitively ruled out. [1–20]</p>
HIV-INFECTED	1	1	1	1	1	1	1	<p>Evidence: Most studies suggest no association between use of hormonal contraception and progression of HIV, as measured by CD4+ count <200 cells/mm³, initiation of antiretroviral (ARV) therapy, or mortality. One randomized controlled trial (RCT) found an increased risk of a composite outcome of declining CD4+ count or death among hormonal contraceptive users when compared with copper intrauterine device (IUD) users, however this study had significant loss to follow-up and method switching among groups limiting its interpretation. One prospective observational study directly assessed the effect of hormonal contraception on female-to-male HIV transmission by measuring seroconversions in male partners of women with known hormonal contraceptive use status. This study reported a statistically significant association between injectable contraception and female-to-male transmission of HIV. This study had several strengths, including statistical adjustment for multiple potential confounders, low loss to follow-up and frequent follow-up visits, large size of the population studied, genetic linkage of HIV transmissions, and measurement of genital viral shedding. However, limitations included the potential for residual confounding in observational data, uncertainty regarding whether the genital shedding data bolster the main findings, and the limited statistical power given small numbers of new HIV infections in men. Studies assessing the effect of hormonal contraception on genital viral shedding have been mixed, and studies overall found no association between hormonal contraceptive use and plasma HIV viral load. Thus, direct evidence is extremely limited. Indirect evidence on genital shedding is inconsistent, and indirect evidence on plasma viral load is largely reassuring. Available data do not establish a clear causal association with female-to-male HIV transmission, nor is the possibility of an association definitively ruled out. [20–44]</p>
AIDS	1	1	1	1	1	1	1	<p>Clarification: Because there may be drug interactions between hormonal contraceptives and ARV therapy, refer to the section on drug interactions.</p>

† Please consult the clarification to this classification.

† Table developed as per the recommendations within the *Medical eligibility criteria for contraceptive use* guideline.

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