World Health Organization

Hormonal contraceptive methods for women at high risk of HIV and living with HIV

2014 guidance statement

Recommendations concerning the use of hormonal contraceptive methods by women at high risk of HIV and women living with HIV

Photo: UNAIDS/J. Naar

During 9–12 March 2014, the World Health Organization (WHO) convened a meeting of the Guideline Development Group (GDG) comprising 52 individuals representing a wide range of stakeholders, for the purpose of reviewing, and where appropriate, revising its *Medical eligibility criteria for contraceptive use, fourth edition* (MEC) guidance. Recommendations concerning the use of hormonal contraceptive methods by women at high risk of HIV and women living with HIV, including women taking antiretroviral therapy (ART), were among the many topics reviewed at this meeting. Given the public health importance of this topic, and at the encouragement of the GDG, the World Health Organization is issuing its contraceptive eligibility guidance for women at high risk of HIV and women living with HIV in advance of the entire guideline revision. It is anticipated that the revised fifth edition of the MEC will be completed in 2015.

Recommendations for hormonal contraceptive use are provided for:

In addition to the recommendations themselves, this publication provides a description of the background and methods used in their development. An executive summary and information on dissemination and evaluation are also included.

The following annexes are available online at: www.who.int/reproductivehealth/publications/family_planning/HC_and_HIV_2014/en/

Annex 1. Summary of recommendations for hormonal contraceptive use for women at high risk of HIV, living with HIV, and taking antiretroviral therapies

Annex 2. GRADE evidence profiles

Annex 3. References

Annex 4. Acknowledgements

Annex 5. Declarations of interest

Acronyms and abbreviations

ART	antiretroviral therapy
ARV	antiretroviral (medication)
CD4	cluster of differentiation 4
CDC	Centers for Disease Control and Prevention (United States of America)
CIC	combined injectable contraceptive
COC	combined oral contraceptive pill
DMPA	depot medroxyprogesterone acetate
ETG	etonogestrel
GDG	Guideline Development Group
GRADE	Grading Recommendations, Assessment, Development and Evaluation
GRC	Guidelines Review Committee
IUD	intrauterine device
LNG	levonorgestrel
MEC	Medical eligibility criteria for contraceptive use (WHO publication)
NET-EN	norethisterone enantate
NIH	National Institutes of Health (United States of America)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OC	oral contraceptive pill
POP	progestogen-only pill
STI	sexually transmitted infection
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

The Guideline Development Group (GDG) reviewed four systematic reviews of the available evidence conducted to address the following key questions:

1. Does the use of a particular method of hormonal contraception directly increase the risk of HIV acquisition in women?
2. Does the use of various hormonal contraceptive methods accelerate HIV disease progression in women living with HIV?
3. Does the use of various hormonal contraceptive methods increase the risk of female-to-male HIV sexual transmission?
4. Are there any possible interactions between hormonal contraceptive methods and antiretroviral medications (ARVs)?

The GDG also reviewed Grading Recommendations, Assessment, Development and Evaluation (GRADE) profiles summarizing the strength of the evidence for recommendations for contraceptive use.

For women at high risk of HIV or for women living with HIV, the World Health Organization (WHO) recommends:

- No restriction (MEC Category 1) on the use of combined hormonal contraceptives (combined oral contraceptive pills, combined contraceptive patches, combined contraceptive vaginal rings, or combined injectable contraceptives).
- No restriction (MEC Category 1) on the use of progestogen-only pills, progestogen-only injectables (DMPA and NET-EN), and levonorgestrel (LNG) and etonogestrel (ETG) implants. Given the unresolved questions surrounding the interaction between progestogen-only injectables and risk of HIV acquisition, the following clarification applies for women using progestogen-only injectable contraception who are at high risk of HIV: Available studies on the association between progestogen-only injectable contraception and HIV acquisition have important methodological limitations hindering their interpretation. Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition; other studies have not found this association. The public health impact of any such association would depend upon the local context, including rates of injectable contraceptive use, maternal mortality, and HIV prevalence. This must be considered when adapting guidelines to local contexts. WHO expert groups continue to actively monitor any emerging evidence. At the meeting in 2014, as at the 2012 technical consultation, it was agreed that the epidemiological data did not warrant a change to the *Medical eligibility criteria for contraceptive use* (MEC). Given the importance of this issue, women at high risk of HIV infection should be informed that progestogen-only injectables may or may not increase their risk of HIV acquisition. Women and couples at high risk of HIV acquisition considering progestogen-only injectables should also be informed about and have access to HIV preventive measures, including male and female condoms.
- Women at high risk of HIV may generally use (MEC Category 2) the levonorgestrel-releasing intrauterine device (LNG-IUD).
- Women living with HIV who have asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) may generally use the LNG-IUD (MEC Category 2). Women living with HIV who have severe or advanced HIV clinical disease (WHO stage 3 or 4) should generally not initiate use of the LNG-IUD (MEC Category 3 for initiation) until their illness has improved to asymptomatic or mild HIV clinical disease. However, women who already have an LNG-IUD inserted and who develop severe or advanced HIV clinical disease need not have their LNG-IUD removed (MEC Category 2 for continuation). LNG-IUD users with severe or advanced HIV clinical disease should be closely monitored for pelvic infection.
- In general, women taking antiretroviral therapy (ART) are eligible for all hormonal contraceptive methods, but special consideration (MEC Category 2) may be necessary for women using some hormonal methods (i.e. combined hormonal methods, progestogen-only pills, or LNG and ETG implants) with certain ART regimens (specifically those containing efavirenz or neviripine, as well as some protease inhibitors).

ART groupings: Based on updated evidence and the GRADE profile summaries, WHO has determined that ARVs previously grouped by class will now be separated and considered individually due to some within-class differences.

Terminology for HIV-related conditions: To ensure the terms for HIV-related conditions are consistent with the terminology now used in current clinical practice and other WHO documents, the GDG recommended an update in terminology for this guidance statement and for the up-coming revised fifth edition of the MEC. Thus, the previously used terms "HIV-infected" and "AIDS" have been replaced with "asymptomatic or mild HIV clinical disease (WHO stage 1 or 2)" and "severe or advanced HIV clinical disease (WHO stage 3 or 4)", respectively.

WHO places high priority on the routine review of these recommendations and is committed to monitoring the evidence. WHO strongly supports the need for further research to identify definitive answers to these issues, with particular emphasis on potential associations between use of progestogen-only injectables and HIV acquisition, as well as potential interactions between some hormonal contraceptive methods and some ARVs.

1. Background

Contraceptive methods contribute to women's ability to maintain their health and that of their children, and to control their reproductive lives. Hormonal contraceptives include: combined oral contraceptive pills (COCs), combined injectable contraceptives (CICs), combined contraceptive patches and rings, progestogen-only injectables (depot medroxyprogesterone acetate [DMPA] and norethisterone enantate [NET-EN]), progestogen-only pills (POPs), levonorgestrel (LNG) and etonogestrel (ETG) implants, and levonorgestrel-releasing IUDs (LNG-IUDs). These are all effective or highly effective methods of pregnancy prevention. These contraceptive methods alleviate overall pregnancy-related morbidity and mortality, improve infant and child health, and reduce vertical transmission of HIV among women living with HIV who wish to prevent pregnancy.

For women at high risk of HIV, living with HIV, or taking antiretroviral medicines (ARVs), consideration must be given to the relationship between the use of hormonal contraceptive methods and HIV-related risks. Additionally, women at high risk of HIV or living with HIV may require information about and access to HIV preventive measures. Such measures include, among others, condoms (male or female), voluntary male circumcision, voluntary HIV counselling and testing, and antiretroviral treatment (ART) for HIV-positive partners in serodiscordant partnerships.[1]

Assisting Member States in achieving the goal of the highest attainable standard of health for all, including sexual and reproductive health, is recognized as the primary mandate of the World Health Organization. The provision of high-quality contraceptive information and services is an essential intervention to achieve this goal. This cannot be achieved without respecting, protecting and fulfilling the human rights of individuals. To this end, in 2014, WHO issued *Ensuring human rights in the provision of contraceptive information and services: guidance and recommendations (1)*[2], which urges the health sector to undertake a set of nine prioritized actions in order to ensure that different human rights dimensions are systematically and clearly integrated into the provision of contraceptive information and services.

WHO's Department of Reproductive Health and Research produces evidence-based guidance, as provided in the *Medical eligibility criteria for contraceptive use*. The latest edition of the MEC is the fourth edition *(2)*[3]. The MEC provides recommendations on the use of various contraceptive methods by women and men, with specific guidance on who can safely use

1 More information on HIV preventive measures is available at: http://www.who.int/publications/guidelines/hiv_aids/en/

2 Available at: http://www.who.int/reproductivehealth/publications/family_planning/human-rights-contraception/en/

3 Available in English, French and Spanish at: http://whqlibdoc.who.int/publications/2010/9789241563888_eng. pdf

Human rights principles and standards

1. Non-discrimination in the provision of contraceptive information and services
2. Availability of contraceptive information and services
3. Accessibility of contraceptive information and services
4. Acceptability of contraceptive information and services
5. Quality of contraceptive information and services
6. Informed decision-making in the provision of contraceptive information and services
7. Privacy and confidentiality in the provision of contraceptive information and services
8. Participation in the provision of contraceptive information and services
9. Accountability in the provision of contraceptive information and services.

Source: WHO, 2014 (*1*)

which methods under which circumstances, including women at high risk of HIV infection, women living with HIV, and women on ART. These recommendations are intended to provide policy- and decision-makers and the scientific community with guidance that can be used for developing or revising national contraceptive guidelines. The MEC recommendations are not intended to be rigid; rather, they provide a basis for rationalizing national guidelines for the provision of various contraceptives in view of the most up-to-date information available, which can then be adapted to local cultural and epidemiological contexts. The Department of Reproductive Health and Research closely monitors the publication of new research evidence and regularly reviews its guidance to ensure that WHO recommendations remain up to date and consistent with the state of knowledge in the field.

Following the publication of new data on the use of certain hormonal contraceptive methods and the risk of HIV acquisition and female-to-male HIV transmission, WHO convened a technical consultation in early 2012 to issue interim guidance on contraceptive use for women at risk of HIV and women living with HIV: *Hormonal contraception and HIV: technical statement (3)*[4]. Since then, new evidence on the use of hormonal contraceptive methods and HIV has been published. This updated body of evidence was reviewed in March 2014 by WHO's Guideline Development Group as part of the Department of Reproductive Health and Research's periodic revision of its entire MEC guidance document. Given the public health importance of this topic, and based on encouragement from the GDG, WHO is issuing its contraceptive eligibility guidance for women living with HIV or at high risk of acquiring the infection in advance of the entire guideline revision. It is anticipated that the revised fifth edition of the MEC will be completed in 2015.

2. Methods

During 9–12 March 2014, WHO convened a meeting of the GDG to review and, where appropriate, revise specific recommendations in the *Medical eligibility criteria for contraceptive use (2)*. Among the multiple topics addressed at this meeting was a review of evidence regarding the use of hormonal contraceptive methods by women at high risk of HIV, living with HIV, or taking ART for HIV.

The GDG included 52 participants from 24 countries, including experts in international family planning and HIV, clinicians, epidemiologists, researchers, programme managers, policy-makers, guideline methodologists, reproductive biologists and pharmacologists. Members of the GDG and members of an external peer review group (who did not participate in the GDG meeting) submitted Declaration of Interest forms to the WHO Secretariat: 12 declared an academic conflict of interest relevant to the MEC guidance, and two declared conflicts

4 Available at: http://www.who.int/reproductivehealth/publications/family_planning/rhr_12_8/en/

of interest relating to the specific subject matter of this statement.[5] The WHO Secretariat and the GDG reviewed all declarations and found no conflicts of interest sufficient to preclude anyone from participating in the deliberations or development of recommendations relevant to hormonal contraception and HIV. For a summary of the declared academic interests see Annex 5.[6]

Existing WHO recommendations on the 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 (GRC) and the Grading Recommendations, Assessment, Development and Evaluation (GRADE) approach to evidence review.[7] Four systematic reviews of the epidemiological and pharmacological evidence were conducted to investigate the following four questions:

1. Does the use of a particular method of hormonal contraception directly increase the risk of HIV acquisition in women?
2. Does the use of various hormonal contraceptive methods accelerate HIV disease progression in women living with HIV?
3. Does the use of various hormonal contraceptive methods increase the risk of female-to-male HIV sexual transmission?
4. Are there any possible interactions between hormonal contraceptive methods and ARV medications?

The *PubMed* and *EMBASE* databases were searched for studies published in any language in a peer-reviewed journal up to 15 January 2014, to inform the systematic reviews on hormonal contraceptive use and HIV acquisition in women; hormonal contraceptive methods and female-to-male HIV transmission; and hormonal contraceptive methods and HIV disease progression in women living with HIV. Reference lists and direct contact with experts in the field were also used to identify other studies, including those in press; neither grey literature nor conference abstracts were included in these reviews. To inform the systematic review on possible interactions between hormonal contraceptive methods and ARV medications, the *PubMed* and *EMBASE* databases, abstracts presented at HIV conferences, and the United States Food and Drug Administration website were searched for studies published in any language up to 1 January 2014. GRADE evidence profiles were prepared to assess the quality of the summarized evidence and include the range of the estimates of effect for each outcome assessed. The four systematic reviews that resulted from this process were peer-reviewed by selected members of the GDG prior to the meeting in March 2014, and final drafts were made electronically available to all GDG members prior to the meeting. The written and orally presented systematic reviews and GRADE evidence profiles served as the basis for the GDG's deliberations during the meeting. Biological and immunological data were not formally reviewed at this meeting.

The GDG 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. Through consensus, the GDG arrived at new and/or revised wording for recommendations on the use of hormonal contraceptive methods for women at high risk of HIV or living with HIV. For certain recommendations, the GDG added a clarification statement to provide further guidance on the numerical classification. For each contraceptive method, the GDG considered the potential benefits and risks of its use with respect to each of the medical conditions or personal characteristics assessed.

5 Chelsea Polis collaborated on a trial investigating the acceptability of a subcutaneous injectable contraceptive; data collection for this study ceased in 2013. Pfizer donated the injectable units, which were not yet commercially available, to her research unit for the conduct of the trial, but did not provide any monetary support. Andy Gray works with a research unit that receives donations from the United States National Institutes of Health (NIH) Clinical Research Products Management Center (including products manufactured by Abbott; Boehringer Ingelheim; Bristol Myers Squibb; Gilead; GlaxoSmithKline; Merck Sharpe & Dohme; and Roche) for antiretroviral medications used in the clinical trials conducted through the AIDS Clinical Trials Group and International Maternal, Paediatric, Adolescent AIDS Clinical Trial network. The unit also received donated microbicide products from Gilead Sciences for a Phase IIb clinical trial, which ceased in 2010.

6 Available at: www.who.int/reproductivehealth/publications/family_planning/HC_and_HIV_2014/en/

7 For more information see: http://www.gradeworkinggroup.org

At the start of the meeting, the GDG endorsed an approach to patient preferences and values that prioritized the availability of a wide range of contraceptive options, as women vary in their preferences regarding contraceptive selection and in the values they place on different beneficial and harmful outcomes. In addition, the availability of a range of contraceptive options is critical because a woman's contraceptive choices are made at a particular time and in a particular societal and cultural context, and these choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires making trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

To ensure the terms used for HIV-related conditions in the MEC are consistent with the terminology now used in current clinical practice and other WHO documents, the GDG recommended an update in terminology for this guidance statement and for the up-coming revised fifth edition of the MEC. Thus, the previously used terms "HIV-infected" and "AIDS" have been replaced with "asymptomatic or mild HIV clinical disease (WHO stage 1 or 2)" and "severe or advanced HIV clinical disease (WHO stage 3 or 4)", respectively.[8]

A draft version of this statement was sent to the external peer review group, comprising five experts who did not participate in the GDG meeting. Comments received from these reviewers were addressed and incorporated into this guidance by the WHO Secretariat as appropriate. The final version of this document was approved by the WHO Guidelines Review Committee on 7 July 2014.

2.1 MEC classification categories

Since 1996, the MEC has applied a four-category scale to indicate eligibility for particular contraceptive methods in the presence of particular conditions or characteristics in the client (e.g. living with HIV). Category 1 indicates medical conditions or personal characteristics for which there are no restrictions on the use of the contraceptive method in question.

Conditions classified as category 2 indicate that the contraceptive method can generally be used, but careful follow-up may be required. Category 3 conditions are those that require careful clinical judgement and access to clinical services; in these situations, the severity of the condition and the availability, practicality and acceptability of alternative methods should be taken into account. Use of a method for a category 3 condition is usually not recommended unless other more appropriate methods are not available or acceptable. Category 4 conditions are those where the method should not be used because the condition represents an unacceptable health risk, i.e. the use of the method is contraindicated. Where it is determined that further guidance is required, in addition to the category assigned, that guidance is provided as a "clarification". In situations where resources for clinical judgement are limited, the four-category classification framework can be simplified into two categories. Thus, a woman with a category 1 or 2 condition can use the contraceptive method, whereas if the woman has a category 3 or 4 condition, she should not use the method.

MEC categories for contraceptive eligibility	
1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used.

8 More information is available at: http://apps.who.int/iris/bitstream/10665/91048/1/WHO_HIV_2013.67_eng.pdf

New studies on HIV acquisition, progression and transmission considered since the February 2012 technical update

HIV acquisition:

Considered "informative with important limitations"

Heffron R, Rees H, Mugo N, Baeten JM. Use of hormonal contraceptives and risk of HIV-1 transmission – authors' reply. The Lancet Infectious Diseases. 2012;12(7):510–1. *(4)*

McCoy SI, Zheng W, Montgomery ET, Blanchard K, van der Straten A, de Bruyn G, et al. Oral and injectable contraception use and risk of HIV acquisition among women in sub-Saharan Africa. AIDS. 2013;27(6):1001–9. *(5)*

Considered "unlikely to inform the primary question"

Lutalo T, Musoke R, Kong X, Makumbi F, Serwadda D, Nalugoda F, et al. Effects of hormonal contraceptive use on HIV acquisition and transmission among HIV-discordant couples. AIDS. 2013;27 Suppl 1:S27–34. *(6)*

HIV progression:

Heffron R, Mugo N, Ngure K, Celum C, Donnell D, Were E, et al. Hormonal contraceptive use and risk of HIV-1 disease progression. AIDS. 2013;27(2):261–7. *(7)*

HIV transmission:

Direct evidence

Lutalo T, Musoke R, Kong X, Makumbi F, Serwadda D, Nalugoda F, et al. Effects of hormonal contraceptive use on HIV acquisition and transmission among HIV-discordant couples. AIDS. 2013;27 Suppl 1:S27–34. *(6)*

Indirect evidence

Low AJ, Konate I, Nagot N, Weiss HA, Kania D, Vickerman P, et al. Cervicovaginal HIV-1 shedding in women taking antiretroviral therapy in Burkina Faso: a longitudinal study. Journal of Acquired Immune Deficiency Syndromes. 2014;65(2):237–45. *(8)*

3. Recommendations

The recommendations are presented here, and further details are provided in Annex 1.[9]

The following recommendations make reference to the four questions that were investigated in four separate systematic reviews, as described in the Methods section. Each of the four questions and the selection criteria for each systematic review are first provided here, to be used as a reference while reading the recommendations.

Question 1: Does the use of a particular method of hormonal contraception directly increase the risk of HIV acquisition in women?

Selection criteria for the systematic review:

Study design	Randomized controlled trials and cohort studies
Population	Women of reproductive age at risk of HIV infection
Intervention	Use of a hormonal contraceptive method (injectables, oral contraceptives, implants, patches, rings or LNG-IUDs)
Comparator	Non-use of a hormonal contraceptive method (i.e. either use of no contraceptive method or use of a non-hormonal method such as condoms or other barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, etc.)
Outcome	Incident, laboratory-confirmed HIV infection in women

Question 2: Does the use of various hormonal contraceptive methods accelerate HIV disease progression in women living with HIV?

Selection criteria for the systematic review:

Study design	Randomized trials and cohort studies
Population	Women of reproductive age living with HIV
Intervention	Use of a hormonal contraceptive method (injectables, oral contraceptives, implants, patches, rings or LNG-IUDs)
Comparator	Non-use of hormonal contraceptive methods (i.e. either use of no method or use of a non-hormonal method such as condoms or other barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, etc.)
Outcomes	Risk of HIV disease progression (as indicated by HIV viral load, CD4 count, progression to AIDS, ART initiation, death or a composite outcome of progression to AIDS, ART initiation or death)

9 Available at: www.who.int/reproductivehealth/publications/family_planning/HC_and_HIV_2014/en/

Question 3: Does the use of various hormonal contraceptive methods increase the risk of female-to-male HIV sexual transmission?

Selection criteria for the systematic review:

Study designs	(a) Randomized trials and cohort studies (reporting direct evidence, with incident HIV infection rates in male sexual partners as an outcome variable); (b) randomized controlled trials, cohort studies, cross-sectional studies (reporting indirect evidence, assessing proxy measures for infectivity in women)
Population	Women of reproductive age living with HIV
Intervention	Use of a hormonal contraceptive method (injectables, oral contraceptives, implants, patches, rings or LNG-IUDs)
Comparator	Non-use of hormonal contraceptive methods (i.e. either use of no method or use of a non-hormonal method such as condoms or other barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, etc.)
Outcome	Risk of HIV transmission to male partners (measured either directly by HIV seroconversion among previously HIV-negative male partners or indirectly by measurement of genital HIV shedding or plasma viral load in women as a proxy for infectivity)

Question 4: Are there any possible interactions between hormonal contraceptive methods and ARV medications?

Selection criteria for the systematic review:

Study design	Clinical trials, observational studies, case series and pharmacokinetic studies
Population	Women of reproductive age
Intervention	Hormonal contraception and ART
Comparator	Hormonal contraception and no ART; non-comparative studies examining changes in outcomes over time
Outcome	Contraceptive hormone pharmacokinetics, contraceptive effectiveness (pregnancy, ovulation, ovarian activity, breakthrough bleeding), ARV pharmacokinetics, ARV effectiveness (HIV disease progression, viral load, CD4 count), and adverse effects of either the hormonal contraceptive or the ARV medication

3.1 Recommendations for hormonal contraceptive use among women at high risk of HIV infection

- Women at high risk of acquiring HIV can use the following hormonal contraceptive methods without restriction: combined oral contraceptive pills (COCs), combined injectable contraceptives (CICs), combined contraceptive patches and rings, progestogen-only pills (POPs), progestogen-only injectables (DMPA and NET-EN), and levonorgestrel (LNG) and etonogestrel (ETG) implants (MEC Category 1)[10] .
- Women at high risk of HIV who are using progestogen-only injectables should be informed that available studies on the association between progestogen-only injectable contraception and HIV acquisition have important methodological limitations hindering interpretation. Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition; other studies have not found this association. The public health impact of any such association would depend upon the local context, including rates of injectable contraceptive use, maternal mortality and HIV prevalence. This must be considered when adapting guidelines to local contexts. WHO expert groups continue to actively monitor any emerging evidence. At the meeting in 2014, as at the 2012 technical consultation, it was agreed that the epidemiological data did not warrant a change to the MEC. Given the importance of this issue, women at high risk of HIV infection should be informed that progestogen-only injectables may or may not increase their risk of HIV acquisition. Women and couples at high risk of HIV acquisition considering progestogen-only injectables should also be informed about and have access to HIV preventive measures, including male and female condoms.
- Women at high risk of acquiring HIV can generally use LNG-releasing IUDs (LNG-IUDs) (MEC Category 2).

Remarks

It is critically important that women and couples at risk of HIV infection be informed about and have access to male and female condoms, and other measures to prevent and reduce their risk of HIV infection and sexually transmitted infections (STIs), regardless of which form of contraception they choose.

Hormonal contraceptives, including COCs, CICs, POPs, progestogen-only injectables, LNG and ETG implants, and LNG-IUDs do not protect against STIs/HIV.

Systematic review Question 1 (HIV acquisition)

Summary of the evidence

Twenty-two prospective observational studies have assessed the risk of HIV acquisition among women using a method of hormonal contraception versus the risk of HIV acquisition in women using a non-hormonal contraceptive method (i.e. condoms, IUD, withdrawal) or no contraceptive method *(4–6, 9–31)*.

Combined hormonal contraceptives[11]

Eight studies assessed the use of COCs and were considered to be "informative but with important limitations" *(32)*. Seven of these studies found no statistically significant association between use of COCs and HIV acquisition *(5, 9–15)*, although one study among sex workers in Kenya did *(16)*.

Progestogen-only contraceptives

Five studies assessed the use of NET-EN injectables and were considered to be "informative but with important limitations" *(32)*. Four of them reported no statistically significant association with HIV acquisition *(5, 12, 13, 17)*, while one did *(15)*.

Nine studies assessed DMPA (or, if a DMPA-specific result was unavailable, assessed non-specified injectables) and were considered to be "informative but with important limitations" *(32)*. These studies had mixed results: three showed a significant increase in risk *(9, 15, 16)*, one showed a significant increase in risk using one statistical model but this association was not statistically significant using

10 These categories are explained at the end of the Methods section.

11 This refers to those contraceptives containing both an estrogen and a progestogen.

another statistical model *(10, 11)*, and five showed no significant increase in risk *(5, 12–14, 17)*.

Two studies assessed implants, one of which was classified as "unlikely to inform the primary question" *(6, 32)*. Neither of these studies reported a statistically significant increased risk of HIV acquisition, but confidence intervals were wide *(6, 25)*.

Quality of the evidence

For progestogen-only injectables (DMPA and NET-EN) and COCs: **low**

For implants: **very low**

3.2 Recommendations for hormonal contraceptive use among women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2)

- Women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) can use the following hormonal contraceptive methods without restriction: COCs, combined injectable contraceptives, combined contraceptive patches and rings, POPs, progestogen-only injectables (DMPA and NET-EN), and LNG and ETG implants (MEC Category 1).
- Women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) can generally use the LNG-IUD (MEC Category 2).
- Because there may be interactions between certain methods of hormonal contraception and certain ARVs, refer to the recommendations on ART medication interactions (see page 13).

Remarks

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 women living with HIV who wish to prevent pregnancy is critical for upholding their reproductive rights and continues to be an important strategy for reducing vertical HIV transmission.

Systematic review Questions 2 (disease progression) and 3 (female-to-male transmission)

Two systematic reviews investigating Questions 2 and 3 informed the contraceptive eligibility recommendations for women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2).

Summary of the evidence

Combined hormonal contraceptives

Out of eight available studies, seven suggested no association between use of COCs and progression of HIV, as measured by CD4 count < 200 cells/mm^3, initiation of ART, or mortality *(7, 33–38)*. One randomized controlled trial found an increased risk of a composite outcome of declining CD4 count or death among COC users when compared with copper-bearing IUDs *(39, 40)*.

Two prospective observational studies directly assessed the effects of different hormonal contraceptive methods on female-to-male HIV transmission by measuring seroconversions in male partners of women known to be using hormonal contraceptives. One of these studies reported an elevated, but not statistically significant, point estimate for COCs *(9)*. The other study also did not find a statistically significant association for COCs *(6)*.

Studies indirectly assessing the effect of various hormonal contraceptive methods on female-to-male HIV transmission by measuring genital viral shedding as a proxy for infectivity have had mixed results. The majority of indirect studies measuring whether various hormonal contraceptive methods affect plasma HIV viral load have found no effect *(41–56)*.

Progestogen-only contraceptives

Out of six available studies, five suggest no association between use of progestogen-only injectable contraceptives and progression of HIV, as measured by CD4 count < 200 cells/mm^3, initiation of ART, or mortality *(34–38)*. One randomized trial found an increased risk of a composite outcome of declining CD4 count or death among OC users (COCs and POPs) when compared with users of copper-bearing IUDs; this study, however, had significant loss to follow-up and method switching among groups,

limiting its interpretation *(39, 40)*. One study found no difference in ART initiation or CD4 count between users and non-users of the LNG-IUD *(57)*.

Two prospective observational studies directly assessed the effects of different hormonal contraceptive methods on female-to-male HIV transmission by measuring seroconversions in male partners of women known to be using hormonal contraceptives. One study reported a statistically significant association between progestogen-only injectable contraception and female-to-male transmission of HIV *(9)*, while another study did not find a statistically significant association between use of DMPA and female-to-male HIV transmission *(6)*. The findings of studies indirectly assessing the effect of various hormonal contraceptive methods on female-to-male HIV transmission by measuring genital viral shedding as a proxy for infectivity have been mixed. Most of indirect studies measuring whether various hormonal contraceptive methods affect plasma HIV viral load have found no effect *(41–56)*.

Quality of the evidence

Disease progression – progestogen-only injectables (DMPA and NET-EN) and OCs (COCs and POPs): **low**

Disease progression – LNG-IUD: **very low**

Disease transmission (direct evidence) – progestogen-only injectables (DMPA and NET-EN) and OCs (COCs and POPs): **very low**

Note: As there remains considerable uncertainty regarding the best way to measure genital HIV shedding (with respect to collection method, RNA versus DNA, and cell-associated versus cell-free measures of DNA and RNA), studies providing indirect evidence assessing proxy measures of transmission were not graded.

3.3 Recommendations for hormonal contraceptive use among women living with severe or advanced HIV clinical disease (WHO stage 3 or 4)

- Women living with severe or advanced HIV clinical disease (WHO stage 3 or 4) can use the following hormonal contraceptive methods without restriction: COCs, combined injectable contraceptives, combined contraceptive patches and rings, POPs, progestogen-only injectables (DMPA and NET-EN), and LNG and ETG implants (MEC Category 1).
- Women living with severe or advanced HIV clinical disease (WHO stage 3 or 4) should generally not initiate use of the LNG-IUD (MEC Category 3 for initiation) until their illness has improved to asymptomatic or mild HIV clinical disease (WHO stage 1 or 2). However, women who already have an LNG-IUD inserted and who develop severe or advanced HIV clinical disease need not have their IUD removed (MEC Category 2 for continuation). LNG-IUD users with severe or advanced HIV clinical disease should be closely monitored for pelvic infection.
- Because there may be interactions between certain methods of hormonal contraception and certain ARVs, refer to the recommendations on ART medication interactions (see page 13).

Remarks

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 women living with HIV who wish to prevent pregnancy is critical for upholding their reproductive rights and continues to be an important strategy for reducing vertical HIV transmission.

Systematic review Questions 2 (disease progression) and 3 (female-to-male transmission)

Two systematic reviews investigating Questions 2 and 3 informed the contraceptive eligibility recommendations for women living with severe or advanced HIV clinical disease (WHO stage 3 or 4).

Summary of the evidence

All of the identified studies excluded women with severe or advanced HIV clinical disease (WHO stage 3 or 4) from enrolment, although some participants experienced progression to severe or advanced disease during the trials.

Combined hormonal contraceptives

Out of eight available studies, seven suggest no association between use of COCs and progression of HIV, as measured by CD4 count < 200 cells/mm^3, initiation of ART, or mortality *(7, 33–38)*. One randomized trial found an increased risk of a composite outcome of declining CD4 count or death among COC users when compared with copper-bearing IUDs *(39, 40)*.

Two prospective observational studies directly assessed the effects of different hormonal contraceptive methods on female-to-male HIV transmission by measuring seroconversions in male partners of women known to be using hormonal contraceptives. One of these studies reported an elevated, but not statistically significant, point estimate for OCs *(9)*. The other study also did not find a statistically significant association for OCs *(6)*.

Studies indirectly assessing the effect of various hormonal contraceptive methods on female-to-male HIV transmission by measuring genital viral shedding as a proxy for infectivity have had mixed results. The majority of indirect studies measuring whether various hormonal contraceptive methods affect plasma HIV viral load have found no effect *(41–56)*.

Progestogen-only contraceptives (including LNG-IUD)

Out of six available studies, five suggest no association between use of progestogen-only injectable contraceptives and progression of HIV, as measured by CD4 count < 200 cells/mm^3, initiation of ART, or mortality *(34–38)*. One randomized trial found an increased risk of a composite outcome of declining CD4 count or death among OC (COC and POP) users when compared with users of copper-bearing IUDs; this study, however, had significant loss to follow-up and method switching among groups, limiting its interpretation *(39, 40)*. One study found no difference in ART initiation or CD4 count between users and non-users of the LNG-IUD *(57)*.

Two prospective observational studies directly assessed the effects of different hormonal contraceptive methods on female-to-male HIV transmission by measuring seroconversions in male partners of women with known hormonal contraceptive use status. One of these studies reported a statistically significant association between injectable contraception and female-to-male transmission of HIV *(9)*, while the other study did not find a statistically significant association between use of DMPA and female-to-male HIV transmission *(6)*.

The findings of studies indirectly assessing the effect of various hormonal contraceptive methods on female-to-male HIV transmission by measuring genital viral shedding as a proxy for infectivity have been mixed. The majority of indirect studies measuring whether various hormonal contraceptive methods affect plasma HIV viral load have found no effect *(41–56)*.

Quality of the evidence

Disease progression – progestogen-only injectables (DMPA and NET-EN) and OCs (COCs and POPs): **low**

Disease progression – LNG-IUD: **very low**

Disease transmission (direct evidence) – progestogen-only injectables (DMPA and NET-EN) and OCs (COCs and POPs): **very low**

Note: As there remains considerable uncertainty regarding the best way to measure genital HIV shedding (with respect to collection method, RNA versus DNA, and cell-associated versus cell-free measures of DNA and RNA), studies providing indirect evidence assessing proxy measures of transmission were not graded.

3.4 Recommendations for women living with HIV using antiretroviral therapy (ART)

- Women taking any nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) can use all hormonal contraceptive methods without restriction: COCs, combined contraceptive patches and rings, combined injectable contraceptives, POPs, progestogen-only injectables (DMPA and NET-EN), and LNG and ETG implants (MEC Category 1).
- Women using ART containing either efavirenz or nevirapine can generally use COCs, patches, rings, combined injectables, POPs, NET-EN, and implants (MEC Category 2). However, women using efavirenz or nevirapine can use DMPA without restriction (MEC Category 1).

- Women using the newer non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs), etravirine and rilpivirine, can use all hormonal contraceptive methods without restriction (MEC Category 1).
- Women using protease inhibitors (for example ritonavir and ARVs boosted with ritonavir) can generally use COCs, contraceptive patches and rings, combined injectable contraceptives, POPs, NET-EN, and LNG and ETG implants (MEC Category 2), and can use DMPA without restriction (MEC Category 1).
- Women using the integrase inhibitor raltegravir can use all hormonal contraceptive methods without restriction (MEC Category 1).
- Women using ARV medication can generally use LNG-IUDs (MEC Category 2), provided that their HIV clinical disease is asymptomatic or mild (WHO stage 1 or 2). Women living with severe or advanced HIV clinical disease (WHO stage 3 or 4) should generally not initiate use of the LNG-IUD (MEC Category 3 for initiation) until their illness has improved to asymptomatic or mild HIV clinical disease. However, women who already have an LNG-IUD inserted and who develop severe or advanced HIV clinical disease need not have their IUD removed (MEC Category 2 for continuation). LNG-IUD users with severe or advanced HIV clinical disease should be closely monitored for pelvic infection.

Remarks

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 women living with HIV who wish to prevent pregnancy is critical for upholding their reproductive rights and continues to be an important strategy for reducing vertical HIV transmission.

Women living with HIV and using ARVs should discuss the potential impact of certain ARVs on contraceptive efficacy with their health-care provider.

Systematic review Question 4 (hormonal contraception–ART interactions)

Summary of the evidence

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

NRTIs do not appear to have significant risk of interactions with hormonal contraceptive methods *(58, 59)*.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Three clinical studies, including one large study, found use of nevirapine-containing ART did not increase ovulation or pregnancy rates in women taking COCs *(60–63)*. For efavirenz-containing ART, a pharmacokinetic study showed consistent significant decreases in contraceptive hormone levels in women taking COCs, and a small clinical study showed higher ovulation rates in women taking efavirenz-containing ART and COCs *(60, 64, 65)*. Etravirine and rilpivirine do not interact with COCs *(66, 67)*. One retrospective chart review of women using efavirenz-containing ART showed increased contraceptive failure rates for women using LNG implants *(68)*. Based primarily on pharmacokinetic data, the effectiveness of DMPA is likely not affected by NNRTIs, and vice versa *(69, 70)*.

Protease inhibitors (PIs)

Pharmacokinetic data suggest decreases in COC progestin levels with ritonavir and ritonavir-boosted PIs. In women using the patch, co-administration resulted in higher progestin levels *(71)*. One study found higher progestin levels with concurrent PI use in users of POPs *(72)*. Based primarily on pharmacokinetic data, the effectiveness of DMPA is likely not affected by PIs, and vice versa *(69, 70)*.

Integrase inhibitors

The integrase inhibitor raltegravir does not appear to interact with COCs *(58, 59, 73, 74)*.

Quality of the evidence

Hormonal contraception + ART versus hormonal contraception alone: **very low**

Efavirenz-containing ART versus other ART in women using hormonal contraception: **very low**

ART + hormonal contraception versus ART alone: **low**

4. Dissemination and evaluation of the 2014 guidance statement on hormonal contraceptive methods for women at high risk and living with HIV

The recommendations in this guidance update will be released on 24 July 2014, at the 20th International AIDS Conference. They will be widely disseminated through the WHO regional and country offices, WHO Member States, the United Nations agencies that are cosponsors of the Special Programme of Research, Development and Research Training in Human Reproduction (HRP) within the WHO Department of Reproductive Health and Research (i.e. UNDP, UNFPA, UNICEF, WHO and the World Bank), WHO collaborating centres, professional organizations, governmental and nongovernmental partner organizations working in the area of sexual and reproductive health, and civil society groups who are engaged in sexual and reproductive health and HIV/AIDS activities and advocacy. A comprehensive dissemination and evaluation plan will be implemented once the revised fifth edition of the *Medical eligibility criteria for contraceptive use* (MEC) is approved. In the immediate term, the recommendations in this guidance will be presented during several upcoming regional workshops addressing sexual and reproductive health issues in the latter part of 2014.

Further information on WHO's work on family planning can be found at:
www.who.int/reproductivehealth/topics/family_planning

Further information on WHO's work on HIV can be found at:
www.who.int/hiv/en/

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