World Health Organization

Hormonal contraceptive eligibility for women at high risk of HIV

Guidance statement

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

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Executive summary

The World Health Organization (WHO) convened a technical consultation during 1–2 December 2016 to review new evidence on the risk of HIV acquisition with the use of hormonal contraception *(1)*. The issue was recognized as a critical one, particularly for sub-Saharan Africa, where women have a high lifetime risk of acquiring HIV, hormonal contraceptives constitute a significant component of the contraceptive method mix and unintended pregnancy is a common threat to the well-being and lives of women and girls.

A wide range of stakeholders were present at this meeting, and serving on the Guideline Development Group (GDG) was global representation from experts in family planning and HIV, representatives from affected populations, clinicians, epidemiologists, researchers, programme managers, policy-makers and guideline methodologists. The GDG considered the following factors in making their determination for each contraceptive method:

- quality of the evidence (GRADE profile) *(2)*;
- values and preferences of contraceptive users and health care providers;
- balance of benefits and harms;
- priority of the problem;
- equity and human rights;
- acceptability; and
- feasibility.

Through consensus, the GDG arrived at new recommendations for progestogen-only injectables. The recommendations for use of progestogen-only injectables among women at high risk of HIV changed from category 1 to category 2, with an accompanying clarification, in the *Medical eligibility criteria for contraceptive use* (MEC) *(1)*. Recommendations for all other methods of hormonal contraception remained unchanged.

In formulating these recommendations, the individuals most affected by the guidance were kept at the centre of the GDG's deliberations – those women wanting to prevent pregnancy who are at high risk of HIV acquisition. At the core of the group's decision-making were the sexual and reproductive health and rights of women and girls, and, in particular, the human rights principles of ensuring informed decision-making and a choice of contraceptive methods. Women have their own individual preferences and values concerning contraception, and their perceptions of the risks and consequences

Content

of unintended pregnancy and HIV acquisition may vary (*Kennedy C., Values and preferences in contraceptive decision making: a systematic review, unpublished data submitted for publication, 2017*). All women have the right to evidence-based information on contraceptives, to quality services and to the assurance of opportunities to make an informed choice without discrimination *(3)*.

Women at high risk of acquiring HIV can use all methods of contraception. The following hormonal contraceptive methods can be used without restriction: combined oral contraceptive pills (COCs), combined injectable contraceptives (CICs), combined contraceptive patches and rings, progestogen-only pills (POPs), and levonorgestrel (LNG) and etonogestrel (ETG) implants (MEC category 1). Women at high risk of acquiring HIV can also use progestogen-only injectables (norethisterone enanthate [NET-EN] and depot medroxyprogesterone acetate [DMPA, intramuscular or subcutaneous]) because the advantages of these methods generally outweigh the possible increased risk of HIV acquisition (MEC category 2). The overall quality of the evidence was rated low to low-to-moderate for progestogen-only injectables, very low for implants, and low-to-moderate for oral contraceptives (including progestogen-only pills). The GDG did not review recommendations for intrauterine devices (IUDs; levonorgestrel [LNG] and copper); recommendations for these methods are available in the *Medical eligibility criteria for contraceptive use (1).*

Combined hormonal contraceptives (CHC)					
Condition	**CATEGORY I = initiation, C = continuation**				**Clarifications/evidence**
	COC	P	CVR	CIC	
High risk of HIV	1	1	1	1	EVIDENCE: Eleven studies, deemed "informative but with important limitations", assessed the use of oral contraceptives (OCs). Ten of these studies found no statistically significant association between use of OCs and HIV acquisition, while one study reported a marginally significant increased risk. No studies of P, CVR or CIC were identified *(4)*.

COC = combined oral contraceptive; P = combined contraceptive patch; CVR = combined contraceptive vaginal ring; CIC = combined injectable contraceptive.

Progestogen-only contraceptives (POCs)				
Condition	**CATEGORY I = initiation, C = continuation**			**Clarifications/evidence**
	POP	DMPA/ NET-EN	LNG/ETG	
High risk of HIV	1	2	1	CLARIFICATION: There continues to be evidence of a possible increased risk of acquiring HIV among progestogen-only injectable users. Uncertainty exists about whether this is due to methodological issues with the evidence or a real biological effect. In many settings, unintended pregnancies and/or pregnancy-related morbidity and mortality are common, and progestogen-only injectables are among the few types of methods widely available. Women should not be denied the use of progestogen-only injectables because of concerns about the possible increased risk. Women considering progestogen-only injectables should be advised about these concerns, about the uncertainty over whether there is a causal relationship, and about how to minimize their risk of acquiring HIV. EVIDENCE: Evidence from 13 observational studies of DMPA, NET-EN or non-specified progestogen-only injectables, which were considered to be "informative but with important limitations" *(4)*, continues to show some association between use of progestogen-only injectables and risk of HIV acquisition, but it remains unclear whether this results from a causal relationship or methodological limitations. Two small studies assessing levonorgestrel implants, which were considered to be "informative but with important limitations" *(4)*, did not suggest an elevated risk, although the risk estimates were imprecise. One study reported no association between use of progestogen-only pills and HIV acquisition *(4)*.

POP = progestogen-only pill; DMPA = depot medroxyprogesterone acetate (injectable), NET-EN = norethisterone enanthate (injectable); LNG/ETG = levonorgestrel and etonogestrel (implants).

Background

Access to sexual and reproductive health services and information, and contraceptive choice, which includes access to a full range of contraceptive methods, is fundamental to the rights and well-being of women and girls *(3,5)*. The World Health Organization's (WHO) primary mandate is to provide assistance to its Member States in achieving the goal of the highest attainable standard of health for all, including sexual and reproductive health *(6)*. Nine guiding human rights principles and standards applied to contraceptive information and services have been defined as a framework for a rights-based approach *(3,5)*.

Hormonal contraceptives include combined oral contraceptive pills (COCs), combined injectable contraceptives (CICs), combined contraceptive patches and rings, progestogen-only injectables (intramuscular and subcutaneous depot medroxyprogesterone acetate [DMPA-IM and DMPA-SC] and norethisterone enanthate [NET-EN]), progestogen-only pills (POPs), levonorgestrel (LNG) and etonogestrel (ETG) implants, and levonorgestrel-releasing intrauterine devices (LNG-IUDs). These are all effective or highly effective methods of pregnancy prevention. The availability and effective use of these contraceptive methods decreases overall pregnancy-related mortality and morbidity, improves infant and child health, and reduces mother-to-child transmission of HIV.

A cornerstone of the World Health Organization's Department of Reproductive Health is to develop and maintain up-to-date, evidence-based guidance on contraceptive safety for individuals with particular medical conditions or personal characteristics. Known as the *Medical eligibility criteria for contraceptive use* (MEC), this guidance offers national family planning programmes a comprehensive set of recommendations on the safety of contraceptive methods *(1)*. The MEC was conceived as a global normative reference for policy-makers and programme managers developing their national policies, programmes, protocols and guidelines, with the overarching goal of removing unnecessary medical barriers to contraception. For over 20 years, the MEC has been used by countries to improve the quality of contraceptive care offered. The guidance is kept up to date through continuous review of the peer-reviewed literature. An automated system known as the Continuous Identification of Research Evidence (CIRE) enables the department to monitor and identify regularly any new publications that may be relevant.

On 1 June 2015, WHO released the fifth edition of the MEC *(1)*. This guidance contains more than 2,000 recommendations for 25 different contraceptive methods and addresses more than 80 medical conditions or personal characteristics. The department carefully monitors the publication of new research evidence to keep this guideline up to date with the state of knowledge in the field. Guidance is updated as new evidence emerges, and a body of existing evidence is maintained.

Since 1991, there has been mixed evidence as to whether the use of hormonal contraceptive methods is associated with an increased risk of a woman acquiring HIV. Interpretation of existing data on the potential biological and immunological effects of hormonal contraception on HIV acquisition is limited by studies that do not account for different types of hormones or varying doses and routes of contraceptive delivery *(7)*. Women using particular hormonal contraceptive methods may also have other behavioural characteristics that could have impact on HIV acquisition risk, such as particular patterns of condom use or non-use, multiple sexual partners or increased coital frequency. In addition, there may be provider bias affecting the choice of methods offered to certain women. In response to continued questions as to whether the use of hormonal contraception increases the risk of HIV acquisition, WHO commissioned an update of a 2014 systematic review, to include new studies *(4)*.

Methods of guideline review and development

This document was prepared according to the standards and requirements specified in the *WHO handbook for guideline development (8)*. In summary, with due attention to human rights standards and principles, the process included determining critical questions and outcomes, retrieving evidence, assessing, synthesizing and grading evidence, presenting the evidence using a structured approach, and formulating the recommendations.

WHO convened a meeting of the GDG during 1–2 December 2016 to review new evidence on the risk of HIV acquisition with hormonal contraception and, where appropriate, revise specific recommendations in the *Medical eligibility criteria for contraceptive use (1)*. The GDG included 19 participants from 12 countries, including experts in family planning and HIV, representatives from affected populations, clinicians, epidemiologists, researchers, programme managers, policy-makers, and guideline methodologists (see Annex 1).

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. The WHO Secretariat and the GDG reviewed these and found no conflicts of interest sufficient to preclude anyone from participating in the deliberations or the development of recommendations. A summary of the declared interests was prepared (see Annex 2).

Existing WHO recommendations on the use of specific hormonal contraceptive methods for women at high risk of HIV were reviewed in accordance with procedures outlined by the WHO Guidelines Review Committee (GRC) and the GRADE approach to evidence review *(2)*. An updated systematic review of the epidemiological and pharmacological evidence was conducted to answer the following PICO question: Does the use of a particular method of hormonal contraception directly increase the risk of HIV acquisition in women? *(4)*

The systematic review was conducted according to the reporting tool, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) *(9)*. The *PubMed* and *EMBASE* databases were searched for studies published in any language in the peer-reviewed literature up to 15 January 2016. Longitudinal studies comparing users of a specific HC method against either non-users of HC, or users of another specific HC method were identified. 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. 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 (see Annex 3). The peer-reviewed systematic review, GRADE evidence profiles, and human rights principles and standards in contraceptive provision served as the basis for the GDG's deliberations during the meeting *(3,5)*.

Biological data pertaining to the plausibility of an effect of individual methods of hormonal contraception on HIV acquisition were reviewed. Several biological mechanisms by which individual methods of hormonal contraception could theoretically increase the risk of HIV acquisition 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 an estrogen as well as a 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. The extent to which data from animal and laboratory studies, including progestogen dosing, can be applied to clinical outcomes in humans remains uncertain *(7)*.

Additionally, a systematic review of the literature was performed for studies (qualitative or quantitative) on contraceptive users' and providers' values, preferences, views, and concerns regarding the contraceptive methods considered under the MEC guidelines (*Kennedy C., Values and preferences in contraceptive decision making: a systematic review, unpublished data submitted for publication, 2017*). Any studies published between January 2005 and October 2016, in any language were searched for in 10 databases. A total of 206 studies were identified that met inclusion criteria. No studies were identified that focused specifically on the issue of potential increased risk of HIV acquisition associated with specific hormonal contraceptive methods. However, key themes in women's preferences were identified. Across studies, women's values and preferences centred on themes of available options for contraception, ease of use, side-effect profiles, and contraceptive efficacy. Contextual factors, such as contraceptive methods

available, counselling and opinions of social networks, influenced decision-making.

The GDG considered the overall quality of the epidemiologic evidence, paying particular attention to the strength and consistency of the data, according to the GRADE approach to evidence review *(2)*. Based on the GRADE process, observational studies start with a strength of evidence grade of "low". Factors that could lower the evidence grade were limitations in the evidence, inconsistency between studies, imprecision of estimates, indirectness of evidence, publication bias; factors that could increase the evidence grade included presence of a dose-response relationship, large magnitude of observed associations, and adjustment for plausible confounders affecting observed associations. The GDG also considered the coherence of various bodies of evidence (for example, DMPA or NET-EN versus non-hormonal contraception or versus COCs, and DMPA versus NET-EN). In addition, the GDG considered the information presented on potential biological mechanisms, as well as providers' and users' values and preferences regarding contraceptive methods. To assist the GDG in systematically incorporating these factors into guidance, existing WHO guidelines on human rights and contraceptive services were followed *(3,5)*. Owing to the focus on contraceptive safety, opportunity costs were not formally assessed during the formulation of the recommendations, since costs may vary widely throughout different regions *(10)*.

After the initial discussions among the entire GDG, a small group prepared a draft based on the preceding discussions of the entire group. The draft was considered and revised by the entire GDG to achieve consensus on the final recommendations. New recommendations for progestogen-only injectables were determined and those for other hormonal contraceptive methods were upheld for women at high risk of HIV. Eligibility recommendations for IUDs (LNG and copper IUDs) were not reviewed by the GDG: these recommendations remain unchanged and are available in the *Medical eligibility criteria for contraceptive use (1)*. For each contraceptive method, the GDG considered the following factors in making their determination:

- quality of the evidence (GRADE profile);
- values and preferences of contraceptive users and health care providers;
- balance of benefits and harms;
- priority of the problem;
- equity and human rights;
- acceptability; and
- feasibility.

A draft version of this statement was sent to the external peer review group of experts who did not participate in the GDG meeting (see Annex 1). Comments received from these reviewers were addressed and incorporated into the guidance as appropriate by the WHO Secretariat. The final version of the document was approved by the WHO Guidelines Review Committee on 18 January 2017.

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 (living with HIV, for example). 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 advantages of using the contraceptive method generally outweigh the theoretical or proven risks; the contraceptive method can generally be used. Category 3 conditions are those for which the theoretical or proven risks usually outweigh the advantages of using the method. Provision of a method to a woman with a condition classified as category 3 requires access to clinical services and careful clinical judgement. Category 4 conditions are those where the method should not be used because the condition represents an unacceptable health risk – the use of the method is contraindicated. Where it is determined that further guidance is needed, it is provided as a "clarification" in addition to the category assigned. 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.

Recommendations

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 (not HIV-infected at baseline)
Intervention	Use of a specific hormonal contraceptive method (injectables, oral contraceptives, implants, patches, rings or LNG-IUDs)
Comparator	One of two possible comparison groups: 1. Non-use of a hormonal contraceptive method (either no use of a contraceptive method, or use of a non-hormonal method such as condoms or other barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, and so on) 2. Use of another specific method of hormonal contraception
Outcome	Incident, laboratory-confirmed HIV infection in women

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

Women and couples at high risk of HIV infection continue to be eligible to use all forms of hormonal contraception. Informed decision-making is a key organizing principle and standard in a human rights-based approach to contraceptive information and services *(5)*. A shared decision-making approach to contraceptive use should be taken with all individuals, but special attention should be paid to using this approach with vulnerable populations, such as women at high risk of acquiring HIV.

Women at high risk can use the following hormonal contraceptive methods without restriction (MEC category 1): combined oral contraceptive pills (COCs), combined injectable contraceptives (CICs), combined contraceptive patches and rings, progestogen-only pills (POPs), and levonorgestrel (LNG) and etonogestrel (ETG) implants.

Women at high risk of acquiring HIV can generally use progestogen-only injectables (NET-EN and IM or SC DMPA) (MEC category 2), but there must be clear provision of information beforehand to enable informed decision-making. There continues to be evidence of a possible increased risk of acquiring HIV among progestogen-only injectable users. Uncertainty exists about whether reports of any possible increased risk are due to methodological issues with the evidence or a real biological effect. In many settings, unintended pregnancies and/or pregnancy-related morbidity and mortality are common, and progestogen-only injectables are among the few methods widely available. Women should not be denied the use of progestogen-only injectables because of concerns about the possible increased risk. Women considering progestogen-only injectables should, however, be advised about this, about the uncertainty over a causal relationship, and about how to minimize their risk of acquiring HIV.

Rationale

In formulating this recommendation, the GDG kept the individuals most affected by the guidance at the centre of the deliberations (that is, women wanting to prevent pregnancy who are at a high risk of acquiring HIV). At the core of the group's decision-making was the human rights principle of promoting informed and free decision-making, and the value of contraceptive choice. It was recognized that all women have their own unique preferences and values, and that they will vary in their perceptions of the risks of unintended pregnancy and HIV infection (*Kennedy C., Values and preferences in contraceptive decision making: a systematic review, unpublished data submitted for publication, 2017*). All women have the right to evidence-based information on contraceptives, to quality services and to the assurance of opportunities to make an informed choice without discrimination *(3)*.

The GDG considered new scientific evidence from recently published studies and concluded that the cumulative body of scientific evidence available to

date continued to indicate an association with an increased risk of acquiring HIV among progestogen-only injectable users. The GDG concluded that it was unknown whether the associations seen in observational studies were due to a true biological effect, or because of limitations of the observational studies, such as bias or confounding. Further observational data are unlikely to reduce the uncertainty. Although there were differences within the GDG in the interpretation of the observational studies, other considerations – primarily related to assuring informed decision-making, such as feedback from women's advocacy groups and programme providers, and consideration of women's values and preferences (*Kennedy C., Values and preferences in contraceptive decision making: a systematic review, unpublished data submitted for publication, 2017*) –were sufficient to lead the entire group to conclude that the recommendation for progestogen-only injectable contraceptive use among women at high risk of HIV infection should be changed from MEC category 1 to category 2.

Factors supporting a category 2 recommendation include women's preferences for fully informed decision-making regarding contraception choices, variability in women's values regarding the trade-offs between the contraceptive benefits and other benefits of progestogen-only injectables versus the potential for increased risk of HIV acquisition, and uncertainty regarding the association between progestogen-only injectables and increased HIV risk, resulting in some uncertainty regarding the balance of benefits and harms. The GDG also determined that a category 2 recommendation would promote WHO principles for human rights and equity, particularly because women who are at risk of HIV infection and require contraception often come from vulnerable populations that are economically and socially disadvantaged and marginalized. Another factor supporting the category 2 recommendation was the greater feasibility for programmes implementing the guidance created by drawing attention to the classification and offering clearer communication from WHO.

It was agreed by programme managers and patient stakeholders that the previous recommendation (MEC category 1 with clarification) had not led to its intended goal of enabling discussion about the association with higher risk with women interested in using progestogen-only injectables, and enabling shared decision-making in contraceptive use and HIV prevention strategies. A category 2 recommendation is not, however, intended to suggest that women at high risk of HIV be denied the use of progestogen-only injectables because of potential concerns. In many areas of the world, the risks of unintended pregnancy and pregnancy-related morbidity and mortality pose a significant threat to the lives and well-being of women and their families *(11,12)*. In many areas where the risks of HIV and maternal mortality are the highest, progestogen-only injectables are among the few effective and acceptable contraceptive methods that are widely available. Their availability saves women's lives, and many women informed of benefits and potential risks may continue to prefer progestogen-only injectables *(12,13)*.

Under these considerations, the GDG felt that the recommendation for use of progestogen-only injectables (all formulations of DMPA and NET-EN) should be changed to MEC category 2. Data about the relationship between NET-EN use and acquisition of HIV infection are limited, and there is no information about the subcutaneous formulation of DMPA. There is therefore insufficient evidence to determine if the HIV acquisition risk associated with NET-EN differs from the risk associated with DMPA. Considering the overall balance of benefits and harms, the GDG decided, on the precautionary principle, to include all progestogen-only injectables in its MEC category 2 recommendation. The group stressed that it was conscious when reaching its decision that in many settings, unintended pregnancies and/or pregnancy-related morbidity and mortality were common, and injectables were among the few types of effective contraceptives widely available. Women should not be denied the use of progestogen-only injectables because of concerns about the possible increased risk. Women considering progestogen-only injectables should be advised about this, about the uncertainty over a causal relationship, and about how to minimize their risk of acquiring HIV.

Summary of the evidence

Thirty-one observational studies assessed the risk of HIV infection among women using a hormonal contraceptive method. This evidence predominantly examined COCs or progestogen-only injectable contraceptives (DMPA [intramuscular] and NET-EN). Scant data were available on the potential relationship between implant use and the risk of HIV. No study assessed the relationship with contraceptive vaginal rings, patches or levonorgestrel intrauterine devices.

Combined hormonal contraceptives

Eleven studies deemed "informative but with important limitations" assessed the use of oral contraceptives. Ten of these studies found no statistically significant association between their use and HIV infection, while one study reported a marginally significant increased risk. No studies related to the use of the combined contraceptive patch, ring or injectable were identified *(4)*. The overall quality was rated

low-to-moderate. Although some limitations were noted in the observational studies, the analysis was restricted to higher-quality studies and limitations were not considered serious enough to warrant further downgrading. Based on the consistency and precision of the evidence, and the coherence of the studies of oral contraceptives versus non-use and studies of progestogen-only contraceptives versus oral contraceptives, the evidence was upgraded from low to low-to-moderate; no factors were present to warrant upgrading the overall quality further.

Progestogen-only contraceptives

Evidence from 13 observational studies of DMPA, NET-EN or non-specified progestogen-only injectables, which were considered to be "informative but with important limitations" *(4)*, continues to show some association between use of progestogen-only injectables and risk of HIV, but it remains unclear whether this results from a causal relationship or methodological limitations. Two small studies assessing levonorgestrel implants, which were considered to be "informative but with important limitations" *(4)*, did not suggest an elevated risk, although the risk estimates were imprecise. One study reported no association between the use of progestogen-only pills and HIV risk *(4)*. The overall quality for the evidence on progestogen-only injectables was rated low to low-to-moderate. Although some limitations were noted in the observational studies, the analysis was restricted to higher-quality studies and limitations were not considered serious enough to warrant further downgrading. Based on the consistency and precision of the evidence, and the coherence of the studies of DMPA versus non-hormonal contraception and DMPA versus NET-EN, the evidence was upgraded from low to low-to-moderate; no factors were present to warrant upgrading the overall quality further. The overall quality for the evidence on implants was rated very low, and for oral contraceptives (including progestogen-only pills), low-to-moderate.

WHO expert groups will continue to actively monitor emerging evidence.

Implications for policies, programmes and providers

The WHO works with Member States both to generate evidence-based contraceptive policy and to translate it into action within countries. Several resources from WHO are available to assist countries in providing high-quality, rights-based contraceptive care. The recommendations made in the MEC are complemented by the following guidance documents: 'Selected practice recommendations for contraceptive use' *(14)*, 'Ensuring human rights in the provision of contraceptive information and services' (both the guidance and the implementation guide) *(3,5)*, 'Decision-making tool for family planning clients and providers' *(15)*, 'Family planning: A global handbook for providers' *(16)*, and The Training Resource Package for Family Planning *(17)*. All of these guidelines and tools are available online and have been widely translated into different languages.

In addition to the above resources, the GDG underscored the importance of the following points when communicating this updated guidance.

What does this evidence mean for policy-makers, programme managers and providers?

- Based on current evidence, family planning programmes delivering services to women at high risk of HIV infection can continue to offer all methods of contraception.
- Comprehensive contraceptive and HIV information and counselling services must be available equally to everyone voluntarily, and free of discrimination, coercion or violence.
- Continued efforts to integrate high-quality family planning and HIV services is an essential strategy to optimize reproductive health for all individuals.
- Hormonal contraception protects against unintended pregnancy, not HIV or other sexually transmitted infections (STIs). All individuals at high risk of HIV or other STI need ready access to prevention strategies, such as condoms and, where appropriate, pre-exposure prophylaxis.
- National programmes are encouraged to systematically introduce, adapt or adopt evidence-based family planning guidelines according to local contexts.
- National programmes are urged to expand on the range of available family planning/contraceptive method options so that women and girls have a wide of range of contraceptive choices.
- Contraceptive counselling is a core component for supporting informed choice and decision-making by clients. Health care providers need support to provide women with comprehensive, evidence-based information on the full range of available methods and the advantages and disadvantages associated with their use.

Knowledge gaps and areas of active research

What actions are needed from the global health community?

Multiple actions are needed from the global health community to address the twin epidemics of HIV and unintended pregnancy. The GDG noted the following:

- One challenge when formulating recommendations for contraceptive use among women at high risk of HIV infection has been the absence of evidence from randomized clinical trials on the topic. Data from observational studies come with a high level of uncertainty (through bias, confounding and limited statistical power, for example), which hampers any assessment of causality regarding the association between hormonal contraception and HIV infection. Randomized clinical trials are needed to provide more information about possible causality.

- The 'Evidence for Contraceptive Options and HIV Outcomes' (ECHO) trial is an ongoing randomized trial that seeks to provide definitive information on the risk of HIV acquisition associated with different contraceptive methods *(18)*. The study population will consist of 7,800 women without HIV who want to prevent pregnancy and are willing to be randomized to using DMPA, an LNG implant or a copper IUD. Enrolment has begun in 12 sites across Kenya, South Africa, Swaziland and Zambia. Study results will not be available before 2019.

- WHO reaffirms its commitment to keeping emerging evidence under close review through its CIRE system. Data from ECHO, and any other relevant study in the future, will be reviewed promptly and incorporated into future guidance.

- WHO will provide assistance to countries with targeted assessments and interventions to improve responses to both the HIV epidemic and unintended pregnancy. In particular, this includes ensuring individuals have access to freely chosen contraceptive methods and HIV preventive therapies that meet a wide range of client preferences and needs.

- WHO encourages research that clearly elucidates women's preferences and values in contraceptive decision-making.

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Plans for dissemination

A comprehensive dissemination and evaluation plan has been developed to ensure that this information is accurately communicated with all affected stakeholders. Priority audiences for this technical statement include health care providers, including students, national family planning and HIV programmes, Member States, and implementing partners, including UN agencies and global leaders in sexual and reproductive health. In addition to this technical statement, derivative communication products will be developed, especially for women and girls, who are the end-beneficiaries and partners in shared decision-making regarding contraception. The technical statement will be translated into a range of languages to reach all stakeholders.

The plan will include widespread dissemination through the WHO regional and country offices, WHO Member States, UNAIDS, the United Nations (UN) agency cosponsors of the Special Programme of Research, Development and Research Training in Human Reproduction (HRP) within the WHO Department of Reproductive Health and Research (that is, UNDP, UNFPA, UNICEF, WHO and the World Bank), WHO collaborating centres, the Implementing Best Practices Initiative, professional organizations, governmental and nongovernmental partner organizations working in the area of sexual and reproductive health, and civil society groups engaged in sexual and reproductive health projects.

The WHO Secretariat will work closely with sexual and reproductive health focal points, as well as HIV focal points in the WHO regional offices to conduct a series of regional events, including webinars in 2017. Active engagement with professional societies, including medical and nursing education associations will be sought.

WHO is committed to working with Member States and partners to ensure that the updated guidance is fully and correctly implemented into national policies and programmes. An evaluation survey targeting ministries of health, WHO offices and partners, professional organizations and civil society will be sent out. The objectives of this survey will be to evaluate the extent and effectiveness of the dissemination, and the implementation of the recommendations into national policies, to identify barriers to effective implementation, and to determine research gaps in contraceptive eligibility criteria for women at high risk of HIV. Information from this survey will be incorporated into subsequent dissemination strategies and guidance updates.

WHO will initiate a review of the recommendations in this statement after four years. WHO will continue to monitor the body of evidence informing these recommendations and will convene additional consultations should new evidence necessitate.

Annex 1. Acknowledgements

The World Health Organization (WHO) would like to thank the members of the Guideline Development Group and the Evidence Secretariat for their contributions throughout the development of these important recommendations for women living with HIV. WHO is very grateful for the suggestions provided by colleagues who peer reviewed the earlier drafts of the statement as members of the external peer review group. The names of the participants in each group are listed below. Drs Caroline Phiri Chibawe and Alison Edelman co-chaired the meeting.

Guideline Development Group

Richard Adanu (University of Ghana, Ghana) [unable to attend], Emily Bass (AVAC, United States of America [USA]), Sharon Cameron (University of Edinburgh, United Kingdom of Great Britain and Northern Ireland [United Kingdom]), Caroline Phiri Chibawe (Ministry of Health, Zambia), Maria del Carmen Cravioto (National Institute of Nutrition, Salvador Zubiran, Mexico)) [unable to attend], Kathryn Curtis (United States Centers for Disease Control and Prevention (CDC), USA), Alison Edelman (Oregon Health Sciences University, USA), Joanne Erdman (Dalhousie University, Canada) [unable to attend], Mohammed Eslami (Ministry of Health and Education, Islamic Republic of Iran), Anna Glasier (University of Edinburgh, United Kingdom), Andy Gray (University of KwaZulu-Natal, South Africa) [unable to attend], Philip Hannaford (University of Aberdeen, United Kingdom), Nathanial Khaole (National Department of Health, South Africa – retired), Address Malata (University of Malawi, Malawi) [unable to attend], Olav Meirik (Institute Chileno de Medicina Reproductiva, Chile), Chelsea Morroni (University of Botswana-University of Pennsylvania Partnership, Botswana), Progestine Muganyizi (Muhimbili University of Health and Allied Sciences, Tanzania) [unable to attend], Lilian Mworeko (International Community of Women Living with HIV Eastern Africa, Uganda), Herbert Peterson (University of North Carolina, USA), Pashang Waiba (AAFNO Nepal-Women Wing, Nepal).

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Writing

The technical statement was written by Mary Lyn Gaffield and Maria Isabel Rodriguez. The systematic review providing summarized evidence for the statement was co-authored by Tsungai Chipato, Kathryn Curtis, Philip Hannaford, James Kiarie, Sharon Phillips, Chelsea Polis (lead author), Petrus Steyn and Daniel Westreich. The GRADE tables and expertise on GRADE methodology were provided by Roger Chou. Preparation of the evidence to decision table and expertise on the literature for values and preferences were provided by Caitlin Kennedy.

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Annex 2. Declarations of conflicts of interest

Following guidance issued on 24 September 2014 by the WHO Office of Compliance, Risk Management and Ethics (CRE), and prior to the 1-2 December 2016 meeting, the name and brief biography of each proposed GDG member was published on the WHO website during 14–31 October 2016 (http://www.who.int/reproductivehealth/topics/family_planning/expert-review-group/en/). The public was able to view and provide their comments to the WHO Secretariat using a general email address (hrx_info@who.int) regarding perceived or real conflicts of interest of these proposed GDG members. In addition, prior to the public announcement period, the WHO Secretariat reviewed the curriculum vitae of each potential participant and conducted Internet searches (PubMed, Open Payments Data, Google Scholar) for information on potential financial and academic conflicts of interest related to the subject of the meeting. Following the public reporting period, and in consultation with CRE, official invitations for GDG membership were extended.

Of the 19 experts who participated in this work, three declared an interest related to contraception. The WHO Secretariat, CRE and Guidelines Development Group 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. Accordingly, the three participants who declared interests related to contraception, as well as the other 16 participants, fully participated in the meeting's deliberations, discussions and final decisions. Although not all of the interests declared were specifically related to hormonal contraception and HIV, they are disclosed and summarized below.

Sharon Cameron works at a research unit that received a grant from Pfizer, UK for less than £90 000 in 2013 to determine the feasibility and acceptability of pharmacist administration of sub-cutaneous injectable contraception. This project has ceased.

Alison Edelman receives a yearly royalty of US$ 1 000 from the Internet information site, UpToDate as the author of the content. During February 2013, she received US$ 2 400 from Genzyme as a consultant to review the potential interactions of hormonal contraception with teriflunomide (a drug to treat multiple sclerosis). Since May 2016, Dr Edelman has been receiving US$ 10 000 a year from Agile Pharmaceuticals as an expert consultant regarding a hormonal contraceptive patch that is currently not FDA approved. Since January 2016, she has been receiving an honorarium of US$ 1 000 a year from Merck Sharp & Dohme to serve as a trainer for the etonogestrel implant Nexplanon and also served as an expert consultant in January 2016 for this company, receiving US$ 1 500 for her services. Her research unit received US$ 540 000 from Merck Women's Health Investigator Initiated Studies Program to conduct research focused on treatment of breakthrough bleeding with the contraceptive implant (from November 2016 to 2018). Her research unit receives funding from the US National Institutes for Health as a site for the Contraceptive Clinical Trials Network. Her unit received US$ 5 million from the Bill and Melinda Gates Foundation to develop the Oregon Permanent Contraception Research Center. From 2015–2017, her research unit is receiving a US$ 250 000 research grant from the Society for Family Planning to investigate the timing of ulipristal acetate and oral contraceptive use, and during March 2013, she received a one-time honorarium to author a guideline for the organization (about US$ 1 500). During 2011 through 2014, she was a member of the American College of OBGYN Society's Scientific Committee. For this role, she received an honorarium of US$ 2 000. During 2013, she received a US$ 1 000 honorarium from Projects in Knowledge as a faculty member for their continuing medical education program. Since 2002, Dr Edelman has been receiving about US$ 3 000 a year from Contemporary Forums as a faculty member for its continuing medical education conferences (the amount varies depending on the number of lectures she gives). From November 2015 through June 2016, she received an honorarium of US$ 3 000 from Oregon State University for expert advice on a health bill to allow direct provision of contraceptives by pharmacists. Since July 2016, Dr Edelman has been receiving US$ 500 a year as an honorarium for serving on the data and safety monitoring board to FHI 360, which is developing a novel contraceptive injectable that is not yet FDA-approved.

Anna Glasier provides expert advice on the safety and effectiveness of an emergency contraceptive pill on a regular basis to the manufacturer of this contraceptive method. The amount was not disclosed. Dr Glasier's research unit receives funding for the salary of one full-time junior clinician from HRA Pharma, Paris. This is ongoing.

Annex 3. GRADE evidence profile for studies of hormonal contraceptive use and HIV acquisition in women at high risk of HIV infection

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Overall quality	Estimate of effect
DMPA versus non-hormonal contraception							
HIV acquisition	9 cohort studies plus 1 individual patient data meta-analysis of 7 studies* (39 562)^	Some limitations**	No serious inconsistency	No serious imprecision	No indirectness	Low-moderate^^	Adjusted HR range 0.46 to 2.04, 8 studies increased risk (HR range 1.25 to 2.04), with statistically significant effects in 3 studies; 2 studies trend towards decreased (HR 0.46 and 0.75 with wide confidence intervals). Pooled adjusted HR 1.40 (1.23-1.59), I2=0%
NET-EN versus non-hormonal contraception							
HIV acquisition	5 cohort studies plus 1 individual patient data meta-analysis of 7 studies* (29 248)^	Some limitations**	No serious inconsistency	Some imprecision**	No indirectness	Low	Adjusted HR range 0.87 to 1.76, 5 studies increased risk (HR range 1.20 to 1.76), none statistically significant; 1 study no effect (HR 0.87, 95% CI 0.60 to 1.25). Pooled adjusted HR 1.15 (0.93-1.42), I2=0%
Oral hormonal contraceptive use versus non-use							
HIV acquisition	11 cohort studies* (43 385)^	Some limitations**	No serious inconsistency	No serious imprecision	No indirectness	Low-moderate^^	Adjusted HR or IRR range 0.66 to 1.80, 3 studies increased risk (HR 1.39 to 1.80), 3 studies decreased risk (HR 0.66 to 0.79), 5 studies no association (HR 0.88 to 0.99); no study reported statistically significant association
Implant use versus non-use							
HIV acquisition	2 cohort studies* (2 665)^	Serious limitations	No serious inconsistency	Serious imprecision	No indirectness	Very low	Adjusted HR 0.96 (0.29–3.14) and 1.6 (0.5–5.7)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Overall quality	Estimate of effect
DMPA versus NET-EN							
HIV acquisition	1 cohort study and 1 individual patient data meta-analysis of 17 studies* (41 608)^	Some limitations**	No serious inconsistency	No serious imprecision	No indirectness	Low-moderate^^	Adjusted HR 1.32 (1.08–1.61) in cohort study and 1.41 (1.06–1.89) in IPD meta-analysis of 17 studies (I2=0%)
DMPA versus combined oral contraceptives							
HIV acquisition	1 individual patient data meta-analysis of 8 studies* (24 853)^	Some limitations**	No serious inconsistency	No serious imprecision	No indirectness	Low-moderate^^	Adjusted HR 1.41 (1.23–1.67) in IPD meta-analysis of 8 studies (I2=0%)
NET-EN versus combined oral contraceptives							
HIV acquisition	1 individual patient data meta-analysis of 9 studies* (25 398)^	Some limitations**	No serious inconsistency	Some imprecision**	No indirectness	Low	Adjusted HR 1.30 (0.99–1.71) in IPD meta-analysis of 9 studies (I2=0%)

CI = confidence interval, HR = hazard ratio, I2 = Inconsistency heterogeneity statistic, IPD = individual participant data, IRR = incidence rate ratio.

Note: Publication bias was not formally assessed; observational studies could not be upgraded for large effects dose-response relationship, or confounders likely to increase observed effects. Estimates based on adjusted risk estimates and results from Cox model analysis when available.

*Restricted to studies classified as "informative with but with important limitations".

^Sample size is for the entire study population.

#Reports more recent estimates from Wand 2012 (included in prior review).

**Some limitations or imprecision noted, but not serious enough to downgrade the level of evidence.

^^Evidence graded low to moderate due to consistent and precise results from well-conducted observational studies, and coherence between studies of use versus non-use and head-to-head studies.

Annex 4. Evidence to decision table – Are women at high risk of HIV medically eligible to use DMPA/NET-EN injectable contraceptive methods?

Factor	Explanation/evidence	Judgement
Quality of evidence	Evidence for DMPA and NeET-EN was considered low to low-to-moderate for the primary outcome of HIV acquisition.	Low to low-to-moderate
Balance of benefits versus harms	Contraception is a life-saving intervention, and progestogen-only injectables are highly effective, reversible methods that are widely used in areas where the risk of maternal mortality and morbidity are very high. Uncertainty exists in scientific data regarding an association between progestogen-only injectables and a possible increased risk of HIV acquisition. This possible increased risk of HIV acquisition was outweighed for the GDG by the very real risk of maternal mortality and morbidity associated with unintended pregnancy. The GDG noted that for individual women, this risk-to-benefit ratio would be different, and it is essential that an informed decision-making approach be taken with women considering progestogen-only injectables, and all contraceptive methods.	Benefits outweigh harms
Values and preferences	Women have the right to informed decision-making. Women prefer to have choice in methods, full information regarding benefits versus harms, and to make a final decision in conjunction with their provider (shared decision-making). Contraception is unique among other medicines because a woman's needs and preferences in method characteristic will vary both between individual women and across a single individual's lifespan. Common themes in contraceptive preferences include that they are discreet, have minimal side-effects, and are long-acting, reversible and easy to use. Women who use progestogen-only injectables generally like them for these reasons, and feel comfortable using them after counselling. Women's preferences for methods are limited by what they have knowledge of, what is available to them, and other factors that foster or limit access. Offering women the choice of a range of methods is important from both a health and a rights perspective.	Support for optimizing informed contraceptive choice and the availability of a wide range of contraceptive options
Priority of the problem	HIV is a life-threatening illness and a major global epidemic. Unintended pregnancy is a very common problem globally, and the risks associated with it are highest where maternal mortality and severe morbidity are also common. Both are priorities for public health.	Hormonal contraception and HIV are a public health priority
Equity and human rights	Human rights principles and standards from existing WHO guidelines on human rights and contraception were followed by the GDG in its deliberations. These include non-discrimination, availability, accessibility, acceptability, quality, informed decision-making, privacy and confidentiality, participation, and accountability.	Recommendations within WHO's human rights guidance for contraception are paramount principles for decision-making on this topic
Feasibility	The importance of clear communication from WHO on this topic was underscored repeatedly by representatives of affected populations, Member States and programme managers. The prior WHO guidance, which included a clarification statement with the MEC category rating, was overlooked and poorly understood. This feedback was incorporated into the updated guidance.	Clear guidance essential for implementation
Resource implications	Owing to the focus of this guidance on the safety of specific contraceptive methods for women at high risk of HIV, opportunity costs and resource implications were not formally assessed during the formulation of the recommendations since costs may vary widely throughout different regions.	Not applicable

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Abbreviations

CDC	Centers for Disease Control and Prevention (United States of America)
CIC	combined injectable contraceptive
CIRE	Continuous Identification of Research Evidence
COC	combined oral contraceptive
DMPA	depot medroxyprogesterone acetate
ETG	etonogestrel
GDG	Guideline Development Group
GRADE	Grading Recom0mendations, Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HC	hormonal contraception
IM	intramuscular
IUD	intrauterine device
LNG	levonorgestrel
MEC	*Medical eligibility criteria for contraceptive use* (WHO publication)
NET-EN	norethisterone enanthate
NIH	National Institutes of Health (United States of America)
OC	oral contraceptive pill
PICO	population, intervention, comparator, outcome
POP	progestogen-only pill
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SC	subcutaneous
STI	sexually transmitted infection
UN	United Nations
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

More information and related documents

The Medical eligibility for contraceptive use, fifth edition (in English, French and Spanish) is available to download from: http://www.who.int/reproductivehealth/publications/family_planning/Ex-Summ-MEC-5/en/

The Selected practice recommendations for contraceptive use, third edition (in English) is available to download from: http://www.who.int/reproductivehealth/publications/family_planning/SPR-3/en/

Family planning: A global handbook for providers, 2011 update is available to download from: http://www.who.int/reproductivehealth/publications/family_planning/9780978856304/en/

Ensuring human rights in the provision of contraceptive information and services: Guidance and recommendations is available to download from: http://www.who.int/reproductivehealth/publications/family_planning/human-rights-contraception/en/

Further information on WHO's Guidelines Review Committee: http://www.who.int/publications/guidelines/guidelines_review_committee/en/

Further information on WHO's work in family planning: http://www.who.int/reproductivehealth/topics/family_planning/en/

Further information on linkages between sexual and reproductive health and HIV: http://www.who.int/reproductivehealth/topics/linkages/en/

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