



Contraceptive eligibility for women at high risk of HIV

Guidance statement

Recommendations on contraceptive methods used by women at high risk of HIV

Contraceptive eligibility for women at high risk of HIV

Guidance statement

Recommendations on contraceptive methods used by
women at high risk of HIV



**World Health
Organization**

Contraceptive eligibility for women at high risk of HIV. Guidance statement: recommendations on contraceptive methods used by women at high risk of HIV

ISBN 978-92-4-155057-4

© World Health Organization 2019

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

Suggested citation. Contraceptive eligibility for women at high risk of HIV. Guidance statement: recommendations on contraceptive methods used by women at high risk of HIV. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

The views expressed in this publication are those alone of the named authors and of the collective views of an international group of experts and do not necessarily represent the decisions or the policies of WHO.

Printed in Switzerland

CONTENTS

	ACKNOWLEDGEMENTS	V
	ABBREVIATIONS	VI
	EXECUTIVE SUMMARY	VII
1	BACKGROUND	1
2	METHODS OF GUIDELINE REVIEW AND DEVELOPMENT	2
	2.1 Guideline Development Group	2
	2.2 Guideline development process	2
	2.3 Evidence Retrieval	3
	2.4 Evidence Synthesis	4
	2.5 Formulation of recommendations	4
3	SUMMARY OF THE EVIDENCE	4
	3.1 Progestogen-only injectables	5
	3.2 Progestogen-only implants	5
	3.3 Progestogen-only pills	5
	3.4 Intrauterine devices	5
	3.5 Combined hormonal contraceptives	5
	3.6 Additional evidence considered by the GDG	5
	3.6.1 Biological data	5
	3.6.2 Values and preferences of contraceptive users	6
4	RECOMMENDATIONS	6
	4.1 Recommendations for contraceptive use among women at high risk of HIV infection	6
	4.2 Rationale	7
5	IMPLICATIONS FOR POLICY-MAKERS, PROGRAMME MANAGERS AND HEALTH-CARE PROVIDERS	8
	5.1 A woman's risk of HIV should not restrict her contraceptive choice	8
	5.2 Efforts to expand access to contraceptive options must continue	8
	5.3 A renewed emphasis on HIV and STI prevention services is urgently needed	9

CONTENTS (continued)

6	KNOWLEDGE GAPS AND AREAS FOR RESEARCH	9
	6.1 Contraceptive methods and HIV acquisition	9
	6.2 HIV prevention	9
	6.3 Community involvement	10
	6.4 Increased funding for high-quality, policy-relevant research	10
7	DISSEMINATION OF THIS GUIDANCE STATEMENT	10
	REFERENCES	11
	ANNEX 1. GUIDELINE DEVELOPMENT GROUP AND EVIDENCE SECRETARIAT	13
	ANNEX 2. DECLARATIONS OF CONFLICTS OF INTEREST	15
	ANNEX 3. GRADE EVIDENCE PROFILES	17
	ANNEX 4. EVIDENCE-TO-DECISION TABLE FOR HORMONAL CONTRACEPTIVE METHODS AND INTRAUTERINE DEVICES (IUDS)	21
	ANNEX 5: SYSTEMATIC REVIEWS	23

ACKNOWLEDGEMENTS

The World Health Organization (WHO) would like to thank the members of the Guideline Development Group and the Evidence Secretariat (Annex 1) for their contributions throughout the development of these important recommendations for women at high risk of HIV. WHO is very grateful for the suggestions provided by colleagues who peer reviewed the draft statement as members of the External Review Group.

The development of this technical statement was financially supported by the Bill & Melinda Gates Foundation, the Netherlands Ministry of Foreign Affairs, the United States Agency for International Development, and the United States National Institutes of Health.

ABBREVIATIONS

CIC	combined injectable contraceptive	HR	hazard ratio
COC	combined oral contraceptive	IRR	incidence rate ratio
CRE	WHO Office of Compliance, Risk Management and Ethics	IUD	intrauterine device
Cu-IUD	copper-bearing intrauterine device	LNG	levonorgestrel
DMPA	depot medroxyprogesterone acetate	LNG-IUD	levonorgestrel-releasing intrauterine device
DMPA-IM	intramuscular depot medroxyprogesterone acetate	MEC	<i>Medical eligibility criteria for contraceptive use</i>
DMPA-SC	subcutaneous depot medroxyprogesterone acetate	NET-EN	norethisterone enanthate
ECHO	Evidence for Contraceptive Options and HIV Outcomes (Study)	OTC	over the counter
ETG	etonogestrel	POP	progestogen-only pill
FDA	United States Food and Drug Administration	PrEP	pre-exposure prophylaxis (for HIV)
GDG	Guideline Development Group	RCT	randomized controlled trial
GRADE	Grading of Recommendations Assessment, Development and Evaluation	STI	sexually transmitted infection
		WHO	World Health Organization

EXECUTIVE SUMMARY

The World Health Organization (WHO) convened a Guideline Development Group (GDG) meeting from 29 to 31 July 2019 to review global guidance on contraceptive eligibility for women at high risk of HIV acquisition to and determine whether revisions to the fifth edition of the *Medical eligibility criteria for contraceptive use* (MEC) were needed. The issue was deemed critical, particularly for sub-Saharan Africa, given the high lifetime risk of acquiring HIV alongside the importance of hormonal contraception in offering women and adolescent girls' choice and in reducing their risk of unintended pregnancy, a common threat to the health, well-being and lives of women and adolescent girls.

The GDG consisted of 28 participants from 19 countries, including 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 when formulating recommendations for each contraceptive method:

- quality of the evidence (i.e. GRADE profile)¹
- values and preferences of contraceptive users
- balance of benefits and harms
- priority of the problem
- equity and human rights
- feasibility.

In formulating these recommendations, the GDG kept at the centre of their deliberations the individuals most affected by the recommendations – that is, those women wanting to prevent pregnancy who are at a high risk of HIV acquisition.

Through consensus, the GDG agreed to the following new recommendations. These revisions mean that women at a high risk of HIV can use all methods of contraception without restriction.

- Women at a high risk of HIV infection are eligible to use all progestogen-only contraceptive methods without restriction (MEC Category 1), including progestogen-only pill (POPs), intramuscular and subcutaneous depot medroxyprogesterone acetate (DMPA-IM and DMPA-SC), norethisterone enanthate (NET-EN), levonorgestrel (LNG) implants and etonogestrel (ETG) implants.
- Women at a high risk of HIV infection are eligible to use copper-bearing intrauterine devices (Cu-IUDs) and LNG-IUDs without restriction (MEC Category 1). In considering the

use of IUDs, many women at a high risk of HIV are also at risk of other sexually transmitted infections (STIs); for these women, providers should refer to the MEC recommendation on women at an increased risk of STIs, and the *Selected practice recommendations for contraceptive use: third edition* on STI screening before IUD insertion.

- Women at a high risk of HIV infection are eligible to use all combined hormonal contraceptive methods without restriction (MEC Category 1), including combined oral contraceptives (COCs), combined injectable contraceptives (CICs), combined contraceptive patches and combined vaginal rings.

These recommendations were strongly informed by new epidemiological evidence, particularly from one high-quality randomized controlled trial (the ECHO trial), which did not demonstrate a statistically significant difference in HIV acquisition among women using the three contraceptive methods studied: DMPA-IM, Cu-IUDs and LNG implants. This high-quality evidence superseded the previously available observational evidence of low and low-to-moderate quality. For COCs and NET-EN injectables, evidence of low and low-to-moderate quality from observational studies indicated no increased risk of HIV infection. While no direct evidence was available for DMPA-SC, LNG-IUDs or ETG implants, there was no biological or clinical reason to believe that a lower hormonal dose, different delivery mechanism or different progestogen would modify HIV risk. A consideration of women's values, preferences, views and concerns regarding contraceptive methods provided support for optimizing informed contraceptive choice and the availability of a wide range of contraceptive options.

There are several key messages from this guidance for policy-makers, programme managers and health-care providers.

- A woman's risk of HIV does not restrict her contraceptive choice.
- Efforts to expand contraceptive method options and ensure full and equitable access to family planning services must continue.
- A renewed emphasis on HIV/STI testing and prevention services is urgently needed, including the integration of family planning and HIV/STI services as appropriate, along with sexual and reproductive health packages.

¹ GRADE = Grading of Recommendations Assessment, Development and Evaluation (for further information, see: <http://www.gradeworkinggroup.org>).

PROGESTOGEN-ONLY CONTRACEPTIVES

Progestogen-only contraceptives (POCs) do not protect against sexually transmitted infections (STIs), including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe, but are not used as widely as male condoms by national programmes.

Condition	MEC category			Clarification/evidence
	POP	DMPA/ NET-EN	LNG/ ETG	
High risk of HIV	1	1	1	EVIDENCE: High-quality evidence from one randomized controlled trial observed no statistically significant differences in HIV acquisition between: DMPA-IM versus Cu-IUD, DMPA-IM versus LNG implant, and Cu-IUD versus LNG implant. Of the low-to-moderate-quality evidence from 14 observational studies, some studies suggested a possible increased risk of HIV with progestogen-only injectable use, which was most likely due to unmeasured confounding. Low-quality evidence from 3 observational studies did not suggest an increased HIV risk for implant users. No studies of sufficient quality were identified for POPs.

Cu-IUD: copper-bearing intrauterine device; DMPA: depot medroxyprogesterone acetate (injectable); IM: intramuscular; LNG/ETG: levonorgestrel and etonogestrel (implants); MEC: *Medical eligibility criteria for contraceptive use*; NET-EN: norethisterone enanthate (injectable); POP: progestogen-only pill

INTRAUTERINE DEVICES

Intrauterine devices (IUDs) do not protect against sexually transmitted infections (STIs), including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe, but are not used as widely as male condoms by national programmes.

Condition	MEC category				Clarification/evidence
	Cu-IUD		LNG-IUD (20 µg/24 hours)		
	Initiation	Continuation	Initiation	Continuation	
High risk of HIV	1	1	1	1	CLARIFICATION: Many women at a high risk of HIV are also at risk of other STIs. For these women, refer to the recommendation in the <i>Medical eligibility criteria for contraceptive use</i> on women at an increased risk of STIs, and the <i>Selected practice recommendations for contraceptive use</i> on STI screening before IUD insertion. EVIDENCE: High-quality evidence from one randomized controlled trial, along with low-quality evidence from two observational studies, suggested no increased risk of HIV acquisition with Cu-IUD use. No studies were identified for LNG-IUDs.

Cu-IUD: copper-bearing intrauterine device; LNG-IUD: levonorgestrel-releasing IUD; MEC: *Medical eligibility criteria for contraceptive use*

COMBINED HORMONAL CONTRACEPTIVES

Combined hormonal contraceptives (CHCs) do not protect against sexually transmitted infections (STIs), including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe, but are not used as widely as male condoms by national programmes.

Condition	MEC category				Clarification/evidence
	COC	P	CVR	CIC	
High risk of HIV	1	1	1	1	EVIDENCE: Low-to-moderate-quality evidence from 11 observational studies suggested no association between COC use (it was assumed that studies that did not specify oral contraceptive type examined mostly, if not exclusively, COC use) and HIV acquisition. No studies of P, CVR or CIC were identified.

COC: combined oral contraceptive; CIC: combined injectable contraceptive; CVR: combined contraceptive vaginal ring; MEC: *Medical eligibility criteria for contraceptive use*; P: combined contraceptive patch

1

BACKGROUND

Access to sexual and reproductive health services and information, including a comprehensive range of contraceptive methods, is fundamental to the rights and well-being of women and adolescent girls (1–4). There is a wide range of hormonal and non-hormonal modern contraceptive methods providing substantial individual and public health benefits. A core part of the work of the World Health Organization (WHO) is the development and maintenance of up-to-date, evidence-based guidance on contraceptive safety for individuals with particular medical conditions or medically relevant characteristics (5). The *Medical eligibility criteria for contraceptive use* (the MEC), fifth edition, offers national policy-makers and family planning programmes a comprehensive set of recommendations on the medical safety of contraceptive methods, allowing for the informed development of national policies, protocols and programmes (5). Global guidance about medical safety and eligibility facilitates the removal of unnecessary medical barriers to contraception.

For over 20 years, the MEC has been used by countries to maximize safety and improve the quality of contraceptive care offered. Guidance about safety is kept up to date through continuous monitoring and reviews of published literature. In 2015, WHO released the fifth edition of the MEC (5). This edition contains more than 2000 recommendations for 25 different contraceptive methods, within the context of more than 80 medical conditions or medically relevant personal characteristics. Depending on the individual, more than one condition may need to be considered when making an informed contraceptive choice (5). The recommendations in the MEC are based on several considerations, including whether the use of a contraceptive method worsens the medical condition or creates

additional health risks, and whether the condition makes the contraceptive method less effective (5).

The MEC is part of a set of tools aiming to improve contraceptive coverage and care throughout the world. The MEC informs decisions about who might use a particular contraceptive method, through information and guidance about the safety and appropriateness of contraceptive care. The *Selected practice recommendations for contraceptive use* (the SPR) provides guidance on how to safely and effectively use various contraceptive methods (6). WHO produces a range of tools to support the use and implementation of contraceptive guidance, such as the MEC wheel and the *Global handbook for providers* (7, 8).

Since 1996, the MEC has applied a four-category scale to indicate medical eligibility for particular contraceptive methods in the presence of particular conditions or individual characteristics (e.g. at high risk of HIV). For each condition or characteristic, contraceptive methods are placed into one of four numbered categories:

1. A condition for which there is no restriction for the use of 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.

The interpretation and application of the categories in practice are shown in Table 1.

TABLE 1. INTERPRETATION AND APPLICATION OF THE MEDICAL ELIGIBILITY CRITERIA (MEC) CATEGORIES

Category	With good resources for clinical judgement	With limited resources for clinical judgement
1	Use the method in any circumstances	Yes, use the method
2	Generally use the method	
3	Use of the method not usually recommended unless more appropriate methods are not available or not acceptable	No, do not use the method
4	Method not to be used	

In the past, there has been mixed evidence about whether hormonal contraceptive methods – particularly depot medroxyprogesterone acetate (DMPA) – are associated with an

increased risk of HIV acquisition. The available evidence consisted of theoretical biological data and observational studies with important limitations. In 2016, the independent

Guideline Development Group (GDG) for the MEC reviewed the accumulating evidence regarding women at high risk of acquiring HIV (9). The GDG concluded that there remained uncertainty about whether the increased risk of HIV acquisition seen in some observational studies was a real effect of the contraceptive method used or whether it was a statistical artefact resulting from key limitations of observational studies (residual confounding in particular) (9). There also continued to be uncertainty about the clinical relevance of the biological data. In addition, there was concern that previous attempts to inform women of the uncertainty about both the epidemiological and biological data (through the use of a MEC clarification, indicated by an asterisk [*]) had not been effective. Given these concerns, the GDG concluded that MEC guidance should be changed. Thus, in 2017, the recommendation for progestogen-only injectable use among women at high risk of HIV infection was changed from MEC Category 1* (no restrictions to use,

with a clarification) to MEC Category 2 (the benefits of use outweigh the risks), with an accompanying clarification (9).

This new classification indicated that progestogen-only injectables could be used by women at high risk of HIV, because the advantages of these methods generally outweighed the possible disadvantages, and it highlighted that, when choosing these methods, there might need to be extra consideration of possible HIV acquisition, and counselling.

As part of the 2017 revision, WHO reaffirmed its commitment to monitoring and assessing any new evidence relevant to contraceptive safety. New information, including results from a large, multinational randomized controlled trial (RCT) (10), led WHO to convene another GDG meeting in July 2019 to review all the available evidence and assess whether the MEC guidance needed revision.

2

METHODS OF GUIDELINE REVIEW AND DEVELOPMENT

2.1 Guideline Development Group

The development of this guidance statement was undertaken by the independent Guideline Development Group (GDG) and an additional panel of external reviewers. The GDG consisted of 28 participants from 19 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). Following WHO guidance, months prior to the July 2019 meeting of the GDG, the name and brief biography of each proposed GDG member was published at the WHO website (<https://www.who.int/reproductivehealth/publications/contraceptives-methods-hiv>). The public was able to view and provide input on any perceived or real conflicts of interest of the proposed members. WHO responded to all comments and accordingly adjusted the final composition of the GDG. Prior to the GDG meeting, the WHO Secretariat and the GDG reviewed the members' declarations of interests (Annex 2) and found no conflicts of interest sufficient to preclude anyone from participating in the deliberations or the development of the recommendations. The members of the GDG were also asked to declare any new conflicts of interest at the start of the meeting. None were declared.

2.2 Guideline development process

This guidance statement was prepared according to the standards and requirements specified in the *WHO handbook for guideline development* (11). This process is used to ensure that WHO guidelines are of the highest quality and follow a transparent, systematic process. Key steps of the guideline process include determining the critical questions and outcomes, retrieving the evidence, synthesizing and grading the evidence, presenting it using a structured approach, and formulating recommendations.

WHO's Family Planning Guideline Steering Group determined the critical questions and outcomes to be considered by the GDG. Distinct types of evidence were identified as essential to review. These included the health evidence (randomized trials and observational epidemiological data), the evidence on biological plausibility and the data on the values and preferences of contraceptive users.

Applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach,² multiple factors are considered when formulating recommendations (12). These include the quality of the epidemiological evidence (found in the GRADE evidence profiles, which are prepared based on up-to-date

² For further information, see: <http://www.gradeworkinggroup.org>

systematic reviews); the values and preferences of contraceptive users; the balance of benefit and harms; the priority of the problem; equity and human rights; acceptability; and feasibility. The human rights principles and standards described in WHO's guidance, *Ensuring human rights in the provision of contraceptive information and services*, were incorporated into deliberations (1). 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 (13). The GRADE evidence-to-decision framework (a tool encompassing quality of evidence, balance of benefits versus harms, values and preferences, priority of the problem, equity and human rights, feasibility) was used to ensure that recommendations were based on the consideration of all standards (11).

2.3 Evidence Retrieval

Existing WHO recommendations on the use of specific contraceptive methods by women at high risk of HIV were reviewed in accordance with procedures outlined by the WHO Guidelines Review Committee and the GRADE approach to evidence review (11, 12). Three systematic reviews were conducted in preparation for the GDG meeting: two reviews pertained to the epidemiological evidence and the third review synthesized qualitative or quantitative studies on users' values, preferences, views and concerns regarding contraceptive

methods. The two systematic reviews of epidemiological evidence conducted for the GDG meeting were:

1. An updated systematic review on hormonal contraception and risk of HIV acquisition was conducted to include new studies published since 2016, when the last systematic review was undertaken (14). The review question was:
 - Among women at risk of HIV, does use of a hormonal contraceptive method compared with non-use of a hormonal contraceptive method (or use of another specific hormonal contraceptive method) increase risk of HIV acquisition?
2. A systematic review on copper-bearing intrauterine device (Cu-IUD) use and risk of HIV acquisition was also conducted. The review questions were:
 - Among women at risk of HIV, does use of a Cu-IUD compared with use of another non-hormonal contraceptive method or no contraceptive method increase risk of HIV acquisition?
 - Among women at risk of HIV, does use of a Cu-IUD compared with use of a specific hormonal contraceptive method increase risk of HIV acquisition?

The selection criteria for the systematic reviews are listed in Table 2. The same study designs, population, comparators and outcomes were considered for all the contraceptive methods reviewed.

TABLE 2. SELECTION CRITERIA FOR THE SYSTEMATIC REVIEWS

Study design	Longitudinal studies (randomized controlled trials and observational studies or meta-analyses containing data not captured in bibliographic database searches)
Population	Women of reproductive age at risk of HIV infection (women who were not living with HIV at baseline)
Intervention	Use of a specific contraceptive method: <ul style="list-style-type: none"> ■ hormonal contraception (injectables, oral contraceptives, implants, patches, rings or levonorgestrel-releasing intrauterine devices) ■ copper-bearing intrauterine devices (Cu-IUDs)
Comparator	One of two comparison groups: <ol style="list-style-type: none"> 1. non-use of a hormonal contraceptive method (either no contraceptive use or use of a non-hormonal method such as condoms or other barrier method, withdrawal, Cu-IUD or tubal ligation/vasectomy) 2. use of another specific method of hormonal contraception
Outcome	Incident, laboratory-confirmed HIV infection in women

The two systematic reviews were conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (15). The PubMed and Embase databases were searched for studies published in any language in the peer-reviewed literature up to 26 June 2019. For individual studies, the risk of bias was assessed using a quality framework described in the previous review (14). Studies were classified into three levels:

1. "Unlikely to inform the primary question": studies that had
 - (a) no adjustment for any measure of condom use or
 - (b) unclear measurement of exposure to contraception.
2. "Informative but with important limitations": studies that had none of the flaws described above, but that still had the potential for unmeasured or residual confounding.
3. "Informative with few limitations": studies that had none of the above flaws – likely to be a randomized controlled trial (RCT) that was assessed as having a low risk of bias on standard criteria for evaluating RCTs.

The focus of the systematic reviews was on information from studies that were considered "informative but with important limitations" or "informative with few limitations." to fall into levels 2 and 3.

The values and preferences of contraceptive users were incorporated in multiple ways. First, an updated systematic review of qualitative or quantitative studies on users' values, preferences, views and concerns regarding the contraceptive methods considered under the *Medical eligibility criteria for contraceptive use* (MEC) guidelines was conducted (16). This review covered studies from any country published in the peer-reviewed literature between January 2005 and December 2017. Just prior to the GDG meeting in July 2019, this review was informally updated for studies in either the peer-reviewed or grey literature that specifically looked at the values and preferences of contraceptive users relating to the issue of hormonal contraception and HIV acquisition. Second, because

the updated systematic review did not identify any information specific to key populations at risk of HIV, consultative engagements were conducted in May through July of 2019, including a global online survey of sex workers and participatory focus group discussions with female sex workers in Zimbabwe (through the Sisters with a Voice programme). Third, stakeholders representing specific affected populations, including women living with HIV, and young women, contributed their perspectives through a presentation and discussion of critical perspectives at the GDG meeting.

An update about the biological data on the theoretical effect that contraception may have on HIV acquisition was prepared, reviewed and discussed at the GDG meeting, including consideration of the theoretical plausibility of individual methods of hormonal contraception having an influence on HIV acquisition.

2.4 Evidence Synthesis

Epidemiological data were synthesized and evaluated according to the GRADE approach to evidence review (12). Based on this, randomized trials begin with a grade for strength of evidence of “high”, and observational studies start with a grade of “low”. The risk of bias was assessed for the summarized data using standard GRADE methods (17). Factors that could lower the evidence grade were limitations in the evidence (bias), inconsistency between studies, imprecision of estimates, indirectness of evidence, and publication bias (17–22). Randomized trials were assessed for bias by systematically evaluating for inadequate randomization/ allocation concealment; inadequate blinding of treatments; attrition and failure to use intention-to-treat analyses; selective outcome reporting; and crossover/contamination (17).

Observational studies were assessed for bias by examining whether there was failure to develop and apply appropriate eligibility criteria, flawed measurement of exposures or outcomes, failure to adequately address confounding, or incomplete follow-up (17). Factors that could increase the evidence grade of observational studies included the presence of a dose-response relationship, a large magnitude of observed associations, and adjustment for plausible confounders affecting observed associations (22).

2.5 Formulation of recommendations

Findings from the systematic reviews and associated GRADE evidence profiles (Annex 3) were presented at the GDG meeting. A presentation on the biological plausibility of hormonal contraception modifying the risk of HIV acquisition, and several presentations on contraceptive users’ values and preferences, were also given. These inputs were used to develop an evidence-to-decision framework (Annex 4), which served as the basis for the GDG’s deliberations during the meeting (12). All recommendations were arrived at by consensus.

After the GDG’s recommendations were made, a small writing group prepared a draft guidance statement summarizing the decision and associated rationale. The draft was reviewed by the entire GDG and the external review group (see Annex 1). Comments received from the GDG and the external review group were considered and addressed by the writing group. The final version of this guidance statement was approved by the WHO Guidelines Review Committee on 22 August 2019.

3

SUMMARY OF THE EVIDENCE

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study³ was the primary source of new evidence since the WHO last reviewed recommendations on contraception for women at high risk of HIV (9). The ECHO Study was a large randomized controlled trial (RCT) conducted in Eswatini, Kenya, South Africa and Zambia specifically designed to compare HIV incidence among users of three contraceptive methods: intramuscular depot medroxyprogesterone acetate (DMPA-IM), levonorgestrel (LNG) implants and copper-bearing intrauterine

devices (Cu-IUDs) (10). The trial randomized 7829 HIV-seronegative women, aged between 16 and 35 years, who desired effective contraception and consented to be randomized to one of the three contraceptive methods. There was no group of non-users of contraception in the ECHO trial because all of the women enrolled desired effective contraception. Women returned every three months for HIV testing, contraceptive counselling, safety monitoring, behavioural assessment and a comprehensive package of HIV

³ For further information, see: <http://echo-consortium.com>

prevention services; for up to 18 months. The main (primary) comparisons used a modified intention-to-treat analysis. In addition, pre-planned (secondary) analyses were conducted, restricted to continuous use of the assigned contraceptive method and adjusted for a number of important confounders, including vaginal sex without a condom, a new sexual partner in the previous three months, and more than one sexual partner.

Statistical significance in the ECHO trial was taken to be a P-value less than 0.04 for the primary comparisons. No statistically significant associations were found for any of the primary comparisons between the three contraceptive methods (Annex 3). The quality of the evidence from this RCT was rated as high, due to its large size, strong randomization and allocation procedures, high follow-up rates, high continuation of the allocated contraceptive method, objective measurement of HIV incidence and comprehensive analysis of the results.

Other evidence on hormonal contraception and HIV acquisition published since the 2016 review (14) was included in the evaluation of the body of evidence, along with a systematic review on Cu-IUDs and risk of HIV acquisition (Annex 3). For hormonal contraception, one new observational study and updated estimates from a previously included study were identified (23, 24). Adding this evidence to the previous 14 observational studies (14) did not change the conclusions of the previous review. Thus, the body of observational evidence suggested some concern about an increased risk of HIV acquisition with DMPA-IM use, but was generally reassuring for other methods of hormonal contraception. For intrauterine devices (IUDs), two observational studies did not suggest an increased risk of HIV acquisition with Cu-IUD use (23, 25). The quality of evidence from these observational studies was rated as low and low-to-moderate.

3.1 Progestogen-only injectables

One RCT (the ECHO trial) observed no statistically significant differences in HIV acquisition when comparing DMPA-IM versus Cu-IUD, and DMPA-IM versus LNG implant (10). The quality of the evidence from this RCT was rated as high.

Evidence from 14 observational studies of DMPA-IM, norethisterone enanthate (NET-EN) or unspecified progestogen-only injectables considered to be “informative but with important limitations” was assessed (14, 23, 24). Additional data from one new observational study and updated estimates from a previously included study did not change the conclusions of the previous review of observational evidence (14). The quality of the evidence from the observational studies was rated as low and low-to-moderate due to limitations that included unmeasured confounding.

3.2 Progestogen-only implants

Three observational studies considered to be “informative but with important limitations” assessed implants. One had been included in the previous review (26), one provided an updated

point estimate to that used for the previous review (24) and one provided an entirely new estimate of risk (23). Two of the studies assessed LNG implants (24, 26) and the third assessed women using either LNG or etonogestrel implants (23). None of the three studies suggested an increased risk of HIV acquisition with implant use, consistent with the conclusion of the previous review (14). The quality of the evidence from these studies was rated as low.

3.3 Progestogen-only pills

No studies considered “informative but with important limitations” or “informative with few limitations” were identified for progestogen-only pills.

3.4 Intrauterine devices

One RCT (the ECHO trial) observed no statistically significant differences in HIV acquisition between DMPA-IM and Cu-IUD, or Cu-IUD and LNG implants (10). The quality of the evidence from this RCT was rated as high.

Two observational studies considered “informative but with important limitations” did not observe an association with HIV acquisition when comparing Cu-IUD use with tubal ligation or no contraceptive method use, DMPA-IM, NET-EN or implants (23, 25). The quality of this observational evidence was rated as low.

No evidence was identified for LNG-IUDs.

3.5 Combined hormonal contraceptives

Eleven observational studies deemed “informative but with important limitations” assessed the use of combined oral contraceptives (COC). (It was assumed that studies that did not specify the oral contraceptive type examined mostly, if not exclusively, examined COC use.) All of these studies were included in the previous review, while an updated estimate came from one newly available study (14, 24). Overall, these studies suggested no association between COC use and HIV acquisition. The quality of the evidence was rated as low-to-moderate.

No evidence was identified for the combined contraceptive patch, ring or injectable.

3.6 Additional evidence considered by the GDG

3.6.1 BIOLOGICAL DATA

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 modify the risk of HIV acquisition have been postulated, but

sparse and contradictory data make it unclear which, if any, of these biological mechanisms are clinically relevant. Potential mechanisms include alteration of the systemic and local immune response and changes in the genital tract environment. It was noted that different forms of hormonal contraception may change these factors in different ways. Combined contraceptives containing both ethinylestradiol and a progestogen may have a different effect than progestogen-only methods. Additionally, various progestogen-only methods, such as DMPA and NET-EN injectables, may change immune function variably. It remains uncertain to what extent data from animal and laboratory studies, including in relation to progestogen type and dosing, can be applied to clinical outcomes in humans.

3.6.2 VALUES AND PREFERENCES OF CONTRACEPTIVE USERS

The systematic review identified 375 studies from all regions of the world (27). Across studies, women's values and preferences centred on themes of choice and available options, ease of use, side-effect profiles and contraceptive efficacy. Contextual factors, such as the contraceptive methods available, counselling from providers, and the opinions of social networks, influenced decision-making. From the grey literature, two additional studies were identified that were relevant to hormonal contraception and HIV specifically (28, 29). Both found that messages from the

2017 WHO guidance were difficult for providers to explain fully and may not be completely understood by clients.

The online survey of sex workers from multiple global regions found that individual preferences around contraception varied widely and could change over time; ongoing partnership and dialogue with sex workers is essential to understanding evolving priorities. In participatory focus groups, Zimbabwean sex workers said their contraceptive choices were shaped by a wide range of factors, including cost, accessibility, the way sex workers are treated at clinics, the influence of male partners, and contraceptive side-effects. Sex without a condom was common, and there was a need to strengthen access to HIV/STI prevention and contraceptive services.

The community stakeholder presentation emphasized that, for some women, any level of increased HIV risk would be too high. It also highlighted that the ECHO trial was not set up to assess the difference in the risk of HIV acquisition between contraceptive users and non-users. Community stakeholders also emphasized that there was a lack of true contraceptive choice for many women and girls, saying the guidance should emphasize full, free and informed contraceptive choice,⁴ the procurement of a range of contraceptive methods, and investment in integrated contraception and HIV services.

4

RECOMMENDATIONS

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

All hormonal contraceptive methods and intrauterine devices (IUDs) now fall into Category 1 of the *Medical eligibility criteria for contraceptive use* (MEC) (5) for women at high risk of HIV. Thus, women at high risk of HIV can use all methods of contraception without restriction.

- Women at high a risk of HIV infection are eligible to use all progestogen-only contraceptive methods without restriction (MEC Category 1), including progestogen-only pills (POPs), intramuscular depot medroxyprogesterone acetate (DMPA-IM),

subcutaneous DMPA (DMPA-SC), norethisterone enanthate (NET-EN) injectables, levonorgestrel (LNG) implants, and etonogestrel implants.

- Women at a high risk of HIV infection are eligible to use copper-bearing IUDs (Cu-IUDs) and LNG implants without restriction (MEC Category 1). In considering the use of IUDs, many women at a high risk of HIV are also at risk of other sexually transmitted infections (STIs); for these women, providers should refer to the MEC recommendation on women at increased risk of STIs and the *Selected practice recommendations for contraceptive use* on STI screening before IUD insertion (5, 6).
- Women at a high risk of HIV infection are eligible to use all combined hormonal contraceptive methods without restriction (MEC Category 1), including combined oral

⁴ "Free" means the freedom and ability to make a voluntary decision about contraceptive use without barriers or coercion; informed means complete, correct and clear information has been given about all the options, plus details about the chosen method

contraceptives (COCs), combined injectable contraceptives (CICs), combined contraceptive patches (P) and combined vaginal rings (CVR).

4.2 Rationale

The Guideline Development Group (GDG) reviewed, and discussed extensively, the new epidemiological and biological evidence, as well as related information about values and preferences, equity and human rights, and feasibility. After deliberating on all of the available evidence, the GDG recommended that the MEC category for DMPA and Cu-IUD should be changed to MEC Category 1. The GDG noted that there was no evidence regarding DMPA-SC and LNG-IUD, and only limited new information regarding NET-EN. Until more information becomes available, the GDG judged it was appropriate to follow the same approach as previously used, i.e. grouping all progestogen-only injectables together (DMPA-IM, DMPA-SC and NET-EN) as MEC Category 1, and to assign the same MEC category to the LNG-IUD as to the Cu-IUD (MEC Category 1).

One key portion of the GDG's deliberations related to evaluating evidence from the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study (see Annex 3). The GDG gave particular attention to this information because of its ability to address unmeasured confounding – a major cause of uncertainty when interpreting results from observational studies. The GDG recognized that the ECHO trial did not address the etiological or causal question of whether DMPA increases the risk of HIV acquisition when compared with not using any contraception. Nevertheless, since the MEC provides guidance for women wishing to use contraception, results from the ECHO trial about the comparative risk of HIV acquisition among users of the three contraceptives tested were highly pertinent to the GDG's deliberations. Furthermore, the GDG noted that the high incidence of HIV infection experienced by each contraceptive group during the ECHO trial was similar to the background incidence assumed when designing the trial. This was deemed to be indirect evidence addressing the question, suggesting no increased risk of HIV acquisition among users of these contraceptives compared with women not using any contraception.

The ECHO trial was considered to be a well conducted study that provided high-quality evidence that superseded the low and low-to-moderate-quality observational evidence previously available to the GDG. This direct epidemiological evidence, from a trial specifically designed to address the issue, was judged to be more informative than theoretical biological evidence.

The reasons for considering the ECHO trial to be of high quality included its large size; robust randomization methods; good adherence to the allocated contraceptive method; a low attrition rate; regular, standardized and objective outcome measurements; and a blinded, comprehensive analysis of the data (including sensitivity analyses for postulated confounders such as sexual activity and condom use). Although women and

providers of services in the ECHO trial could not be blinded to the intervention allocation, there was no evidence that this led to the different groups of participants acting, or being managed, differently with respect to important issues such as HIV prevention counselling. This ensured that residual confounding, particularly in relation to condom use or sexual activity, was highly unlikely to have affected the ECHO trial.

The GDG noted that although the ECHO trial was designed to detect a 50% increase in the risk of HIV acquisition between contraceptive groups assessed, the observed high HIV incidence and small losses to follow up meant that it could detect a 30% increase. When considering the ECHO trial results, the GDG focused on the point estimates for each primary comparison. The group noted that none of the point estimates for the primary comparisons were statistically significant. The 96% confidence intervals surrounding these point estimates included unity, and so encompassed the possibility of a small increased or decreased difference in risk between contraceptives. The GDG acknowledged, however, that for an individual woman at a high risk of HIV, any change in this risk may be important.

After a full discussion, the GDG judged that unmeasured confounding was the most likely explanation for the apparent increased risk of HIV acquisition among DMPA-IM users seen in some observational studies.

The GDG's decisions to revise the MEC classifications for DMPA and IUDs were further grounded by the values and preferences of women towards optimizing informed contraceptive choice and the availability of a wide range of contraceptive options, based on a systematic review of qualitative and quantitative evidence, consultative engagements with sex workers and the perspectives of GDG members representing specific affected populations.

In previous editions of the MEC, IUDs were classified as MEC Category 2 for women at a high risk of HIV. This recommendation was given because of the absence of high-quality, direct evidence about the risk of acquiring HIV among IUD users. In addition, there was an assumption that most women at a high risk of HIV were also at an increased risk of other STIs. The ECHO trial provided direct, high-quality evidence about the risk of HIV acquisition risk among women using the Cu-IUD, enabling the GDG to review its recommendation regarding these women. Any new evidence related to IUD use in women at a high risk of other STIs will be reviewed for the next MEC update.

The GDG was concerned about the high rates of both HIV and STIs among women in the ECHO trial, reflecting the background risk factors among women seeking contraception in the study areas. The high incidence of HIV was particularly striking given the extensive efforts made during the ECHO trial to provide HIV prevention counselling and interventions. Thus, while the GDG concluded that the risk of HIV acquisition was not affected by the contraceptive method used, it emphasized the need for renewed efforts to reduce the incidence of HIV and STIs.

5

IMPLICATIONS FOR POLICY-MAKERS, PROGRAMME MANAGERS AND HEALTH-CARE PROVIDERS

While the main audiences for the *Medical eligibility criteria for contraceptive use* (MEC) are policy-makers and programme managers, a fundamental tenet of the MEC is that they are woman-centred. The following were the key messages that came from the deliberations of the Guideline Development Group.

5.1 A woman's risk of HIV should not restrict her contraceptive choice

While a risk of HIV should not restrict a woman's choice to use hormonal contraception or an intrauterine device, it is important to note that these methods do not protect her against acquiring HIV or other sexually transmitted infection (STI). The new MEC recommendations should not be interpreted as indicating that HIV and STI testing and prevention are no longer important. Indeed, the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study highlighted the critical need to strengthen and expand HIV and STI prevention services (10). Testing for HIV and STIs should be part of high-quality family planning services for women at risk, particularly for those living in areas of high HIV and STI incidence.

5.2 Efforts to expand access to contraceptive options must continue

Women have the right to a range of short-acting, long-acting and permanent contraceptive methods, as well as to emergency contraception (1). A comprehensive range of contraceptive methods enables women to respond to changing needs and preferences during their reproductive lives. Informed decision-making and woman-centred, high-quality counselling are key components in the human rights-based provision of contraceptive information and services (2). The ECHO trial reinforced that offering a range of methods is possible and acceptable to women (10). Family planning and HIV services should be included in national universal health coverage initiatives. Efforts to expand safe and effective contraceptive options, and to ensure their availability and the access to them, must continue. Technical resources are available to support countries to introduce more contraceptive options into their programmes and services (Box 1).

BOX 1. TECHNICAL RESOURCES TO SUPPORT PROGRAMMES

- o *Medical eligibility criteria for contraceptive use* (in English, French and Russian)
<https://apps.who.int/iris/handle/10665/181468>
- o *Selected practice recommendations for contraceptive use* (in English, French and Spanish)
<https://apps.who.int/iris/handle/10665/252267>
- o *Implementation guide for the medical eligibility criteria and selected practice recommendations for contraceptive use* (available in English, French, Portuguese and Spanish)
<https://apps.who.int/iris/handle/10665/272758>
- o *Global handbook for family planning providers*
<https://apps.who.int/iris/handle/10665/260156>
- o Training Resource Package for Family Planning website (available in English and French)
<https://www.fptraining.org>
- o Mobile application for the *Medical eligibility criteria for contraceptive use* (free, for android and iOS platforms)
<https://www.who.int/reproductivehealth/mec-app>
- o *Policy brief: consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations, 2016 update*
<https://apps.who.int/iris/handle/10665/258967>
- o Treat all: policy adoption and implementation status in countries (fact sheet)
<https://apps.who.int/iris/handle/10665/258538>

5.3 A renewed emphasis on HIV and STI prevention services is urgently needed

The ECHO trial showed high rates of both HIV and STIs in the study sites (10), highlighting the need for appropriate prevention, diagnosis and treatment of all STIs. Current HIV prevention measures remain unavailable or unsatisfactory for many women and adolescent girls living in settings of high HIV incidence. In such areas, the integration of family planning and HIV prevention services for all women is essential if the health of women and adolescent girls is to be improved. In settings of low HIV prevalence, there is a need for family planning providers to evaluate personal risk factors that may increase a woman's risk of acquiring HIV and then to provide appropriate services. The ECHO trial also showed that syndromic management did not decrease the prevalence of STIs at baseline and at the end of follow-up. STI programmes need to be strengthened, including a move towards diagnostic management.

- In settings with high HIV prevalence, HIV testing and prevention should be included in family planning services. HIV testing should be offered to all women and to partners of all women with HIV. HIV prevention options should be offered to all women, including pre-exposure prophylaxis (PrEP), as recommended in WHO guidelines (30). The offer

of PrEP to women could also be considered where HIV incidence is high (but below 3/100 person-years overall) following, for example, a simple risk assessment. A risk assessment could include: desire to take PrEP (reflecting a self-identified risk); history of an STI; more than one sex partner in the last six months; or women with a sex partner with HIV who is not virally suppressed on antiretroviral therapy.

- In settings with low HIV prevalence, the routine offer of HIV testing and prevention services in family planning settings is unlikely to be cost-effective. HIV testing and prevention services could nonetheless be offered to women who request these services.

BOX 2. WORK TO IDENTIFY WOMEN AT HIGH RISK OF HIV

A person's HIV risk depends on the incidence of HIV in the area where they live, and their individual risk factors. Family planning programmes must work closely with their national and subnational HIV programmes to use local epidemiological data to identify geographical areas and risk factors that put women at a high risk of HIV infection.

6

KNOWLEDGE GAPS AND AREAS FOR RESEARCH

6.1 Contraceptive methods and HIV acquisition

The existing body of evidence is sufficient to guide practice on intramuscular depot medroxyprogesterone acetate (DMPA-IM), levonorgestrel (LNG) implants and copper-bearing intrauterine devices; additional observational data will not add substantially to the evidence base for these methods. However, in the absence of trial data similar to those in the ECHO Study (10), observational data about subcutaneous DMPA (DMPA-SC), LNG IUDs, etonogestrel implants, or future contraceptive or multi-purpose prevention technologies could still be useful, although unmeasured confounding would likely remain a concern. Studies should consider the potential impact of contraceptive use on other sexually transmitted infections as well as HIV. Additional research on the specific effects of contraception-related bleeding changes in relation to the risk of HIV or STI acquisition is also needed.

6.2 HIV prevention

The Guideline Development Group was deeply concerned by the high HIV incidence found among women seeking family planning services in the ECHO Study sites, despite the fact that trial participants received an extensive HIV prevention package (including repeated HIV testing and counselling, partner HIV testing and condom distribution, as well as pre-exposure prophylaxis (PrEP) late in the study as this became the standard of care). More research is needed on ways to increase the acceptability and uptake of effective HIV prevention strategies for women at a high risk of HIV, tailored to settings of both high and low HIV prevalence and to women with a range of personal risk factors. In the ECHO trial, the uptake (and hence impact) of PrEP was minimal as it became available only late in the trial (10). Where it was available on site, as opposed to requiring referral to another site, acceptability and uptake were high. Ways to include HIV self-testing and PrEP in family planning services should be

explored. This should include behavioural and implementation science research on the effective integration of HIV and contraception services.

6.3 Community involvement

The ECHO trial employed a range of strategies for directly engaging with civil society at the study site, and at regional and global levels (10). An in-depth assessment of the strengths and limitations of each strategy is likely to provide models for community engagement in contraceptive and HIV prevention research that could be adopted in the future.

6.4 Increased funding for high-quality, policy-relevant research

The ECHO Study demonstrated that a well conducted, adequately powered randomized controlled trial is possible in contraceptive research, and can make an important contribution to global decision-making. Global policy should be based on comprehensive high-quality evidence, but additional investment in contraceptive research is critically overdue, including research addressing whether financial barriers affect the contraceptive choices of women.



DISSEMINATION OF THIS GUIDANCE STATEMENT

The World Health Organization (WHO) will work to communicate this guidance statement clearly and widely. WHO will evaluate whether the guidance achieves its intentions. The guidance will be published on the WHO website and in a limited quantity of printed documents. The guidance will be widely disseminated through the WHO regional and country offices, WHO Member States, other United Nations agencies, civil society, the Implementing Best Practices (IBP) initiative, professional organizations, governmental and non-governmental partner organizations, and WHO collaborating centres working in the area of HIV and sexual and reproductive health.

The WHO Secretariat will work closely with sexual and reproductive health and HIV focal points in regional and country offices of WHO, the United Nations Population Fund and the Joint United Nations Programme on HIV and AIDS to conduct a series of regional learning and knowledge-sharing events. This engagement will target opportunities where sexual and reproductive health issues are being discussed; examples include the 25th Conference on Population and Development in July 2019 and the 20th International Conference on AIDS and Sexually Transmitted Infections in Africa in December 2019. The Secretariat will also work closely with country task teams and working groups leading HIV and contraception programme efforts to share the guidance with grassroots and community-level organizations and providers.

Additionally, webinars for stakeholders in multiple languages will be organized during 2020 to ensure Member States and stakeholders are fully informed of the new recommendations. These opportunities will enable WHO to disseminate the updated guidance effectively and efficiently. Derivative communication products highlighting key counselling issues (e.g. short briefs for front-line health-care providers and community-based organizations) will be prepared in collaboration with WHO's implementing partners, and in consultation with the GDG during 2020.

A policy brief in the six official languages used by WHO will be developed to inform policy-makers about the contraception updates.

As part of the dissemination of the recommendations in this guidance statement, WHO will update its digital contraceptive decision-support tools – the MEC mobile app (31), the humanitarian contraceptive delivery app (32) and the postpartum compendium (33). These mobile applications are free to download and available for both iOS and Android platforms. Additionally, the *Global handbook for family planning providers* and the online Family Planning Training Resource Package will be updated accordingly (8, 34).

WHO will continue to monitor the body of evidence informing these recommendations and will convene additional consultations when needed.

REFERENCES

1. Ensuring human rights in the provision of contraceptive information and services: guidance and recommendations. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/102539>, accessed 24 August 2019).
2. Framework for ensuring human rights in the provision of contraceptive information and services. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/133327>, accessed 24 August 2019).
3. The thirteenth general programme of work, 2019–2023: promote health, keep the world safe, serve the vulnerable. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/handle/10665/324775>, accessed 24 August 2019).
4. Reproductive health strategy to accelerate progress towards the attainment of international development goals and targets. Geneva: World Health Organization; 2004 (<https://apps.who.int/iris/handle/10665/68754>, accessed 24 August 2019).
5. Medical eligibility criteria for contraceptive use, fifth edition. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/handle/10665/181468>, accessed 24 August 2019).
6. Selected practice recommendations for contraceptive use: third edition. Geneva: World Health Organization; 2016 (<https://apps.who.int/iris/handle/10665/252267>, accessed 24 August 2019).
7. WHO medical eligibility criteria wheel for contraceptive use, 2015 update. Geneva: World Health Organization; 2004 (<https://apps.who.int/iris/handle/10665/173585>, accessed 24 August 2019).
8. World Health Organization, Johns Hopkins Bloomberg School of Public Health. Family planning: a global handbook for providers: evidence-based guidance developed through worldwide collaboration, third edition. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/260156>, accessed 24 August 2019).
9. 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. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/254662>, accessed 24 August 2019).
10. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet*. 2019;394(10195):303–13. doi: 10.1016/S0140-6736(19)31288-7.
11. WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/145714>, accessed 24 August 2019).
12. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J et al. GRADE guidelines: 1. Introduction –GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383–94. doi: 10.1016/j.jclinepi.2010.04.026.
13. Singh S. Adding it up: costs and benefits of contraceptive services – estimates for 2017. New York (NY): Guttmacher Institute; 2017.
14. Polis CB, Curtis KM, Hannaford PC, Phillips SJ, Chipato T, Kiarie JN et al. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. *AIDS*. 2016;30(17):2665–83. doi: 10.1097/QAD.0000000000001228.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; The Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.
16. Kennedy CE, Yeh PT, Gaffield ME. Contraception values and preferences: protocol and methods for a global systematic review. *Contraception*. 2019 (in press). doi: 10.1016/j.contraception.2018.05.006Get.
17. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol*. 2011;64(4):407–15. doi: 10.1016/j.jclinepi.2010.07.017.
18. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D et al. GRADE guidelines 6. Rating the quality of evidence – imprecision. *J Clin Epidemiol*. 2011;64(12):1283–93. doi: 10.1016/j.jclinepi.2011.01.012.

19. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M et al. GRADE guidelines: 8. Rating the quality of evidence – indirectness. *J Clin Epidemiol.* 2011;64(12):1303–10. doi: 10.1016/j.jclinepi.2011.04.014.
20. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M et al. GRADE guidelines: 7. Rating the quality of evidence – inconsistency. *J Clin Epidemiol.* 2011;64(12):1294–302. doi: 10.1016/j.jclinepi.2011.03.017.
21. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J et al. GRADE guidelines: 5. Rating the quality of evidence – publication bias. *J Clin Epidemiol.* 2011;64(12):1277–82. doi: 10.1016/j.jclinepi.2011.01.011.
22. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P et al. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol.* 2011;64(12):1311–6. doi: 10.1016/j.jclinepi.2011.06.004.
23. Palanee-Phillips T, Brown ER, Szydlo D, Matovu Kiweewa F, Pather A, Harkoo I et al. Risk of HIV-1 acquisition among South African women using a variety of contraceptive methods in a prospective study. *AIDS.* 2019;33(10):1619–22. doi: 10.1097/QAD.0000000000002260.
24. Sabo MC, Richardson BA, Lavreys L, Martin HL, Jr, Jaoko W, Mandaliya K et al. Does bacterial vaginosis modify the effect of hormonal contraception on HIV seroconversion. *AIDS.* 2019;33(7):1225–30. doi: 10.1097/QAD.0000000000002167.
25. Lavreys L, Baeten JM, Martin Jr HL, Overbaugh J, Mandaliya K, Ndinya-Achola J et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. *AIDS.* 2004;18(4):695–7.
26. Wall KM, Kilembe W, Vwalika B, Htee Khu N, Brill I, Chomba E et al. Hormonal contraception does not increase women’s HIV acquisition risk in Zambian discordant couples, 1994–2012. *Contraception.* 2015;91(6):480–7. doi: 10.1016/j.contraception.2015.02.004.
27. Yeh PT, Kennedy CE, Gaffield ME. Contraception values and preferences: a global systematic review. *Contraception.* 2019; (accepted pending revisions).
28. Miller L, Ntinginya M, Makula J, Juma A, Mackay A, Wadegu E et al. Final report: a pilot study to assess training and communication materials on progestogen-only injectable use and risk of HIV acquisition in Tanzania. London: Marie Stopes International; 2019 (<https://resultsforinformedchoice.org/wp-content/uploads/2019/02/Injectables-and-HIV-Pilot-Study-Report-TZ.pdf>, accessed 24 August 2019).
29. Littlepage S, Dam A, Nakyanjo N, Polis C, Nalugoda F, Kennedy CE. Contraceptive decision-making in the context of HIV risk and changing World Health Organization guidelines: a qualitative study in Rakai, Uganda. 2019 (personal communication).
30. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, second edition. Geneva: World Health Organization; 2016. (<https://apps.who.int/iris/handle/10665/208825>, accessed 24 August 2019).
31. New app for WHO’s medical eligibility criteria for contraceptive use. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (<https://www.who.int/reproductivehealth/mec-app>, accessed 24 August 2019).
32. Delivering contraceptive services in humanitarian settings: new tool for front-line health care workers. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (<https://www.who.int/reproductivehealth/publications/humanitarian-settings-contraception>, accessed 24 August 2019).
33. New WHO tool helps guide contraception choices following childbirth. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<https://www.who.int/reproductivehealth/news/pfpc>, accessed 24 August 2019).
34. TRP: Training Resource Package for Family Planning [website]. Baltimore (MD): Johns Hopkins University; 2019 (<https://www.fptraining.org>, accessed 24 August 2019).

ANNEX 1. GUIDELINE DEVELOPMENT GROUP AND EVIDENCE SECRETARIAT

Guideline Development Group

Sharon Achilles (University of Pittsburgh, United States of America), Richard Adanu (University of Ghana, Ghana), Rachid Bezad (University Roi Mohammad VI, Morocco), Sharon Cameron (University of Edinburgh, United Kingdom of Great Britain and Northern Ireland), Tsungai Chipato (University of Zimbabwe, Zimbabwe), Maria del Carmen Cravioto (National Institute of Nutrition, Salvador Zubiran, Mexico) [unable to attend], Alison Edelman (Oregon Health & Science University, United States), Mohammad 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), Philip Hannaford (University of Aberdeen, United Kingdom), Felicita Hikuam (AIDS and Rights Alliance for Southern Africa, Namibia), Unnop Jaisamrarn (Chulalongkorn University, Thailand), Loveleen Johri (family planning and reproductive health independent consultant, India), Natasha Kaoma (Copper Rose Zambia, Zambia), Seni Kouanda (Institute of Research in Health Sciences, Burkina Faso), Elizabeth Lule (global health and international development independent consultant, Uganda), Vimbai Magwenzi (Centre for Sexual Health and HIV/AIDS Research, Zimbabwe) [unable to attend], Loyce Maturu (Zvandiri Mentor with Africaid, Zimbabwe), Olav Meirik (Instituto Chileno de Medicina Reproductiva, Chile), Placid Mihayo (Ministry of Health, Uganda), Lilian Mworeko (International Community of Women Living with HIV Eastern Africa, Uganda), Hiromi Obara (National Center for Global Health and Medicine, Tokyo, Japan), Herbert Peterson (University of North Carolina, United States), John Pile (independent consultant, Thailand), Carolina Sales Vieira (University of Sao Paulo, Brazil), Sarah Simpson (EquiACT, France), Aminata Wurie (Youth Coalition for Sexual and Reproductive Rights, Sierra Leone).

Philip Hannaford and Natasha Kaoma co-chaired the meeting Guideline Development Group (GDG) meeting.

Evidence Secretariat

Centre for Sexual Health and HIV/AIDS Research – Euphemia Sibanda
FHI 360 – Timothy Mastro
Independent Consultant – Ania Shapiro
Johns Hopkins University – Caitlin Kennedy
Oregon Health & Science University – Maria Isabel Rodriguez

United States Centers for Disease Control and Prevention – Kathryn Curtis
University of Washington – Jared Baeten
Wits Reproductive Health and HIV Institute – Helen Rees

Observer

Zandile Mnisi (Ministry of Health, Eswatini)

External Review Group

Florence Anam (Doctors Without Borders, South Africa), Winfred Apio (Uganda Youth and Adolescents Forum, Uganda), Lynn Bakamjian (independent consultant, United States), Milena Brito (University of Sao Paulo, Brazil), Roy Jacobstein (IntraHealth, United States), Ernest Maya (University of Ghana, Ghana), Mari Ngai (National Center for Global Health and Medicine, Japan), Cristina Puig Borràs (European Consortium for Emergency Contraception, Spain), Nusrat Shah (Society of Obstetrics & Gynaecology, Pakistan), Bulbul Sood (Jphiego, India).

WHO Secretariat

The WHO Secretariat attended the meeting and several WHO staff provided background presentations (Rachel Baggaley, Mary Lyn Gaffield, James Kiarie, Nancy Kidula). The WHO Secretariat was present to serve as a background resource, if request by the GDG. Neither WHO, the Joint United Nations Programme on HIV/AIDS (UNAIDS) nor the United Nations Population Fund (UNFPA) staff participated in the decision-making or formulation of the recommendations, which was the sole responsibility of the GDG. Several WHO staff contributed to the systematic reviews (Mary Lyn Gaffield, James Kiarie, Petrus Steyn) and the writing of the statement.

WHO headquarters

WHO Department of Reproductive Health and Research – Ian Askew, Mary Lyn Gaffield, James Kiarie, Antonella Lavelanet, Manjulaa Narasimhan (unable to attend), Petrus Steyn
WHO Department of HIV – Rachel Baggaley, Virginia MacDonald, Michele Rodolph
WHO Department of Regulation of Medicines and other Health Technologies – Ray Corrin

WHO regional offices

WHO Regional Office for Africa – Nancy Kidula, Léopold Ouedraogo

Joint United Nations Programme on HIV/AIDS (UNAIDS)

Peter Godfrey-Fausett

United Nations Population Fund (UNFPA)

Technical Division – Gifty Addico, Mieke Yabuta (unable to attend)

Overall coordination

WHO Department of Reproductive Health and Research – Mary Lyn Gaffield, with logistical support from Jane Werunga-Ndanareh.

Writing

The guidance statement was drafted on behalf of WHO by Caitlin Baumhart, Kathryn Curtis, Mary Lyn Gaffield, Philip Hannaford, Natasha Kaoma, Caitlin Kennedy and Maria Isabel Rodriguez. The systematic review examining the use of copper-bearing intrauterine devices and HIV acquisition was co-authored by Tsungai Chipato, Kathryn Curtis, Philip Hannaford and Angeline Ti. The update of the 2016 systematic review focusing on hormonal contraception and HIV acquisition was co-authored by Tsungai Chipato, Kathryn Curtis, Philip Hannaford, James Kiarie and Petrus Steyn.

The GRADE tables and expertise on GRADE methodology were provided by Maria Isabel Rodriguez. Preparation of the evidence-to-decision table and expertise on the literature for values and preferences were provided by Caitlin Kennedy.

Editing was done by Markus MacGill and Jane Patten of Green Ink (www.greenink.co.uk) and layout by Lushomo (www.lushomo.net).

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 29–31 July 2019 meeting, the name and brief biography of each proposed Guideline Development Group (GDG) member was published on the WHO website during 27 May to 10 June 2019 (<https://www.who.int/reproductivehealth/publications/contraceptives-methods-hiv>). The public was able to view and provide their comments to the WHO Secretariat using a general email address (hrx_info@who.int) regarding any 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 (Google Scholar, Open Payments, PubMed) 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. Additionally, the WHO Secretariat reviewed potential financial and academic conflicts of interest related to the subject of the meeting of the proposed External Review Group: no conflicts were declared among this 11-member group.

Of the 28 experts who participated in this work, six declared an interest related to contraception. The WHO Secretariat, CRE and GDG reviewed all declarations and found no conflicts of interest sufficient to preclude anyone from participating in the deliberations or the development of the recommendations relevant to hormonal contraception and HIV. Accordingly, the six participants who declared interests related to contraception, as well as the other 22 participants, fully participated in the meeting's deliberations, discussions and final decisions. Although not all interests declared were specifically related to contraception and susceptibility to HIV, they are disclosed and summarized below.

Sharon Achilles received US\$ 4225 on 10 May 2016 to give expert advice on the latest HIV therapies during a one-day meeting sponsored by Merck Sharp & Dohme. Her research unit received US\$ 2 638 373 from the United States National Institutes of Health/National Institute of Allergy and Infectious Diseases to conduct a study titled, Quantification of immune cells in women using contraception, during 2012–2019. For 2012–2019, her research unit is receiving US\$ 4 999 999 from the Bill & Melinda Gates Foundation to conduct a study titled, HIV-target cell response in women initiating contraception in high HIV-incidence areas. During 2014–2016, Dr Achilles's research unit received US\$ 240 225 from the Bill & Melinda Gates Foundation to conduct a study addressing IFN-epsilon and hormonal contraceptive modulation of the risk of HIV acquisition. Currently, for 2018–2020, Dr Achilles's research unit receives US\$ 535 958 from the United States Food and Drug Administration (FDA) to conduct a study supporting new approaches to improve product manufacturing and quality titled, Physiologically-based model of the female reproductive tract: vaginal and intrauterine delivery components.

Sharon Cameron works at a research unit that received a grant from Pfizer, UK, for £99 000, which ceased in 2016. The study was implemented to determine the feasibility and acceptability of the pharmacist administration of subcutaneous injectable contraception.

Alison Edelman receives a yearly royalty of around US\$ 1000 from the Internet information site, UpToDate as an author of the content. Between May 2016 and May 2017, she received US\$ 10 000 a year from Agile Pharmaceuticals as an expert consultant regarding a hormonal contraceptive patch that is currently not FDA-approved. This consultation has ended. Since January 2016, she served as a trainer for Nexplanon, an FDA mandate, for Merck Sharp & Dohme, but has received no honorarium for these sessions and as an expert consultant in January 2016 for this company, receiving US\$ 1500 for her services. Her research unit received US\$ 540 000 from the Merck Women's Health Investigator Initiated Studies Program to conduct research focused on treatment of breakthrough bleeding with the contraceptive implant (2016–2019). From 2015 to 2017, her research unit received a US\$ 250 000 research grant from the Society for Family Planning to investigate the timing of ulipristal acetate and oral contraceptive use. Since 2002, Dr Edelman has been receiving about US\$ 3000 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\$ 3000 from Oregon State University for expert advice on the mandated state training to allow the 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. From April to September 2017, Dr Edelman was a consultant for HRA Pharma for a study investigating a progestin-only pill. Since July 2017, she had been an expert consultant for the Sugar Palm Foundation; this contract was then channelled through her institution and ended in 2019. Since June 2017, she has been providing expert consulting to Ipas to train health-care workers in Bangladesh: this contract is now administered by her institution. On an ongoing basis since 2016, Dr Edelman has received an honorarium from the University of California, San Francisco, for speaking and family planning fellowship site audits. During 2018 through to January 2019, she received an honorarium from Exeltis to provide an expert review on a contraceptive method not currently FDA-approved. This consultation has ended.

Anna Glasier provides expert medical advice on the ulipristal acetate emergency contraceptive pill on a regular basis to the manufacturer (HRA Pharma). The amount was not disclosed. She works with them to try to obtain approval for the over-the-counter (OTC) use of ulipristal acetate emergency contraception and a progestin-only pill in the United States of America, and to

get a progestin-only pill approved for OTC use in the United Kingdom of Great Britain and Northern Ireland, and Europe. This is ongoing.

Andy Gray is the chair of the Names and Scheduling Advisory Committee of the South African Health Products Regulatory Authority and serves on its Legal Advisory and Regulatory Advisory Committees. He is a member of the South African National Essential Medicines List Committee, responsible for medicines selection and the development of standard treatment guidelines for the public sector.

Carolina Sales Vieira receives an honorarium (US\$ 4000/year) for serving on Merck Sharpe & Dohme's medical advisory board and giving ad hoc invited lectures. This role is ongoing. Dr Sales Vieira receives an honorarium (US\$ 3000/year) for serving on Bayer's medical advisory board and giving ad hoc lectures. This role is ongoing. Dr Sales Vieira received a one-time honorarium (US\$ 1000) for serving on the medical advisory board for Exeltis in 2019.

ANNEX 3. GRADE EVIDENCE PROFILES

GRADE EVIDENCE PROFILE FOR HORMONAL CONTRACEPTIVE USE IN HIV-NEGATIVE WOMEN

Outcome	Type and number of studies (total number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Overall quality	Estimate of effect
DMPA versus non-hormonal contraception or no method							
HIV acquisition	1 RCT ¹ (7829) ^a	Few limitations ^b	No serious inconsistency	No serious imprecision	No indirectness	High	Adjusted HR 1.04 (0.82–1.33) for DMPA versus Cu-IUD
HIV acquisition	10 cohort studies ^{2–11} + 1 individual patient data meta-analysis of 7 studies ^{12,c} (40 506) ^a	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low to moderate ^e	Adjusted HR range 0.46–2.04, 8 studies increased risk (HR range 1.25–2.04), with statistically significant effects in 3 studies; 2 studies trended towards decreased risk (HR 0.46 and 0.75 with wide confidence intervals) Pooled adjusted HR 1.40 (1.24–1.58)
NET-EN versus non-hormonal contraception or no method							
HIV acquisition	6 cohort studies ^{2,5,7,8,10,11} + 1 individual patient data meta-analysis of 7 studies ^{12,c} (29 922) ^a	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low	Adjusted HR range 0.87–1.76, 5 studies increased risk (HR range 1.20–1.76), none statistically significant; 2 studies no effect (adjusted HR range 0.87–1.05) Pooled adjusted HR 1.14 (0.93–1.39)
Implant^f use versus non-hormonal contraception							
HIV acquisition	1 randomized trial ¹ (7829) ^a	Few limitations ^b	No serious inconsistency	No serious imprecision	No indirectness	High	Adjusted HR 1.18 (0.91–1.53) for Cu-IUD versus LNG implant
HIV acquisition	3 cohort studies ^{2–4,c} (4514) ^a	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low ^g	Adjusted HR range 0.46–0.99 Adjusted HRs: 0.96 (0.29–3.14), 0.99 (0.40–2.45), and 0.46 (0.13–1.70); none statistically significant Pooled adjusted HR 0.82 (0.44–1.53)
Implant^f use versus NET-EN							
HIV acquisition	1 cohort study ² (1136) ^a	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low	Adjusted HR 0.45 (0.13–1.53) for implant use versus NET-EN
Oral hormonal contraceptive use versus non-hormonal contraception or no method							
HIV acquisition	11 cohort studies ^{3–6,8–14,c} (43 482) ^a	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low to moderate ^e	Adjusted HR or IRR range 0.66–1.80 3 studies increased risk (HR 1.39–1.80) Only 1 study reported a statistically significant finding (adjusted HR 1.48 [1.05–2.09]) The remaining 8 studies reported a decreased risk (adjusted HR range 0.66–0.99), none of which was statistically significant Pooled adjusted HR 1.02 (0.88–1.19)

GRADE EVIDENCE PROFILE FOR HORMONAL CONTRACEPTIVE USE IN HIV-NEGATIVE WOMEN

Outcome	Type and number of studies (total number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Overall quality	Estimate of effect
DMPA versus NET-EN							
HIV acquisition	2 cohort studies ^{2,15} and 1 individual patient data meta-analysis of 17 studies ^{12,c} (42 788) ^a	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low to moderate ^e	Adjusted HRs 1.32 (1.08–1.61) and 0.89 (0.55–1.44) in cohort studies and 1.41 (1.06–1.89) in individual participant data meta-analysis of 17 studies Pooled adjusted HR 1.27 (1.05–1.55)
DMPA versus combined oral contraceptives							
HIV acquisition	1 individual patient data meta-analysis of 8 studies ^{12,c} (24 853) ^a	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low to moderate ^e	Adjusted HR 1.41 (1.23–1.67) in individual participant data meta-analysis of 8 studies
NET-EN versus combined oral contraceptives							
HIV acquisition	1 individual patient data meta-analysis of 9 studies ^{12,c} (25 398) ^a	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low	Adjusted HR 1.30 (0.99–1.17)

Cu-IUD: copper-bearing intrauterine device; DMPA-IM: intramuscular depot medroxyprogesterone acetate; ETG: etonogestrel; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: hazard ratio; IRR: incidence rate ratio; LNG: levonorgestrel; NET-EN: norethisterone enanthate; RCT: randomized controlled trial

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, results from Cox model analysis used when available.

^a Sample size is for the entire study population.

^b Few limitations noted in the trial, but not serious enough to downgrade the level of evidence. While the study was unblinded for participants and health-care providers, data were analysed centrally by statisticians who were blinded to the group.

^c Restricted to studies classified as “informative with but with important limitations”.

^d Some limitations or imprecision noted across the body of evidence, but not serious enough to downgrade the level of evidence.

^e 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.

^f No direct evidence for ETG implants was identified for the comparisons of interest. For ETG implants, recommendations were extrapolated from other implant studies.

^g Upgraded from very low-quality evidence (2016 assessment).

References:

- Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet*. 2019;394(10195):303–13. doi: 10.1016/S0140-6736(19)31288-7.
- Palanee-Phillips T, Brown ER, Szydlo D, Matovu Kiweewa F, Pather A, Harkoo I et al. Risk of HIV-1 acquisition among South African women using a variety of contraceptive methods in a prospective study. *AIDS*. 2019;33(10):1619–22. doi: 10.1097/QAD.0000000000002260.
- Sabo MC, Richardson BA, Lavreys L, Martin HL, Jr, Jaoko W, Mandaliya K et al. Does bacterial vaginosis modify the effect of hormonal contraception on HIV seroconversion. *AIDS*. 2019;33(7):1225–30. doi: 10.1097/QAD.0000000000002167.
- Wall KM, Kilembe W, Vwalika B, Htee Khu N, Brill I, Chomba E et al. Hormonal contraception does not increase women's HIV acquisition risk in Zambian discordant couples, 1994–2012. *Contraception*. 2015;91(6):480–7. Doi: 10.1016/j.contraception.2015.02.004.

5. Crook AM, Ford D, Gafos M, Hayes R, Kamali A, Kapiga S et al. Injectable and oral contraceptives and risk of HIV acquisition in women: an analysis of data from the MDP301 trial. *Hum Reprod*. 2014;29(8):1810–7. doi: 10.1093/humrep/deu113.
6. Heffron R, Donnell D, Rees H, Celum C, Mugo N, Were E et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis*. 2012;12(1):19–26. doi: 10.1016/S1473-3099(11)70247-X.
7. Kleinschmidt I, Rees H, Delany S, Smith D, Dinat N, Nkala B et al. Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort. *Contraception*. 2007;75(6):461–7. doi: 10.1016/j.contraception.2007.02.002.
8. 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. doi: 10.1097/QAD.0b013e32835da401.
9. Morrison CS, Richardson BA, Mmiro F, Chipato T, Celentano DD, Luoto J et al. Hormonal contraception and the risk of HIV acquisition. *AIDS*. 2007;21(1):85–95. doi: 10.1097/QAD.0b013e3280117c8b.
10. Morrison CS, Skoler-Karppoff S, Kwok C, Chen PL, van de Wijgert J, Gehret-Plagianos M et al. Hormonal contraception and the risk of HIV acquisition among women in South Africa. *AIDS*. 2012;26(4):497–504. doi: 10.1097/QAD.0b013e32834fa13d.
11. Myer L, Denny L, Wright TC, Kuhn L. Prospective study of hormonal contraception and women's risk of HIV infection in South Africa. *Int J Epidemiol*. 2007;36(1):166–74. doi: 10.1093/ije/dyl251.
12. Morrison CS, Chen PL, Kwok C, Baeten JM, Brown J, Crook AM et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. *PLoS Med*. 2015;12(1):e1001778. doi: 10.1371/journal.pmed.1001778.
13. Balkus JE, Brown ER, Hillier SL, Coletti A, Ramjee G, Mgodini N et al. Oral and injectable contraceptive use and HIV acquisition risk among women in four African countries: a secondary analysis of data from a microbicide trial. *Contraception*. 2016;93(1):25–31. doi: 10.1016/j.contraception.2015.10.010.
14. Reid SE, Dai JY, Wang J, Sicalwe BN, Akpomiemie G, Cowan FM et al. Pregnancy, contraceptive use, and HIV acquisition in HPTN 039: relevance for HIV prevention trials among African women. *J Acquir Immune Defic Syndr*. 2010;53(5):606–13. doi: 10.1097/QAI.0b013e3181bc4869.
15. Noguchi LM, Richardson BA, Baeten JM, Hillier SL, Balkus JE, Chirenje ZM et al. Risk of HIV-1 acquisition among women who use different types of injectable progestin contraception in South Africa: a prospective cohort study. *Lancet HIV*. 2015;2(7):e279–87. doi: 10.1016/S2352-3018(15)00058-2.

GRADE EVIDENCE PROFILE FOR CU-IUD USE IN HIV-NEGATIVE WOMEN

Outcome	Type and number of studies (total number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Overall quality	Estimate of effect
IUD^a versus no contraception or tubal ligation							
HIV acquisition	1 prospective study ^{1,b} (1498) ^c	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low	Adjusted HR 1.1 (0.4–3.0) for Cu-IUD versus no contraception or tubal ligation
IUD^a versus implant,^e DMPA, NET-EN							
HIV acquisition	1 prospective study ^{2,b} (1136) ^c	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low	Adjusted HR 0.90 (0.45–1.76) for DMPA, implants, NET-EN versus Cu-IUD
IUD^a use versus DMPA							
HIV acquisition	1 RCT ^{3,b} (7829) ^c	Few limitations ^f	No serious inconsistency	No serious imprecision	No indirectness	High	Adjusted HR 1.04 (0.82–1.33) for DMPA-IM versus Cu-IUD
HIV acquisition	1 prospective study ^{2,b} (1136) ^c	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low	Adjusted HR 0.91 (0.44–1.87) for DMPA versus Cu-IUD
IUD^a versus NET-EN							
HIV acquisition	1 prospective study ^{2,b} (1136) ^c	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low	Adjusted HR 0.98 (0.47–2.03) for Cu-IUD versus NET-EN
IUD^a versus implant^e							
HIV acquisition	1 RCT ³ (7829) ^c	Few limitations ^f	No serious inconsistency	No serious imprecision	No indirectness	High	Adjusted HR 1.18 (0.91–1.53) for Cu-IUD versus LNG implant
HIV acquisition	1 prospective study ^{2,b} (1136) ^c	Some limitations ^d	No serious inconsistency	No serious imprecision	No indirectness	Low	Adjusted HR 2.17 (0.59–7.69) for Cu-IUD versus implants (LNG or ETG)

Cu-IUD: copper-bearing intrauterine device; DMPA-IM: intramuscular depot medroxyprogesterone acetate; ETG: etonogestrel; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: hazard ratio; IUD: intrauterine device; LNG: levonorgestrel; NET-EN: norethisterone enanthate; RCT: randomized controlled trial

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, results from Cox model analysis used when available.

^a No direct evidence for LNG-IUDs was identified for the comparisons of interest. For LNG-IUDs, recommendations were extrapolated from the evidence on Cu-IUDs and other LNG containing products.

^b Restricted to studies classified as “informative with but with important limitations”.

^c Sample size is for the entire study population.

^d Some limitations or imprecision was noted across the body of evidence, but not serious enough to downgrade the level of evidence.

^e No direct evidence for ETG implants was identified for the comparisons of interest. For ETG implants, recommendations were extrapolated from the evidence on LNG implants.

^f Few limitations noted in the trial, but not serious enough to downgrade the level of evidence.

References:

- Lavreys L, Baeten JM, Martin Jr HL, Overbaugh J, Mandaliya K, Ndinya-Achola J et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. *AIDS*. 2004;18(4):695–7.
- Palanee-Phillips T, Brown ER, Szydlo D, Matovu Kiweewa F, Pather A, Harkoo I et al. Risk of HIV-1 acquisition among South African women using a variety of contraceptive methods in a prospective study. *AIDS*. 2019;33(10):1619–22. doi: 10.1097/QAD.0000000000002260.
- Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet*. 2019;394(10195):303–13. doi: 10.1016/S0140-6736(19)31288-7.

ANNEX 4. EVIDENCE-TO-DECISION TABLE FOR HORMONAL CONTRACEPTIVE METHODS AND INTRAUTERINE DEVICES (IUDS)

Factor	Explanation/evidence	Judgement	
Quality of evidence	Progestogen-only contraceptives (POCs)	For the primary outcome of HIV acquisition, evidence was considered to be of high quality for intramuscular depot medroxyprogesterone acetate (DMPA-IM) and for levonorgestrel (LNG) implants. Evidence was considered to be of low quality for norethisterone enanthate (NET-EN), and absent for subcutaneous DMPA (DMPA-SC), LNG intrauterine devices (IUDs) and etonogestrel (ETG) implants. For NET-EN and DMPA-SC, the recommendations were extrapolated from the evidence on DMPA-IM. For ETG implants, the recommendations were extrapolated from the evidence on LNG implants.	High, low or absent, depending on method
	IUDs	For the primary outcome of HIV acquisition, evidence was considered to be of high quality for copper-bearing IUDs (Cu-IUDs). Evidence was absent for LNG-IUDs. For LNG-IUDs, recommendations were extrapolated from the evidence on Cu-IUDs and other LNG-containing products.	High or absent, depending on method
	Combined hormonal contraceptives (CHCs)	Evidence was considered to be of low-to-moderate quality for CHCs.	Low-moderate
Balance of benefits versus harms	POCs	<p>Contraception is a life-saving intervention with well recognized health, social and economic benefits. All POCs are effective or highly effective, reversible methods.</p> <p>High-quality evidence from one randomized controlled trial (RCT) observed no statistically significant differences in HIV acquisition between: DMPA-IM versus Cu-IUD, DMPA-IM versus LNG implant, and Cu-IUD versus LNG implant.</p> <p>Of the low-to-moderate-quality evidence from 14 observational studies, some studies suggested a possible increased risk of HIV with progestogen-only injectable use, which was most likely due to unmeasured confounding.^{a,b}</p> <p>Low-quality evidence from three observational studies did not suggest an increased HIV risk for implant users.^{a,b}</p> <p>No studies of sufficient quality were identified for progestogen-only pills.</p> <p>While no direct evidence was available for DMPA-SC or ETG implants, indirect evidence for DMPA-IM and LNG implants was used, given that there was no biological or clinical reason to believe that a lower hormonal dose, different delivery mechanism, or different progestogen would modify HIV risk.</p>	Balance is in favour of benefits of POCs
	IUDs	<p>Contraception is a life-saving intervention with well recognized health, social and economic benefits. All IUDs are highly effective, reversible methods.</p> <p>High-quality evidence from one RCT, along with low-quality evidence from two observational studies, suggested no increased risk of HIV acquisition with Cu-IUD use.^{c-e}</p> <p>While no direct evidence was available for LNG-IUDs, recommendations were extrapolated from the evidence on Cu-IUDs and other LNG-containing products.</p>	Balance is in favour of benefits of IUDs
	CHCs	<p>Contraception is a life-saving intervention with well recognized health, social and economic benefits. All hormonal contraceptives are effective or highly effective, reversible methods.</p> <p>Low-moderate quality evidence from 11 observational studies suggested no association between combined oral contraceptive (COC) use (it was assumed that studies that did not specify oral contraceptive type examined mostly, if not exclusively, COC use) and HIV acquisition.^{a,b}</p> <p>While no direct evidence was available for combined contraceptive patch, combined contraceptive vaginal ring or combined injectable contraceptive, indirect evidence from COCs was used given that there was no biological or clinical reason to believe that a lower hormonal dose, different delivery mechanism, or different progestogen would modify HIV risk.</p>	Balance is in favour of benefits of CHCs

Factor	Explanation/evidence	Judgement
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 (informed decision-making). Contraception is unique among medicines because a woman's needs and preferences with regard to the characteristics of contraceptive methods 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 serious 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.	Effective contraception and HIV prevention are both public health priorities
Equity and human rights	Human rights principles and standards from existing World Health Organization (WHO) guidelines on human rights and contraception were followed by the Guideline Development Group (GDG) in its deliberations. These include non-discrimination, availability, accessibility, acceptability, quality, informed decision-making, privacy and confidentiality, participation, and accountability. During its deliberations, the GDG considered both potential positive and negative effects of its considerations. For example, it considered and emphasized the continuing need for integrated family planning and HIV services in settings with high HIV incidence. It also emphasized the need for expanding and optimizing contraceptive options.	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. This was reinforced by recent studies that suggested that messages based on the 2017 WHO guidance were difficult to explain and may not be fully understood by clients or providers.	Clear guidance and a woman-centred approach are essential for successful implementation

References:

- a. Polis CB, Curtis KM, Hannaford PC, Phillips SJ, Chipato T, Kiarie JN et al. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. *AIDS*. 2016;30(17):2665–83. doi: 10.1097/QAD.0000000000001228.
- b. Sabo MC, Richardson BA, Lavreys L, Martin HL, Jr, Jaoko W, Mandaliya K et al. Does bacterial vaginosis modify the effect of hormonal contraception on HIV seroconversion. *AIDS*. 2019;33(7):1225–30. doi: 10.1097/QAD.0000000000002167.
- c. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet*. 2019;394(10195):303–13. doi: 10.1016/S0140-6736(19)31288-7.
- d. Palanee-Phillips T, Brown ER, Szydlo D, Matovu Kiweewa F, Pather A, Harkoo I et al. Risk of HIV-1 acquisition among South African women using a variety of contraceptive methods in a prospective study. *AIDS*. 2019;33(10):1619–22. doi: 10.1097/QAD.0000000000002260.
- e. Lavreys L, Baeten JM, Martin Jr HL, Overbaugh J, Mandaliya K, Ndinya-Achola J et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. *AIDS*. 2004;18(4):695–7.

ANNEX 5: SYSTEMATIC REVIEWS

Three systematic reviews were conducted as part of the development of this guidance statement. The details of the methods and search strategies are included in the reviews. Reviews published in peer-reviewed journals are available through open access. This appendix will be periodically updated as reviews are published. Access to unpublished reviews can be requested by sending an email to hrx-info@who.int.

1. Hormonal contraceptive method use and HIV acquisition in women

There was a previously published review on hormonal contraceptive use and HIV acquisition. The search strategies from that review were used to search for new evidence since. The following four new publications were identified that met the inclusion criteria.

PREVIOUSLY PUBLISHED REVIEW

1. Polis CB, Curtis KM, Hannaford PC, Phillips SJ, Chipato T, Kiarie JN et al. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. *AIDS*. 2016;30(17):2665–83. doi: 10.1097/QAD.0000000000001228.

UNPUBLISHED REVIEW

1. Curtis KM, Hannaford PC, Rodriguez MI, Chipato T, Steyn PS, Kiarie JN. Hormonal contraceptive method use and HIV acquisition in women: an updated systematic review. Working paper developed for the World Health Organization meeting. July 2019.

NEW ARTICLES

1. Haddad LB, Wall KM, Kilembe W, Vwalika B, Khu NH, Brill I et al. Bacterial vaginosis modifies the association between hormonal contraception and HIV acquisition. *AIDS*. 2018;32(5):595–604. doi: 10.1097/QAD.0000000000001741.
2. Hofmeyr GJ, Singata-Madliki M, Lawrie TA, Bergel E, Temmerman M. Effects of injectable progestogen contraception versus the copper intrauterine device on HIV acquisition: sub-study of a pragmatic randomised controlled trial. *J Fam Plann Reprod Health Care*. 2017;43(3):175–80. doi: 10.1136/jfprhc-2016-101607.
3. Palanee-Phillips T, Brown ER, Szydlo D, Matovu Kiweewa F, Pather A, Harkoo I et al. Risk of HIV-1 acquisition among South African women using a variety of contraceptive methods in a prospective study. *AIDS*. 2019;33(10):1619–22. doi: 10.1097/QAD.0000000000002260.
4. Sabo MC, Richardson BA, Lavreys L, Martin HL, Jr., Jaoko W, Mandaliya K et al. Does bacterial vaginosis modify the effect of hormonal contraception on HIV seroconversion. *AIDS*. 2019;33(7):1225–30. doi: 10.1097/QAD.0000000000002167.

2. Copper-bearing intrauterine device (Cu-IUD) use and HIV acquisition in women

A systematic review was conducted on Cu-IUD use and HIV acquisition in women. The following six articles met the inclusion criteria.

UNPUBLISHED REVIEW

1. Hannaford PC, Ti A, Chipato T, Curtis KM. Copper intrauterine device use and HIV acquisition in women: an updated systematic review. Working paper developed for the World Health Organization meeting. July 2019.

NEW ARTICLES

1. Hofmeyr GJ, Singata-Madliki M, Lawrie TA, Bergel E, Temmerman M. Effects of injectable progestogen contraception versus the copper intrauterine device on HIV acquisition: sub-study of a pragmatic randomised controlled trial. *J Fam Plann Reprod Health Care*. 2017;43(3):175–80. doi: 10.1136/jfprhc-2016-101607.
2. Kapiga SH, Lyamuya EF, Lwihula GK, Hunter DJ. The incidence of HIV infection among women using family planning methods in Dar es Salaam, Tanzania. *AIDS*. 1998;12(1):75–84. doi: 10.1097/00002030-199801000-00009.
3. Lavreys L, Baeten JM, Martin Jr HL, Overbaugh J, Mandaliya K, Ndinya-Achola J et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. *AIDS*. 2004;18(4):695–7.
4. Palanee-Phillips T, Brown ER, Szydlo D, Matovu Kiweewa F, Pather A, Harkoo I et al. Risk of HIV-1 acquisition among South African women using a variety of contraceptive methods in a prospective study. *AIDS*. 2019;33(10):1619–22. doi: 10.1097/QAD.0000000000002260.
5. Saracco A, Musicco M, Nicolosi A, Angarano G, Arici C, Gavazzeni G et al. Man-to-woman sexual transmission of HIV: longitudinal study of 343 steady partners of infected men. *J Acquir Immune Defic Syndr*. 1993;6(5):497–502.
6. Sinei SK, Fortney JA, Kigonda CS, Feldblum PJ, Kuyoh M, Allen MY et al. Contraceptive use and HIV infection in Kenyan family planning clinic attenders. *Int J STD AIDS*. 1996;7(1):65–70. doi: 10.1258/0956462961917104.

3. Contraceptive values and preferences

A systematic review was conducted on contraceptive values and preferences. The protocol and methods are published, and the manuscript presenting the main results of the review is under review for publication. As this review did not identify information specific to key populations at risk of HIV, consultative engagements were conducted in the spring of 2019, including a global online survey of sex workers, and participatory focus group discussions with female sex workers

in Zimbabwe through the Sisters with a Voice programme. Presentations showing the findings from these engagements are listed below and available on request. A presentation shared by stakeholders representing affected populations to highlight their perspectives on the topic was part of the Guideline Development Group's discussions and is available on request.

1. Kennedy CE, Yeh PT, Gaffield ME. Contraception values and preferences: protocol and methods for a global systematic review. *Contraception*. 2019 (in press). doi: 10.1016/j.contraception.2018.05.006Get.
2. Yeh PT, Kennedy CE, Gaffield ME. Contraception values and preferences: a global systematic review. *Contraception*. 2019; (accepted pending revisions).
3. Shapiro A. Female sex workers' contraceptive practices, values and preferences. contraception and risk of HIV infection: a WHO Guideline Development Group review of the current evidence. 29 July 2019, Geneva, World Health Organization.
4. Sibanda E. Views on contraceptive methods among female sex workers in Harare, Zimbabwe: a participatory qualitative study. 29 July 2019, Geneva, World Health Organization.
5. Mworeko L. What do recommendations on contraceptives and HIV risk mean to women?, 29 July 2019, Geneva, World Health Organization.

For more information, please contact:
Department of Reproductive Health and Research,
World Health Organization, Avenue Appia 20,
CH-1211 Geneva 27, Switzerland.
E-mail: reproductivehealth@who.int
www.who.int/reproductivehealth

