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Department:
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SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 7: FAMILY PLANNING
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2016 -2018)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the family planning chapter.

SECTION	MEDICINE	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
Introduction to contraception *(Table comparing various contraceptive methods)*	Copper IUCD	Amended
	Hormonal subdermal: progestin-only implant	Amended
	Hormonal injectable: progestin-only	Amended
	Hormonal oral: combined oral contraceptive	Amended
	Barrier: male and female condoms	Amended
7.1 Intrauterine contraceptive device (IUCD)	Copper IUCD	Directions for use amended (postpartum)
	Azithromycin, oral	Not added as a prophylactic antibiotic
	Ceftriaxone, IM	Not added
-For mild pain and discomfort after insertion:	Ibuprofen, oral	Directions for use amended
7.2.1 Subdermal implant	Progestin-only subdermal implants	- Caution amended with the removal of nevirapine as an enzyme inducer - Caution box and directions for use amended
7.2.2 Injectable	Progestin-only injectable	- Retained as a therapeutic class - Directions for use amended and risk of HIV acquisition caution not added - Statement regarding the uncertainty of the risk of HIV acquisition was added.
	Norethisterone injectable	Medicine in therapeutic group, but not listed as an example of class in the STG
7.2.3 Oral (Medicine interactions)	Oral contraceptive	Drug-drug interaction amended (added: efavirenz)
	Oral contraceptive	Drug-drug interaction amended (deleted: antibiotics)
	Monophasic-progestin only pills	Therapeutic class alternatives listed
	Monophasic- progestin/estrogen combined pills	Therapeutic class alternatives listed
	Triphasic-progestin/estrogen combined pills	Therapeutic class alternatives listed
	Progestin only pill	Contraindication (myocardial infarction or stroke) not amended
7.3 Missed pills	Combination of progestin and estrogen in each pill	Directions for use amended
7.4 Contraception, emergency	Levonorgestrel, oral	Amended (double-dose with concomitant enzyme inducers and in obesity)
	Metoclopramide, oral	Not added
7.5 Breakthrough bleeding with contraceptive use	Ethinylestradiol, oral 50 mcg	Not added
	COC containing 30mcg ethinylestradiol	Added
	Ethinylestradiol/levonorgestrel, oral, 30/150 mcg	Added
	COCs containing 35mcg ethinylestradiol	Added
	Ibuprofen, oral	Not added
	Tranexamic acid, oral	Not added
7.5 Voluntary sterilisation, male and female	n/a	n/a

INTRODUCTION TO CONTRACEPTION

Advantages and disadvantages of contraceptive methods

The text of the table comparing the various types of contraceptives was amended for clarity purposes with alignment to the NDoH National Contraception Guidelines, 2012 and the WHO medical eligibility criteria for contraceptive use guideline, 2015, where applicable. The table does not list all the contra-indications or adverse effects of the related contraceptive method; but the text does recommend referral to the package inserts for detailed information.

Copper IUCD: *advantages and disadvantages amended*

Advantages: The currently MCC registered IUCD has a lifespan of 5 years only, and the text of the STG was amended to reflect this.

Disadvantages: Previous text, "Pain" was delineated to describe" discomfort or cramping during and following insertion" and severe pain probably associated with complications where IUCDs should not be used.

Text updated as follows:

Contraceptive method	Advantages include:	Disadvantages include:
Copper IUCD (see Section 7.1)	» Suitable for most women, including nulliparous women. » Provides long-term protection i.e. 5years » Convenient, does not require regular follow up. » Works immediately on insertion. » Non-hormonal therefore no interaction with other medication and no hormonal side effects. » Fertility returns on removal of IUCD in women of child-bearing age.	» Some discomfort or cramping during and following insertion. » IUCD must be inserted or removed by a trained health care professional. » Should not be used in women with menorrhagia, active pelvic inflammatory disease (PID), purulent cervicitis, unexplained uterine bleeding, cervical and endometrial cancers or other uterine abnormalities.

Hormonal subdermal: progestin-only implant: *disadvantages amended*

The STG provides for either subdermal implant (one requiring incision and the other inserted via an auto-injector) and the text was updated as follows:

Contraceptive method	Advantages include:	Disadvantages include:
Hormonal subdermal: progestin-only implant (see Section 7.2.1)	» Provides long-term protection i.e. 3 years (etonogestrel) or 5 years (levonorgestrel). » Convenient, does not require regular follow up. » Can be used in women >35 years who are obese, who smoke, have diabetes, hypertension, or a history of venous thromboembolism. » Fertility returns on removal of implant in women of child-bearing age.	» Frequent bleeding irregularities. » Implant must be inserted or removed by a trained health care professional under aseptic conditions to prevent infection. » Incorrect insertion and removal technique may result in complications.

Hormonal injectable: progestin-only: *advantages and disadvantages amended*

Advantages: Text updated to reflect duration of contraception for currently available products.

Disadvantages: Bleeding irregularities described, aligned with guidelines[1] [2] [3]

Text updated as follows:

Contraceptive method	Advantages include:	Disadvantages include:

[1] SAMF, 2016

[2] Faculty of Sexual & Reproductive Healthcare Clinical Guidance: Problematic Bleeding with Hormonal Contraception Clinical Effectiveness Unit, July 2015.

[3] World Health Organisation. Medical eligibility criteria for contraceptive use, Fifth edition, 2015. http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/

	Hormonal injectable: progestin-only (see Section 7.2.2)	» Daily adherence is not required. » Long-acting i.e. given every 8 or 12 weeks. » Interactions with other medicines do not lower contraceptive effect. » Can be used postpartum. » Can be used in women >35 years who are obese, who smoke, has diabetes, hypertension, or a history of venous thromboembolism.	» Delayed return to fertility of up to ≥ 9 months, after last injection. » Frequent bleeding irregularities (irregular, prolonged and/or heavy bleeding, or amenorrhoea).

Weight gain in young women: Authors of a Cochrane review[4]concluded that, "The overall quality of evidence was moderate to low, given that the studies were evenly divided across the evidence quality groups (high, moderate, low, or very low quality). We found limited evidence of weight gain when using POCs. Mean gain was less than 2 kg for most studies up to 12 months. Weight change for the POC group generally did not differ significantly from that of the comparison group using another contraceptive".
Recommendation: " *Weight gain in young women*" not be listed as a disadvantage for progestin-only injectable contraceptives.
Rationale: Limited evidence showed little difference in weight gain users in progestin-only contraceptives compared to use of a non-hormonal method (<2kg).
Level of Evidence: I Systematic review

Bone mineral density: Cochrane review[5] showed, "Four trials involving DMPA showed some positive effects of an estrogen supplement on BMD, a negative effect of DMPA-subcutaneous on lumbar spine BMD, and a negative effect of DMPA on a bone formation marker".
Recommendation: " *Loss of bone mineral density*" not be listed as a disadvantage for progestin-only injectable contraceptives.
Rationale: Although evidence suggests that DMPA reduces bone mineral density, this has not been sown to translate into reduced risk of fractures.
Level of Evidence: I Systematic review

Risk of cervical intra-epithelial neoplasia and invasive cervical carcinoma in women with persistent human papilloma virus: There is a weak association between cervical cancer and use of DMPA for 5 years or longer[6], and this increased risk diminishes after stopping DMPA. There's also a strong view that the increased risk is due to confounding factors (e.g. age, number of sexual partners, alcohol consumption, and parity).
Recommendation: "*Risk of cervical intra-epithelial neoplasia and invasive cervical carcinoma in women with persistent human papilloma virus"* not be listed as a disadvantage for progestin-only injectable contraceptives.
Rationale: Aligned with International Guidelines[7].
Level of Evidence: III Guidelines

Risk of chlamydial infection and cervicitis: WHO Medical Eligibility criteria[8] mentions that "Evidence suggests that there may be an increased risk of chlamydial cervicitis among DMPA users at high risk of STIs. For other STIs, there is either evidence of no association between DMPA use and STI acquisition or too limited evidence to draw any conclusions". A routine recommendation is included in the text of the STG: **Dual protection i.e. the use of a condom in combination with another contraceptive method is recommended to reduce the risk of STIs, including HIV.**

[4] Lopez LM, Edelman A, Chen M, Otterness C, Trussell J, Helmerhorst FM. Progestin-only contraceptives: effects on weight. Cochrane Database Syst Rev. 2013 Jul 2;(7):CD008815. http://www.ncbi.nlm.nih.gov/pubmed/21491411
[5] Lopez LM, Grimes DA, Schulz KF, Curtis KM, Chen M. Steroidal contraceptives: effect on bone fractures in women. Cochrane Database Syst Rev. 2014 Jun 24;(6):CD006033. http://www.ncbi.nlm.nih.gov/pubmed/24960023
[6] McFarlane-Anderson N, Bazuaye PE, Jackson MD, Smikle M, Fletcher HM. Cervical dysplasia and cancer and the use of hormonal contraceptives in Jamaican women. BMC Womens Health. 2008 May 30;8:9. doi: 10.1186/1472-6874-8-9. http://www.ncbi.nlm.nih.gov/pubmed/18513406
[7] Faculty of Sexual & Reproductive Healthcare Clinical Guidance: Progestogen-only Injectable Contraception Clinical Effectiveness Unit December 2014 (Updated March 2015). https://www.fsrh.org/documents/cec-ceu-guidance-injectables-dec-2014/
[8] World Health Organisation. Medical eligibility criteria for contraceptive use, 5th edition, 2015. http://apps.who.int/iris/bitstream/10665/181468/1/9789241549158_eng.pdf

Recommendation: "*Risk of chlamydial infection and cervicitis*" not be listed as a disadvantage for progestin-only injectable contraceptives.
Rationale: The STG routinely recommends "**Dual protection i.e. the use of a condom in combination with another contraceptive method is recommended to reduce the risk of STIs, including HIV".**
Level of Evidence: III Expert opinion

Risk of HIV acquisition: The currently available evidence is not sufficiently robust to support the association of the risk of HIV acquisition with the progestin-only injectable contraceptives. It was reported that a Zambian study[9] of discordant couples showed that hormonal contraception does not increase the risk of HIV acquisition. Authors of a Cochrane review[10] concluded: "There is currently no robust evidence from randomized trials on the possible effect of hormonal contraception on HIV acquisition. High quality trials in this area are needed to inform counselling of individual woman and public health policy".
Recommendation: "*Risk of HIV acquisition*" not be listed as a disadvantage for progestin-only injectable contraceptives.
Rationale: No robust RCT data is currently available to show the effect of progestin-only injectable hormonal contraception on HIV acquisition.
Level of Evidence: I Systematic review

Hormonal oral: combined oral contraceptive (COC): *disadvantages amended*
Evidence regarding the benefits and risks of cancers associated with combined oral contraceptives are contradictory; and combined COCs cannot be used immediately postpartum.
Text was updated as follows:

Contraceptive method	Advantages include:	Disadvantages include:
Hormonal oral: combined oral contraceptive (COC) (see Sections 7.2.3 and 7.2.4)	» Non-contraceptive benefits, e.g.: alleviation of dysmenorrhoea, premenstrual syndrome and menorrhagia. » Fertility returns within 3 months of discontinuing COC.	» Daily adherence is required. » Interactions with other medicines can lower contraceptive effect. » Cannot be used in women with heart disease, stroke and a history of active venous thromboembolism. » Cannot be used immediately postpartum.

Barrier: male and female condoms: *disadvantages amended*
Text of the STG amended to include "Lower efficacy than other contraceptive methods therefore advised as dual contraception".

Effectiveness of family planning methods
The table was updated to list sterilisation and progestin-only pill (breastfeeding and not breastfeeding), aligned with the NDoH National contraception Guidelines, 2012[11], WHO medical eligibility criteria for contraceptive use guideline, 2015[12] and population survey estimates[13].

Contraceptive method	Failure rate in 1st year (%)	
	Consistent and correct use	As typically used
Copper IUCD	0.6	0.8
Progestin-only subdermal implant	0.05	0.05
Progestin-only injectable	0.3	3
Progestin-only oral pill (not breastfeeding)	0.3	8

[9] Wall KM, Kilembe W, Vwalika B, Khu NH, Brill I, Chomba E, Johnson BA, Haddad L, Tichacek A, Allen S. Hormonal contraception does not increase women's HIV acquisition risk in Zambian discordant couples, 1994–2012. Contraception. 2015 June;1(6):480-487. http://www.ncbi.nlm.nih.gov/pubmed/25708502
[10] Hofmeyr GJ, Singata M, Sneden J. Hormonal contraception for women exposed to HIV infection. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD009741. http://www.ncbi.nlm.nih.gov/pubmed/24844211
[11] National Contraception and Fertility Planning and Service Delivery Guidelines, 2012. http://www.health.gov.za/
[12] World Health Organisation. Medical eligibility criteria for contraceptive use, Fifth edition, 2015. http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/
[13] Trussell J. Contraceptive failure in the United States. Contraception. 2011 May;83(5):397-404.

Progestin-only oral pill (during breast feeding)	0.5	1
Combined oral contraceptive (COC) pill	0.3	3
Barrier: female condoms	5	21
Barrier: male condoms	2	15
Sterilisation: male - vasectomy	0.15	0.1
Sterilisation: female - tubal ligation	0.5	0.5
No method	85	85

Level of Evidence: III Guidelines, Survey

7.1 INTRAUTERINE CONTRACEPTIVE DEVICE (IUCD)

Copper IUCD: *directions for use amended*

Text was updated as follows to emphasise the advantages of using this method of contraception:

HIV infection is NOT a contra-indication to the use of an IUCD.
IUCDs are often the most suitable contraceptive for women on ARVs and other enzyme-inducing medicines, because of the absence of drug interactions.

A Cochrane review[14] suggests that "Immediate post-partum insertion of IUDs appeared safe and effective, though direct comparisons with other insertion times were limited. Advantages of immediate post-partum insertion include high motivation, assurance that the woman is not pregnant, and convenience. Expulsion rates appear to be higher than with interval insertion".

Recommendation: The following text was added to the STG:

Copper IUCDs may be inserted immediately postpartum (within 48 hours) by specially trained heath care professionals, providing that no contra-indications are present (chorioamnionitis, ruptured membranes for more than 18 hours and postpartum haemorrhage). Women should be counselled to return if they experience complications (excessive bleeding, excessive pain, fever or foul smelling discharge). Alternatively, an IUCD may be inserted at least 4 weeks postpartum.

Rationale: RCTs reviewed in the Cochrane review[15] compared immediate insertion (within 48 hours of placenta delivery) vs. standard insertion 4 to 12 weeks postpartum. The authors of the review had concluded that the benefit of effective contraception immediately after delivery may outweigh the disadvantage of increased risk for expulsion and that clinical follow-up and adequate counselling can help detect early expulsion.

Level of Evidence: I Systematic review, Expert opinion

Prophylactic antibiotics

Azithromycin, oral: *not added*

Ceftriaxone, IM: *not added*

The use of prophylactic antibiotics (e.g. azithromycin and/or ceftriaxone single dose) prior to Copper IUCD remains a contentious subject as several studies found that these provided little benefit. However, a reduction in unscheduled clinic visits was marginally significant, although routine prophylaxis may not be cost-effective. Furthermore, Grimes *et al*[16] found that the risk of IUCD-associated pelvic infection was low, regardless of antibiotic prophylaxis.

Recommendation: Antibiotics not be added to the STG as prophylaxis prior to insertion of an IUCD.

Rationale: Cochrane review showed that the risk of IUCD-associated pelvic infection was low, regardless of antibiotic prophylaxis.

Level of Evidence: I Systematic review

For mild pain and discomfort after insertion:

Ibuprofen, oral: *directions for use amended*

[14]Grimes DA, Lopez LM, Schulz KF, Van Vliet HA, Stanwood NL. Immediatepost-partum insertion of intrauterine devices. Cochrane Database Syst Rev. 2010 May 12;(5):CD003036. Review. Update in: Cochrane Database Syst Rev. 2015;6:CD003036. http://www.ncbi.nlm.nih.gov/pubmed/20464722

[15] Grimes DA, Lopez LM, Schulz KF, Van Vliet HA, Stanwood NL. Immediatepost-partum insertion of intrauterine devices. Cochrane Database Syst Rev. 2010 May 12;(5):CD003036. Review. Update in: Cochrane Database Syst Rev. 2015;6:CD003036. http://www.ncbi.nlm.nih.gov/pubmed/20464722

[16] Grimes DA, Schulz KF. Antibiotic prophylaxis for intrauterine contraceptive device insertion. Cochrane Database Syst Rev. 2001;(2):CD001327. http://www.ncbi.nlm.nih.gov/pubmed/11405986

Indication described more clearly as "for mild pain and discomfort after insertion" and duration of treatment amended from "5 days" to "3 days". (See above for further details regarding pain associated with IUCD insertion).

Level of Evidence: III Expert opinion

7.2.1 SUBDERMAL IMPLANT

Caution box regarding subdermal implants

Nevirapine: Pharmacokinetic study has shown that nevirapine is a weak enzyme inducer[17], and unlikely to result in a clinically significant reduction in progestin concentrations. It is noted that the caution differs from the WHO medical eligibility criteria for contraceptive use, 2015[18].

Enzyme inducers: The WHO MEC category[19] for subdermal implants when a patient is on efavirenz-containing ART is 2, but category 1 for other enzyme inducers. However, the PHC Committee was of the opinion that observational and pharmacokinetic studies[20] [21] [22] [23] suggest drug-drug interaction with enzyme inducers and a reduction in contraceptive efficacy of subdermal implants.

Etonogestrel + DMPA: There is no available published evidence for supplementing etonogestrel implant with DMPA when on enzyme inducers.

Recommendation: The caution be retained but wording amended to emphasise counselling re-iterating the philosophy of women's choice.

Level of Evidence: III Pharmacokinetic studies

And, the caution box was updated to:

CAUTION
Medicines that induce the metabolism of progestins could reduce contraceptive efficacy. These medicines include efavirenz, rifampicin, phenytoin, carbamazepine and phenobarbital. Women on these medicines should be advised to use alternate contraceptive methods such as the copper IUCD or DMPA. If the client chooses to use the implant, then she should be advised to use dual contraception.

Subdermal implant: *directions for use amended*

STG was updated to describe insertion and removal of implants in detail, with a note to refer to the package insert for detailed instructions. Also, bleeding irregularities, commonly associated with use of subdermal implants described in the STG with a cross referral to Section 7.6: Breakthrough bleeding with contraceptive use for management.

Of note is the attached circular that provides information regarding the expiry date and insertion date of etonogestrel subdermal implants:

Etonogestrel implants expiration

[17] Landolt NK et al. Significant Decrease of Ethinylestradiol With Nevirapine, and of Etonogestrel With Efavirenz in HIV-Positive Women. J Acquir Immune Defic Syndr 1 June 2014;66(2): e50-52.

[18] WHO medical eligibility criteria for contraceptive use, 2015. http://apps.who.int/iris/bitstream/10665/181468/1/9789241549158_eng.pdf

[19] World Health Organisation. Medical eligibility criteria for contraceptive use Fifth edition, 2015.

[20] Scarsi KK, Darin KM, Nakalema S, Back DJ, Byakika-Kibwika P, Else LJ, Penchala SD, Buzibye A, Cohn SE, Merry C, Lamorde M. Unintended Pregnancies Observed With Combined Use of the Levonorgestrel Contraceptive Implant and Efavirenz-based Antiretroviral Therapy: A Three-Arm Pharmacokinetic Evaluation Over 48 Weeks. Clin Infect Dis. 2016 Mar 15;62(6):675-82. -Perry SH, Swamy P, Preidis GA, Mwanyumba A, Motsa N, Sarero HN. Implementing the Jadelle implant for women living with HIV in a resource-limited setting: concerns for drug interactions leading to unintended pregnancies. AIDS. 2014 Mar 13;28(5):791-3.

[21] Landolt NK, Phanuphak N, Ubolyam S, Pinyakorn S, Kerr S, Ahluwalia J, Thongpaeng P, Thammajaruk N, Cremers S, Thomas T, Chaithongwongwatthana S, Lange JM, Ananworanich J. Significant decrease of ethinylestradiol with nevirapine, and of etonogestrel with efavirenz in HIV-positive women. J Acquir Immune DeficSyndr. 2014 Jun 1;66(2):e50-2.

[22] Vieira CS, Bahamondes MV, de Souza RM, Brito MB, Rocha Prandini TR, Amaral E, Bahamondes L, Duarte G, Quintana SM, Scaranari C, Ferriani RA. Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on etonogestrel-releasing implant pharmacokinetics in HIV-positive women. J Acquir Immune DeficSyndr. 2014 Aug 1;66(4):378-85.

[23] Perry SH, Swamy P, Preidis GA, Mwanyumba A, Motsa N, Sarero HN. Implementing the Jadelle implant for women living with HIV in a resource-limited setting: concerns for drug interactions leading to unintended pregnancies. AIDS. 2014 Mar 13;28(5):791-3.

7.2.2 INJECTABLE

Progestin-only injectable: *retained as a therapeutic class and directions for use amended*

No available evidence could be retrieved from the published literature for recommending that progestin injectables not be used within 48 hours of child birth. The NDoH National Contraceptive Policy, 2012 recommends use within 5 days postpartum if not breastfeeding and if breast feeding at 6 weeks postpartum.

Text of the STG was amended as follows:

~~» Do not use within 48 hours of child birth.~~
» Can be used postpartum.

Level of Evidence: III Guidelines

Progestin-only injectable: *risk of HIV acquisition caution not added*

The PHC Committee was of the opinion that statements regarding the possible associated risk of HIV acquisition not be included in the STG, pending the results of the ECHO RCT.

NEMLC Discussion at the NEMLC meeting, 14 December 2017.

RCT evidence: Recommendations are preferably based on level one evidence (as per the SORT criteria) and the pragmatic implications of advising that there is a possible risk associated with DMPA was discussed. Observational data suggested that the risk was low. However, it was argued that remaining silent on this matter would be unethical.

Circular: It was proposed that the warning not be included in the STG, but that a circular be developed informing prescribers of the possible risk.

STG: As access to information on the STGs and EML on the mobile phone platform was greater than communication via circulars, it was recommended that a statement be included in the STG. It was reported that the NDoH Contraceptive Guidelines would not be updated anytime soon.

IUCDs: The advantages of copper IUCDs as a contraceptive was discussed and the need to promote use of this agent amongst women.

NEMLC Recommendation: The STG contain a statement advising prescribers there is uncertainty of the risk of HIV acquisition associated with progestin injectable contraceptives; as indicated in the WHO MEC 2017 guidelines[24]) and that dual protection is recommended.

Rationale: Advising prescribers of the possible risk of HIV acquisition associated with progestin-injectables trigger to assist women in making a choice regarding contraceptive mode; and to further encourage dual contraception.

And, the following text was added to the STG:

There is uncertainty of the risk of HIV acquisition associated with progestin injectable contraceptives (Refer to the WHO MEC 2017 guidelines). Dual protection is recommended.

Northethisterone injectable: *Medicine in therapeutic group, but not listed as an example of class.*

Medroxyprogesterone acetate (DMPA) and Northethisterone injectable (NET-EN) contraceptives were considered comparable in efficacy and safety[25]. Thus, the more cost-effective option (DMPA) was listed as an example of class[26].

Current tender prices are:

- DMPA, administered every 3 months: R 6.49
- NET-EN, administered every 2 months: R 11.00

[24] World Health Organisation. Guidance statement: Hormonal contraceptive eligibility for women at high risk of HIV, 2017. http://www.who.int/reproductivehealth/publications/family_planning/HC-and-HIV-2017/en/

[25] Draper BH, Morroni C, Hoffman M, Smit J, Beksinska M, Hapgood J, Van der Merwe L. Depot medroxyprogesterone versus norethisterone oenanthate for long-acting progestogenic contraception. *Cochrane Database Syst Rev.* 2006 Jul 19;(3):CD005214. http://www.ncbi.nlm.nih.gov/pubmed/16856087

[26] Contract circular HP03-2015CHM

7.2.3 ORAL

Medicine interactions

Efavirenz

Oral contraceptive: *drug-drug interaction amended (efavirenz)*

Pharmacokinetic study[27] (28 HIV-uninfected women) showed a drug-drug interaction between norgestimate and efavirenz, but a non-significant alteration in ethinyl estradiol concentrations. Efavirenz lowered the 17-deacetyl norgestimate (the active metabolite of norgestimate) AUC by 64 %, Cmax by 46 % and minimum concentration (Cmin) by 82 %. Tittle et al[28] mentioned that, "Importantly, the clinical significance of these effects is unclear; therefore, it is recommended that additional reliable methods of barrier contraception are used with oral hormonal contraceptives".

Recommendation: Drug-drug interaction for efavirenz with progesterone containing oral contraceptives was added to the text of the STG.

Rationale: Limited evidence shows a drug-drug interaction of efavirenz with contraceptives.

Level of Evidence: III Pharmacokinetic study, Expert opinion

Antibiotics

Oral contraceptive: *drug-drug interaction amended (antibiotics)*

The following text was deleted from the STG:

» ~~Possible lowering of contraceptive effect. For the duration of the current menstrual cycle, use a condom as well.~~

Rationale: Evidence from controlled shows that antibacterial have no effect in reducing ethinylestradiol concentrations[29], except one small study[30] that showed a reduction in ethinylestradiol, but progestin levels and contraceptive efficacy were not affected.

Level of Evidence: III Pharmacokinetic studies

[27] Sevinsky H, Eley T, Persson A, Garner D, Yones C, Nettles R, Krantz K, Bertz R, Zhang J. The effect of efavirenz on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy HIV-negative women. Antivir Ther. 2011;16(2):149-56. http://www.ncbi.nlm.nih.gov/pubmed/ 21447863

[28] Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. Clin Pharmacokinet. 2015 Jan;54(1):23-34. http://www.ncbi.nlm.nih.gov/pubmed/25331712

[29]Wermeling DP, Chandler MH, Sides GD, Collins D, Muse KN. Dirithromycin increases ethinyl estradiol clearance without allowing ovulation. Obstet Gynecol. 1995 Jul;86(1):78-84.

- Blode H, Zeun S, Parke S, Zimmermann T, Rohde B, Mellinger U, Kunz M. Evaluation of the effects of rifampicin, ketoconazole and erythromycin on the steady-state pharmacokinetics of the components of a novel oral contraceptive containing estradiol valerate and dienogest in healthy postmenopausal women. Contraception. 2012 Oct;86(4):337-44.
- Meyer B, Müller F, Wessels P, Maree J. A model to detect interactions between roxithromycin and oral contraceptives. Clin Pharmacol Ther. 1990 Jun;47(6):671-4.
- Joshi JV, Joshi UM, Sankholi GM, Krishna U, Mandlekar A, Chowdhury V, HazariK, Gupta K, Sheth UK, Saxena BN. A study of interaction of low-dose combination oral contraceptive with Ampicillin and Metronidazole. Contraception. 1980 Dec;22(6):643-52.
- Viswanathan MK; Govindarajulu P. Metronidazole therapy on the efficacy of oral contraceptive steroid pills. Journal of reproductive biology and comparative endocrinology. 1985; 5(2):69-72.
- Friedman CI, Huneke AL, Kim MH, Powell J. The effect of ampicillin on oral contraceptive effectiveness. Obstet Gynecol. 1980 Jan;55(1):33-7.
- Back DJ, Breckenridge AM, MacIver M, Orme M, Rowe PH, Staiger C, Thomas E, Tjia J. The effects of ampicillin on oral contraceptive steroids in women. Br J Clin Pharmacol. 1982 Jul;14(1):43-8.
- Maggiolo F, Puricelli G, Dottorini M, Caprioli S, Bianchi W, Suter F. The effect of ciprofloxacin on oral contraceptive steroid treatments. Drugs Exp Clin Res. 1991;17(9):451-4.
- Scholten PC, Droppert RM, Zwinkels MG, Moesker HL, Nauta JJ, Hoepelman IM. No interaction between ciprofloxacin and an oral contraceptive. Antimicrob Agents Chemother. 1998 Dec;42(12):3266-8.
- Zeun S, Lu M, Uddin A, Zeiler B, Morrison D, Blode H. Pharmacokinetics of an oral contraceptive containing oestradiol valerate and dienogest. Eur J Contracept Reprod Health Care. 2009 Jun;14(3):221-32. 16.
- Grimmer SF, Allen WL, Back DJ, Breckenridge AM, Orme M, Tjia J. The effect of cotrimoxazole on oral contraceptive steroids in women. Contraception. 1983 Jul;28(1):53-9.
- Neely JL, Abate M, Swinker M, D'Angio R. The effect of doxycycline on serum levels of ethinyl estradiol, norethindrone, and endogenous progesterone. Obstet Gynecol. 1991 Mar;77(3):416-20.
- Murphy AA, Zacur HA, Charache P, Burkman RT. The effect of tetracycline on levels of oral contraceptives. Am J Obstet Gynecol. 1991 Jan;164(1 Pt 1):28-33.

[30]Back Dj. Tjia J, Martin C. Millar E. Salmon P, Orme M. The interaction between clarithromycin and combined oral-contraceptive steroids. *j* Phorm *Med* (1991) 2. 81 - 7.

Therapeutic classes

Generally, low dose estrogen (20-35 mcg) is preferred to minimise nausea and vomiting; whilst the progestin component is the more expensive component of the pill and is related to the risk of venothromboembolism (VTE).

Evidence for the risk of VTE:

i. Estrogen:

- Population based case-control study[31] showed that the risk of venous thrombosis was positively associated with estrogen dose:

Ethinylestradiol (mcg)	OR ADJUSTED FOR AGE (95% CI)		
	Levonorgestrel	Gestodene	Desogestrel
20	1.1 (0.4 to 3.1)	0.3 (0.2 to 0.7)	0.7 (0.4 to 1.2)
30*	1	1	1
50	2.2 (1.3 to 3.7)	-	-

*Reference category is the most commonly used dose of oestrogen among controls.

ii. Progestin:

The newer progestins (desogestrel, gestodene, cyproterone and drospirenone) all are more expensive than levonorgestrel, and carry a significantly higher risk of VTE compared vs. levonorgestrel.

- The relative risk of confirmed VTE compared to levonorgestrel was reported as follows in a Danish historical registry based cohort study[32]:
  - Desogestrel: 2.2 (95% CI 1.7 to 3.0)
  - Gestodene: 2.1 (95% CI 1.6 to 2.8)
  - Drospirenone: 2.1 (95% CI 1.6 to 2.8).
- Population based case-control study[33] showed a fivefold increased risk of VTE associated with oral contraceptives vs non-use (OR 5.0, 95% CI 4.2 to 5.8); differentiated by type of progestogen and dose of oestrogen: Risk of venous thrombosis (including DVT and PE) with oral contraceptives vs non-use was reported as follows for the various progestogen-containing oral contraceptives:
  - Levonorgestrel: OR 3.6, 95% CI 2.9 to 4.6
  - Norethisterone: OR 3.9, 95% CI 1.4 to 10.6
  - Gestodene: OR 5.6, 95% CI 3.7 to 8.4
  - Lynestrenol: OR 5.6, 95% CI 3.0 to 10.2
  - Norgestimate: OR 5.9, 95% CI 1.7 to 21.0
  - Drospirenone: OR 6.3, 95% CI 2.9 to 13.7
  - Cyproterone acetate: OR 6.8, 95% CI 4.7 to 10.0
  - Desogestrel: OR 7.3, 95% CI 5.3 to 10.0

[31] van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ. 2009 Aug 13;339:b2921. https://www.ncbi.nlm.nih.gov/pubmed/19679614

[32] Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ. 2011 Oct 25;343:d6423. https://www.ncbi.nlm.nih.gov/pubmed/22027398

[33] van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ. 2009 Aug 13;339:b2921. https://www.ncbi.nlm.nih.gov/pubmed/19679614

Table 5: Risk of different types of venous thrombosis associated with oral contraceptive use by different type of progestogen. Patients with venous thrombosis of the arm omitted from this analysis

		Deep venous thrombosis of leg		Pulmonary embolism*	
Type of progestogen	No of controls	No of patients	Odds ratio (95% CI)†	No of patients	Odds ratio (95% CI)†
All	65	66	6.6 (5.4 to 8.0)	407	3.9 (3.2 to 4.8)
Levonorgestrel‡	37	30	5.0 (3.8 to 6.5)	171	2.8 (2.1 to 3.8)
Gestodene‡	67	74	8.1 (5.2 to 12.7)	43	3.8 2.2 to 6.3)
Desogestrel‡	10	15	8.7 (6.1 to 12.4)	122	7.1 (4.9 to 10.4)
Lynestrenol‡	19	27	7.3 (3.7 to 14.2)	15	4.5 (2.1 to 9.6)
Norethisterone	7	7	5.4 (1.8 to 16.6)	4	3.1 (0.8 to 11.5)
Cyproterone	62	77	9.4 (6.1 to 14.3)	41	5.6 (3.4 to 9.2)
Norgestimate	4	5	8.7 (2.1 to 35.5)	4	5.2 (1.1 to 23.7)
Drospirenone	14	12	9.1 (3.9 to 21.5)	7	6.2 (2.2 to 17.6)
No oral	110	19	1	198	1

*With or without deep venous thrombosis.

†Odds ratio per type of progestogen adjusted for age and period of inclusion (categorical; divided per 6 calendar months).

‡Analysis restricted to preparation with most commonly used dose of oestrogen. For levonorgestrel, gestodene, and desogestrel, this was 30 µg (388 patients with deep venous thrombosis of the leg, 242 patients with pulmonary embolism, and 385 controls). For lynestrenol, this was 37.5 µg (25 patients with deep venous thrombosis of the leg, 15 with pulmonary embolism, and 19 controls).

Recommendation: The following therapeutic alternatives for classes: (i) monophasic progestogen only pills; (ii) monophasic low dose preparations: combination of estrogen and progestin in each pill and (iii) triphasic low dose preparations: combination of estrogen and progestin be recommended in order of preference (**based on cost and progestin with low risk of VTE**)

Therapeutic class	INN	DDD	unit	ATC	Price (Contract/SEP)
MONOPHASIC-PROGESTIN ONLY PILLS					
Monophasic-progestin only pills	Levonorgestrel	30	mcg	G03AC03	R 2.27*
Monophasic-progestin only pills	Norethisterone	350	mcg	G03AC01	R 104.19 **
MONOPHASIC LOW DOSE PILLS: COMBINATION OF ESTROGEN AND PROGESTIN IN EACH PILL					
Monophasic low dose preparations: combination of estrogen and progestin in each pill	levonorgestrel and ethinylestradiol	150/30	mcg	G03AA07	R 2.21*
Monophasic low dose preparations: combination of estrogen and progestin in each pill	desogestrel and ethinylestradiol	150/30	mcg	G03AA09	R 85.95**
Monophasic low dose preparations: combination of estrogen and progestin in each pill	desogestrel and ethinylestradiol	150/20	mcg	G03AA09	R 72.96**
Monophasic low-dose preparations: combination of estrogen and progestin in each pill	gestodene and ethinylestradiol	75/ 30	mcg	G03AA10	R 15.00*
Monophasic low-dose preparations: combination of estrogen and progestin in each pill	gestodene and ethinylestradiol	75/ 20	mcg	G03AA10	R101.40**
TRIPHASIC LOW DOSE PREPARATIONS: COMBINATION OF ESTROGEN AND PROGESTIN					
Triphasic low dose preparations: combination of estrogen and progestin	levonorgestrel and ethinylestradiol	50/30; 75/40; 125/30	mcg	G03AB07	R 2.63*
Triphasic low dose preparations: combination of estrogen and progestin	norethisterone and ethinylestradiol	50/35; 75/35; 100/35	mcg	G03AB05	R 85.90**
Triphasic low dose preparations: combination of estrogen and progestin	gestodene and ethinylestradiol	50/30; 70;40; 100/30	mcg	G03AB06	R 96.87**

* Contract circular price: HP03-2015CHM

**SEP Database price, 27 May 2017

Based on cost and lower dose of estrogen and progestin with low risk of VTE (DVT: cyproterone>drosperinone>desogetsrel, norgestimate>gestodene>northethisterone>levonorgestrel)
(PE: desogestrel> drosperinone> cyproterone >norgestimate>gestodene>norethisterone>levonorgestrel

Level of Evidence: II Population based case control studies, Expert opinion

Progestin only pill: *contraindication (myocardial infarction or stroke) not amended*

Meta-analysis of 6 RCTs[34] showed low risk of myocardial infarction (MI) in users of progestin-only-pill (PoP) in healthy patients: Pooled OR 1.07 95% CI 0.62 to1.84. However, SAMF (2016) states that PoPs are contraindicated in patients with arterial thrombosis (MI or stroke).No available studies could be retrieved, where a patient with history of myocardial infarction was given PoP and then outcomes assessed. International, multicenter, case-control study[35] showed little or no increased risk of stroke, venothrombolic events, or acute myocardial infarction associated with the use of oral or injectable progestogen-only or combined injectable contraceptives. However, the study was reported to be underpowered and further investigation into a possible adverse effect on stroke risk of progestogen-only contraceptives used by women with a history of high blood pressure are indicated.

Recommendation: Contra-indication of myocardial infarction or stroke for progestin only oral contraceptives be retained in the STG.

Rationale: Aligned with the SAMF, 2016.

Level of Evidence: III Guidelines

7.3 MISSED PILLS

Combination of progestin and estrogen in each pill**:** *directions for use amended*

Aligned with the NDoH National Contraception Policy, 2012.

Level of Evidence: III Guidelines

7.4 CONTRACEPTION, EMERGENCY

Levonorgestrel, oral: *caution amended*

There is limited evidence for the effect of antiretrovirals on the hormone concentrations in emergency contraception. The recommendation to double the dose of levonorgestrel to 3 g is off-label[36].

A pharmacokinetic study[37] (21 HIV-uninfected women) showed a 56 % (95 % CI 49 to 62) reduction in AUC and 41 % reduction in Cmax of levonorgestrel when taken with efavirenz.

Recommendation: The option of either copper IUCD or double-dose levonorgestrel, oral be recommended as emergency contraception, where women are using concomitant enzyme-inducing medicines.

Rationale: Although copper IUCD would be the preferred emergency contraception, women should be offered a choice. There is limited data to support the off-label use of double-dose levonorgestrel, oral (3 mg) as emergency contraception in women using concomitant enzyme inducers.

Level of Evidence: III Pharmacokinetic study, Expert opinion

Caution in the text of the STG was amended as follows:

CAUTION

Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.

Enzyme inducers (including efavirenz, carbamazepine) cause a significant reduction in LNG concentrations. Women on these medicines should preferably have copper IUCD EC inserted or alternatively double the dose of levonorgestrel, because of significant reduction of LNG EC. Women > 80 kg or BMI ≥ 30 should also be given twice the standard dose.

[34]Chakhtoura, Z., et al. (2011). "Progestogen-only contraceptives and the risk of acute myocardial infarction: a meta-analysis." J ClinEndocrinolMetab**96**(4): 1169-1174.

[35] Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Contraception. 1998 May;57(5):315-24. https://www.ncbi.nlm.nih.gov/pubmed/9673838

[36] Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. Clin Pharmacokinet. 2015 Jan;54(1):23-34. http://www.ncbi.nlm.nih.gov/pubmed/25331712

[37] Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. Infect Dis Obstet Gynecol. 2012;2012:137192. http://www.ncbi.nlm.nih.gov/pubmed/22536010

Levonorgestrel, oral: *directions for use amended*

Double-dose emergency contraception recommended for obese women was considered feasible:

Evidence:

- *Jatlaoui et al, 2016*[38]showed that limited data of poor quality suggests that obesity (>80 kg and/or BMI ≥ 30) was associated with an increased risk of pregnancy with emergency contraception. The following analyses were undertaken:
    - Secondary analysis using LNG data from meta-analysis of 2 RCTs[39]:
        - Between 70 and 80 kg: pregnancy rates rose from2% to 6%.
        - Women <75 kg with various BMI's had a low pregnancy rate of< 2%.
    - Secondary analysis pooled data from 3 RCTs on LNG ECPs[40] found no increase in pregnancy risk with increasing weight or BMI and found no consistent association between pregnancy and both factors when adjusted for other covariates.
- *Edelman et al, 2016*[41]*:* Small pharmacokinetic study (n=10) concluded that "obesity adversely impacts both the levels of LNG EC and this likely explains its lack of efficacy in obese women. Doubling the dose appears to correct the obesity-related PK changes but additional research is needed to determine if this also improves EC effectiveness in obese women".
  "The total LNG Cmax for obese subjects following ECx1 (5.57±2.48 ng/mL) was significantly lower than the level observed in normal BMI women (10.30±2.47, p=0.027). Notably, ECx2 increased the Cmax".

Recommendations:

- Dose of LNG EC be doubled for obese women (> 80 kg with a BMI ≥ 30)

Rationale: Limited data of poor quality suggests that obese women had an increased risk of pregnancy with LNG EC. PK study showed that doubling the dose increases Cmax.

Level of Evidence: II Systematic review of poor quality RCTs, Pharmacokinetic study

Metoclopramide, oral: *not added*

WHO MEC Guidelines, 2015 does not recommend routine antiemetic use.

Rationale: Aligned with WHO MEC Guidelines, 2015.

Level of Evidence: III Guidelines

7.4 VOLUNTARY STERILISATION, MALE AND FEMALE

The following STG was recommended for inclusion to the chapter, as the method of contraception is the users choice:

Voluntary sterilisation is only provided at some primary healthcare facilities with appropriate skills and resources.

Female sterilisation

Also known as tubal occlusion or tubal ligation. This is a permanent, surgical contraceptive method for women who do not intend to have more children.

Women who opt for sterilisation should be adequately counselled and referred.

Male sterilisation

Also known as vasectomy. This is a permanent surgical contraceptive method for men who do not want more any children. Men who opt this method should be adequately counselled and referred.

CAUTION

Sterilisation does 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.

Level of Evidence: III Guidelines[42]

[38]Jatlaoui TC, Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception. 2016 Dec;94(6):605-611.

[39]Glasier A, Cameron ST, Blithe D, Scherrer B, Mathe H, Levy D, Gainer E, UlmannA. Can we identify women at risk of pregnancy despite using emergencycontraception? Data from randomized trials of ulipristal acetate andlevonorgestrel. Contraception. 2011 Oct;84(4):363-

[40]Gemzell-Danielsson K, Kardos L, von Hertzen H. Impact of bodyweight/body mass index on the effectiveness of emergency contraception with levonorgestrel: a pooled-analysis of three randomized controlled trials. Curr Med Res Opin. 2015 Dec;31(12):2241-87.

[41]Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception. 2016 Jul;94(1):52-7.

[42] World Health Organisation. Medical eligibility criteria for contraceptive use, Fifth edition, 2015. http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/

7.5 BREAKTHROUGH BLEEDING WITH CONTRACEPTIVE USE

The following new STG was recommended for inclusion to the chapter, to provide guidance on unscheduled bleeding associated with contraceptive use at primary level of care:

Description

Breakthrough bleeding refers to unscheduled or irregular vaginal bleeding which often presents as spotting, prolonged or frequent bleeding in women using hormonal contraception. The pattern and duration of these unscheduled bleedings vary with the contraceptive method used.

General measures

Pre-hormonal contraceptive counselling must be offered to women regarding possible bleeding patterns, both initially and in the longer term.

Clinical assessment

- Current method of contraception and duration of use.
- Drug interactions.
- Cervical screening history.
- Risk of sexual transmitted infections (e.g. *Chlamydia trachomatis*).,
- Bleeding pattern before starting hormonal contraception since starting and currently.
- Exclude pregnancy.

Medicine treatment

CAUTION

Before starting hormonal contraception, women should be advised about the expected bleeding patterns, both initially and in the longer term.

Hormonal contraceptives causing breakthrough bleeding	**Treatment**
Progestin-only injectables	• COC containing 30 mcg ethinylestradiol, oral, for 14 days.
Progestin subdermal implants	• Ethinylestradiol/levonorgestrel, oral, 30/150 mcg, daily for 20 days.
Combined oral contraceptive pill » Unscheduled bleeding with COC usually settles with time. » Changing to another COC in the 1st 3 months is not recommended.	• Change COC to a COC containing the lowest dose of ethinylestradiol, oral, daily. If bleeding persists: • Change COC to a COC containing 35 mcg ethinylestradiol, oral, daily.

Referral

- » Pelvic pain.
- » Pelvic mass.
- » Heavy menstrual bleeding.
- » Endometrial cancer or hyperplasia.
- » Abnormal Cervix on speculum examination (e.g. polyps)
- » Suspected or confirmed Cervical cancer
- » Postcoital bleeding.

Level of Evidence: III Guidelines[43]

Ibuprofen, oral:*not added*

Tranexamic acid, oral: *not added*

The Committee was of the opinion that breakthrough bleeding with contraceptive use that is not managed on oral combined hormonal contraceptives, should be referred to secondary level of care for further management.

Level of Evidence: III Expert opinion

[43] Faculty of Sexual & Reproductive Healthcare Clinical Guidance: Problematic Bleeding with Hormonal Contraception Clinical Effectiveness Unit, July 2015. https://www.fsrh.org/standards-and guidance/documents/ceuguidanceproblematicbleedinghormonalcontraception/

Available evidence for NSAIDs and tranexamic acid is limited and authors of a Cochrane review[44] concluded: "Several regimens offer promise in regulating bleeding, but findings need to be reproduced in larger trials. The results of this review do not support routine clinical use of any of the regimens included in the trials, particularly for long-term effect". Also, conflicting results were reported regarding NSAIDs ability to treat abnormal bleeding associated with progestin-only contraceptives.

[44] Abdel-Aleem H, d'Arcangues C, Vogelsong KM, Gaffield ML, Gülmezoglu AM. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. Cochrane Database Syst Rev. 2013 Oct 21;(10):CD003449.