

Hormonal contraception and antiretroviral therapy (ART)

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HIV-infected women on successful antiretroviral therapies are faced with issues such as family planning and non-barrier contraception. This requires appropriate counselling that considers the use of oral and hormonal contraceptives. Data from pharmacokinetic studies on ART and hormonal contraceptives are increasing and can provide valuable support in finding the right combination. In this newsletter, we will review various contraceptive products and present recommendations for their use in combination with ART.

Hormonal contraception – an overview

Numerous formulations have become available, including combined oral contraceptives (COCs) in either monophasic or sequential-phasic products, the minipill, depot injection, transdermal patch, vaginal ring and implant.

Monophasic products contain a constant dose of both ethinylestradiol for the estrogen component and a progestin component, taken for 21 days. The progestin component can be a standard one, such as levonorgestrel, chlormadinone acetate or norethisterone, or a new progestogen, such as desogestrel,

drospirenone, gestodene, norgestimate or dienogest. Micropills contain less than 50 µg ethinylestradiol.

Sequential oral contraceptives (usually two- or three-phasic) also contain these estrogen and progestin components, but with sequential dosing to reflect the natural menstrual cycle. QLIRA, ZOLELY are two new products with a novel (four-phasic) formulation and contain estradiol as the estrogen component. Estradiol is a naturally occurring estrogen and not a synthetic estrogen found in other COCs. Its advantage is a natural hormone profile with fewer side effects, but available for a higher cost.

Minipills contain only one progestogen (levonorgestrel oder desogestrel). Discontinuation rates due to side effects, such as break-through bleeding, decrease in libido and acne, are high. Also **depot injections** and **implants** contain only the progestin component. Implants are effective for three years. These consist of a small synthetic rod that is implanted subcutaneously on the inside of the upper arm. The current product is more easily removed using x-ray or computed tomography than previous products. The progestin is

evenly released in miniscule amounts. Its tolerability can be tested using the minipill prior to implantation.

The **vaginal ring** and the **patch** reflect monophasic COCs containing ethinylestradiol (EE) for the estrogen component and etonogestrel or norelgestromin as the progestin component. The vaginal ring is inserted into the vagina and removed after three weeks. In the following seven-day ring-free interval, menstruation sets in.

Risk for venous thromboembolism (VTE)

Since hormonal contraception is not used in the treatment of an illness, but rather for the change of normal bodily function in healthy women, its risk profile has to be evaluated accordingly. All hormonal contraceptives have side effects, for example headache, nausea, weight gain, mood alterations, fatigue, acne and chest pain. Its use is further linked with a thromboembolic risk. This risk is mostly due to the estrogen component and is dose-related, but also in part to the progestin type. The European Pharmacovigilance Risk Assessment Committee (PRAC) published a report on the risk of venous thromboembolism with low-dose combination hormonal contraceptives in 2013 (table 1).

Table 1: Frequency of VTE with low-dose contraceptives

combination	Tradenames (examples)	VTE per 10.000 women years
No use of hormonal contraceptive	–	2
EE + LNG	ASUMATE, MINISISTON, SWINGO	5-7
EE + NET	CONCEPLAN, EVE	5-7
EE + DSG	BELINDA, LAMUNA, PREVIVA	9-12
EE + DSR	AIDA, YASMIN, YAZ	9-12
EE + GES	AIDULAN, FEMODENE, MINULET	9-12
EE + NGM	CILEST, LYSANDRA, PRAMINO	5-7
EE + CMD	BELARA, MADINETTE, VERANA	n.a.
EE + DNG	BONADEA, MAXIM, VALETTE	n.a.
EE + NES	EVRA	6-12
EE + ETG	NUVARING, CIRCLET	6-12
EDV + DNG	QLAIRA	n.a.
EDV + NMG	ZOELY	n.a.

CMD= Chloromadinone acetate; DNG= Dienogest; DSG= Desogestrel; DSR= Drospirenone; EDV= Estradiol valerate; EE= Ethinylestradiol; ETG= Etonogestrel; GES= Gestodene; LNG= Levonorgestrel; MDP= Medroxyprogesterone; NMG= Norgestimate; NES= Norelgestromin; NET= Norethisterone; NGM= Norgestimate; n.a.= not available, no mention in the PRAC-report;

The most commonly used COCs are monophasic with small doses of estrogen (20-35µg), also called micropills. Unlike minipills, they contain estrogen. Drugs of choice also contain standard progestogens, such as levonorgestrel, norethisterone and norgestimate, since these have a lower risk for thromboembolism. Formulations containing chlormadinone and dienogest may be more suitable for women with acne or androgenic symptoms, though the thromboembolic risk profile is difficult to evaluate due to insufficient data. COCs with higher doses of the estrogen components are only to be used in cases of abnormal menstrual cycle with lower-dose pills or in cases of increased estrogen elimination due to drug interactions (e.g. with atazanavir/ritonavir or elvitegravir/cobicistat). Two- and three-phasic pills are less reliable contraceptives and need to be taken accurately as prescribed. Off-label use is not possible, and pills are not interchangeable. Levonorgestrel, the active ingredient in the minipill, requires dose administration at the same time every day. This can be said for all minipills, although desogestrel has a wider time window. All pills in the package have the same dose and are interchangeable. Since these do not have an estrogen component, the risk for thromboem-

bolism may be lower, and they can be taken when breast-feeding. However, currently it is not recommended that HIV-infected women breast-feed.

Depot injections provide contraception lasting for three months. These are only recommended for women that cannot take an oral contraceptive regularly. An additional consideration is the high pill burden associated with antiretroviral therapy. It is important that the next injection is scheduled. Vaginal rings and transdermal patches contain newer progestogens with a thromboembolic risk profile that remains to be clearly defined. Higher concentrations of the estrogen are possible with the patch in comparison to monophasic COCs. Hence the risk for thromboembolism may be higher in the presence of other risk factors. These include: obesity (BMI>30), immobilization for prolonged periods, major surgery, surgery on legs or hips, family history, illnesses associated with VTE (e.g. cancer), systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Morbus Crohn or ulcerative colitis) and sickle cell anemia, as well as increasing age (>35 years). Air travel longer than four hours can increase the risk, especially in women with other factors. Hormonal contraceptives should not be

used in women with several such risk factors, especially if they are older than 40 years.

Case

A 38-year old female patient has been on treatment with efavi-renz/tenofovir/emtricitabine for 5 years. The viral load is undetectable. Her gynecologist wishes to prescribe a micropill, for example Microgynon® (ethinylestradiol (EE) 30 ug, levonorgestrel 150 ug). Can this be combined with efavirenz? What alternatives are available? [5]

Can hormonal contraceptives be co-administered with ART?

Efavirenz: teratogenicity

The product monograph of efavirenz (EFV) states that it is contraindicated in pregnancy due to its teratogenic effects documented in animal studies. [6] A systematic review and meta-analysis of HIV-cohorts in 2010/2011 looked at outcomes in women, who took EFV in the first trimester of pregnancy. It found no increase in birth defects when compared to those exposed to other ART in utero. [7, 8] A review of live births given by HIV-infected women in England and Ireland from 1990 to 2007, who had taken EFV in the first trimester, also found no increased risk for abnormalities. [9] Further research is needed to confirm that pre-partum use of ART poses no additional risk. Until then it is important to inform pregnant HIV-positive patients about the data available. [10] Further information on ART is found in the guidelines for HIV-therapy in pregnancy. [11]

Efavirenz: drug interactions

It is difficult to combine EFV with an oral contraceptive. After co-administering EE 35 µg/norgestimate 25 µg and EFV 600 mg QD for 14 days, EE-concentrations re-mained stable, but those of the norgestimate metabolites decreased by 64 and 83%. [12] A higher dose of norgestimate may need to be considered.

The remaining progestogens, such as desogestrel, [13] levonorgestrel, [14] nore-thindrone, [15] medroxyprogesterone, [16] gestodene [17] and etonogestrel [13] are metabolized via CYP3A4 and can at least

theoretically be affected by the inducing effect of EFV. Drospirenone is not metabolized by CYP3A4^[18] and may in theory be an alternative option, which should be investigated in pharmacokinetic study.

Other antiretroviral agents

1. no interaction:

NRTIs, maraviroc, rilpivirine, etravirine, raltegravir and dolutegravir.^[19]

2. limited potential for interaction:

When combined with atazanavir/ritonavir (ATV/r) and elvitegravir/cobicistat (EVG/Co), it is recommended to choose an oral contraceptive with a high EE-component of > 30 µg.^[20] Both ATV/r and EVG/Co decreased EE concentrations in two pharmacokinetic studies using 25 µg of EE by 19 % and 25 % respectively. Norgestimate concentrations increased by 68 % and 126 % respectively.^[21] Long-term effects of higher norgestimate levels are unknown. It is important to monitor for progestogen-induced side effects, such as acne, lower HDL-cholesterol and higher insulin resistance in women with diabetes mellitus.^[22] The use of contraceptives containing another progestin component (eg. Levonorgestrel) has not been investigated.^[23]

Commercially available products:

Ethinylestradiol 35 µg /norgestimate: Amicette®, Lysandra beta®, Cilest® and Pramino® were taken off the market due to a slightly slower release.^[24]

Ethinylestradiol 30 µg/levonorgestrel: Levostrol®, Microgynon®, Madonella®, Ov-ranette®, Selina®

3. data on progestogen-containing oral contraceptives:

In a pharmacokinetic study, 15 subjects on a PI-containing ART-regimen (ATV/r (n=10), ATV (n=1), lopinavir/ritonavir (LPV/r) (n=3), darunavir/ritonavir (DRV/r) (n=2)) were also given 0.35 mg norethindrone. Norethindrone levels were found to be 50 % higher than in controls. There was no change in half-life. The higher concentrations were explained by the inhibitory effect of protease inhibitors on CYP3A4, the primary elimination pathway for norethindrone.^[25] Nore-

thindrone has a broad therapeutic window. Some products with EE contain 1.5mg norethindrone, which is more than four times the dose found in a pill containing only the latter (0.35 mg). The range of norethindrone concentrations in this study was comparable to those found in earlier clinical trials. Therefore this may provide an option for women on protease inhibitor-based ART.

Commercially available products:

Norethisterone 0,35 mg (Norethindrone): Noriday®, Micronovum®

Depot Injection

As indicated by pharmacokinetic study, the combination of depot medroxyprogesterone acetate (DMPA) with LPV/r, EFV and nevirapine (NVP) is possible.^[15] No significant changes in EFV concentrations were seen four weeks after administering DMPA in 17 HIV-infected women. NVP levels slightly increased in 16 HIV-positive women. After 12 weeks, there were no cases of pregnancy nor of progesterone-induced ovulation. DMPA did not affect CD4 cell count or HIV-RNA.^[26,27] LPV/r can also be combined with DMPA. Its use in 24 HIV-infected women had a good tolerability and no ovulation. DMPA concentrations were 46 % higher than in historical controls, but the side effect profile was comparable. One needs to monitor for toxicity.^[28] Also, bone density should be measured regularly. Reduced estrogen levels for over a year can reduce bone density.^[5,29]

Transdermal patch Evra® (Ethinylestradiol und norelgestromin)

The pharmacokinetics of the transdermal patch (EE und norelgestromin (NGMN)) were studied in 8 HIV-positive women on LPV/r and 24 HIV-negative controls. Additionally, EE-levels were measured after a single dose of a COC (EE/ Norelgestromin) prior to applying the patch and compared to those after its application. Co-administration of LPV/r reduced median EE-concentrations by 45 % with the patch and by 55 % with the pill. The concentration of the progestin component in the patch (NGMN) increased by 83 % with LPV/r. Vogler et al. concluded that despite the altered kinetics of EE and NGMN with LPV/r, the contraceptive effect of the patch is maintained.^[34]

Vaginal ring: NuvaRing® (Ethinylestradiol und Etonogestrel)

It is recommended that the vaginal ring not be used with ART^[35] due to the absence of data and the theoretical potential for interactions. können.

Implant: Implanon® (Etonogestrel)

A study in Kenia with 33 women documented no pregnancy when Implanon® was combined with NVP,^[36] indicating that this combination may be possible. Failure of contraception when combined with EFV has been reported. There are not data on its use with other antiretroviral agents, leading to the recommendation to avoid concomitant use.^[37] In addition, it should be noted that the implant rod is often difficult to remove.

Intrauterine devices

Intrauterine devices that do not contain hormones can be used with ART. IUDs containing hormones (Mirena®-Levonorgestrel) or copper can be used with ART in theory, because the device itself already has contraceptive properties. wirkt.

Conclusion

Micropills can be administered with NRTIs, maraviroc, rilpivirine, etravirine, raltegravir and dolutegravir. When treated with ATV/r or EVG/c, a COC with ethinylestradiol > 30 µg and norgestimate can be considered. The depot injection can be combined with NVP and LPV/r, the patch with LPV/r.

The „morning-after-pill“-PiDaNa® (Levonorgestrel)/Ellaone® (Ulipristal)

Levonorgestrel should be taken within 72 hours after sexual intercourse. Protease inhibitors are expected to increase levonorgestrel levels. With EFV they decreased by 54 %. Literature has suggested an off-label recommendation of doubling the levonorgestrel dose to 3mg with EFV.^[38] Ulipristal is metabolized by CYP3A4. CYP3A4 inducers, eg. EFV and NVP, can therefore reduce Ulipristal levels in theory and hence its efficacy. Combining these agents would be difficult.^[39,40]

Potential drug interactions between ART and hormonal contraceptives						
	Oral contraceptive estrogen/progestogen	Oral contraceptive progestogen	Depot injection (DMPA)	Transdermal patch	Vaginal ring	Morning-after-pill PiDaNa®, Ellaone®
NRTIs						
TDF/3TC		n. d.	n. d.	n. d.	n. d.	n. d.
PIs						
ATV/r 300/100 mg QD [20, 21, 25]	Amicette®, Lysandra® EE: ≥ 30 ug, proges-togen tested: NGM, monitor for toxicity	small n possible, NED 50 % ↑	n. d.	n. d.	n. d.	theoretical ↑ in progestogen
DRV/r DRV/C 600/100 mg BID [19, 25, 32]	DRV/r: EE-Cmin ↓ 62 %, NED-Cmin ↓ 30 % .	DRV/r small n possible, NED 50 % ↑	n. d.	n. d.	n. d.	n.d. DRV/r theoretical ↑ in progestogen
FPV/r [19]	APV-Cmin 20%, possible reduced efficacy EE-Cmin ↑ 45 %, NED-Cmin: ↑ 18 %	n. d.	n. d.	n. d.	n. d.	
LPV/r [19, 25]	EE-C min ↓ 58 % NED-Cmin ↓ 32 %	small n: possible, NED 50 % ↑	possible, monitor for toxicity	contraceptive efficacy	n.d.	theoretical ↑ in progestogen
NNRTIs						
EFV [19, 14]	Potentially reduced progestogen levels EE, norgestimate unchanged, active metabolites: norelgestromine ↓ 64 %, L ↓ 83 % [2]	L ↓ 54 %	possible, monitor for toxicity	n.d.	n.d.	L ↓ 54 %
NVP [19]	1. EE: AUC ↓ 20 %, NED: AUC ↓ 19 % [16] 2. EE: AUC ↓ 29 %, NED: AUC ↓ 18 % [33]	n.d. theoreticall induced progestogen elimination	possible, monitor for toxicity	n.d.	n.d.	n.d.
ETV [19]	EE ↑ 22 %, NED Cmin ↓ 22 % => possible	n.d.	n.d.	n.d.	n.d.	n.d.
RLV [19]	EE ↑ 17 % NED unchanged	n.d.	n.d.	n.d.	n.d.	n.d. theoretically possible
CCR5 INH						
MVC [19] 100 mg 2 x tgl.	EE, L unchanged No data on MVC 300 mg BID. [3]	n.d.	n.d.	n.d.	n.d.	n.d.
IGH						
RAL [19]	EE, NGM-metabolite unchanged	n.d. theoretically possible	n.d.	n.d.	n.d.	n.d. theoretically possible
EVG/Co [19, 20]	Amicette®, Lysandra® EE: > 30 ug EE, studied progestogen: NGM, monitor for side effects	theoretical ↑ in progestogen	n.d.	n.d.	n.d.	theoretical ↑ in progestogen
DTG [15]	EE, NGM-metabolite unchanged	n.d. theoretically possible	n.d.	n.d.	n.d.	n.d. theoretically possible

Ethinylestradiol (EE) / Norethindrone (NED) o. Norgestimate (NGM) o. Levonorg-estrel (L), no data (n.d.)
 may combine contraindicated combination possible on the basis of available data or theoretical consideration
1. No data, but potentially possible on the basis of theoretical consideration
2. Insufficient data



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