1. Contraception in women living with HIV
2. Hormonal contraceptives and drug interactions

Advanced slide kit complementing the WHO training tool www.fptraining.org

Updated May 2023 K. Sedlecky / F. Roumen / G. Merki / A. Kubba

Part 1
Women with HIV infection

This advanced slide kit is complementing the WHO training tool which can be found at www.fptraining.org

Update May 2023 K.S., F.R., G.M., A.K.

Contents
Part 1 HIV

- Main characteristics of HIV infection, classification and clinical stages of HIV infection
- Concerns regarding contraception:
  - Possible impact on progression of HIV infection
  - Impact on HIV transmission and acquisition
  - Potential risks related to HIV infection/AIDS
  - Drug interactions

Epidemiology of HIV infection

Estimates	Number of people living with HIV in 2019	38.0 (31.6–44.5) million
	Number of women (15+) living with HIV in 2018	18.8 milion
	HIV prevalence in 2017	- higher in women across Sub-Saharan Africa - higher in men across most other regions
	Women with HIV on antiretroviral therapy (ART) in 2019	73% (60-86%)

As a consequence of the improvements in life expectancy with combined ART, contraception and reproductive issues have become increasingly important.

Ref 1-2

Stages of untreated HIV infection

CD4+T
500 - 1,600
cells/mm^3

Acute HIV Infection (2-4 weeks)

acute retroviral syndrome

the greatest risk for HIV transmission

Chronic HIV Infection (~ 8 years)

asymptomatic HIV infection or clinical latency

AIDS (Acquired immune deficiency syndrome)

CD4+T count < 200 cells/mm^3 and/or one or more opportunistic infections or related cancers

CD4+T
< 200 cells/mm^3

HIV transmission

Concerns regarding contraception

- Possible impact on progression of HIV infection
- Impact on HIV transmission and acquisition
- Potential risks related to HIV infection/AIDS
- Drug interactions

Dual protection is needed

Possible impact of contraceptives on progression of HIV infection

Theoretical mechanisms by which contraception reduces the effect of antiretroviral treatment (ART) on HIV progression:

1. Drug-drug interactions?

Lower concentrations of some antiretrovirals (e.g. efavirenz, ritonavir, nelfinavir, atazanavir) with hormonal contraception (HC).

No evidence for a reduction in the efficacy of ART by HC.

2. Additional suppression of the immune system by contraception?

No major changes in CD4 count/viral load/HIV RNA levels or clinically relevant outcomes with:

CHC, DMPA, LNG implants, copper-IUD, LNG-IUS

Ref 1-9

Influence of contraception on HIV transmission and acquisition

World Health Organization (WHO) recommended ART for all persons living with HIV infection.

ART contributes the most to reducing the risk of HIV transmission in serodiscordant couples.

Risk for HIV transmission and acquisition:

- in DMPA users very likely increased by 40 - 50% – related to HSV-2 infection?
- other hormonal contraceptive methods – not changed

⟶ In order to reduce the risk of HIV transmission or acquisition regular condom use should be strongly recommended, particularly in women who use DMPA.

Ref 1-6

Potential risks related to HIV infection/AIDS

- Reduced contraceptive efficacy due to drug-drug interactions (treatment of HIV and HIV-related diseases)

** The rate of unintended pregnancy remains lower in women using hormonal contraception compared to women not using contraception.*

** The efficacy of LNG-IUS is not reduced.*

- Increased risk for venous thromboembolism (VTE) due to HIV disease, ART, co-morbidities/infections, smoking/alcohol intake
- HIV infection increases the risk of cardiovascular diseases

Safety of IUD use in HIV positive women according to WHO Medical eligibility criteria

Condition	Copper-IUD		LNG-IUS	
	I	C	I	C
High risk of HIV (if also at risk of STIs)	1 (2/3)	1 (2)	1 (2/3)	1 (2)
Asymptomatic or mild HIV clinical disease	2	2	2	2
Severe or advanced HIV clinical disease ** IUD users should be closely monitored for pelvic infection*	3	2	3	2

Safety of IUD/IUS use among women with HIV

Pelvic infections

- no statistically significant difference in infection-related complications between IUD/IUS users with and without HIV
- rates of symptomatic PID with IUD are low

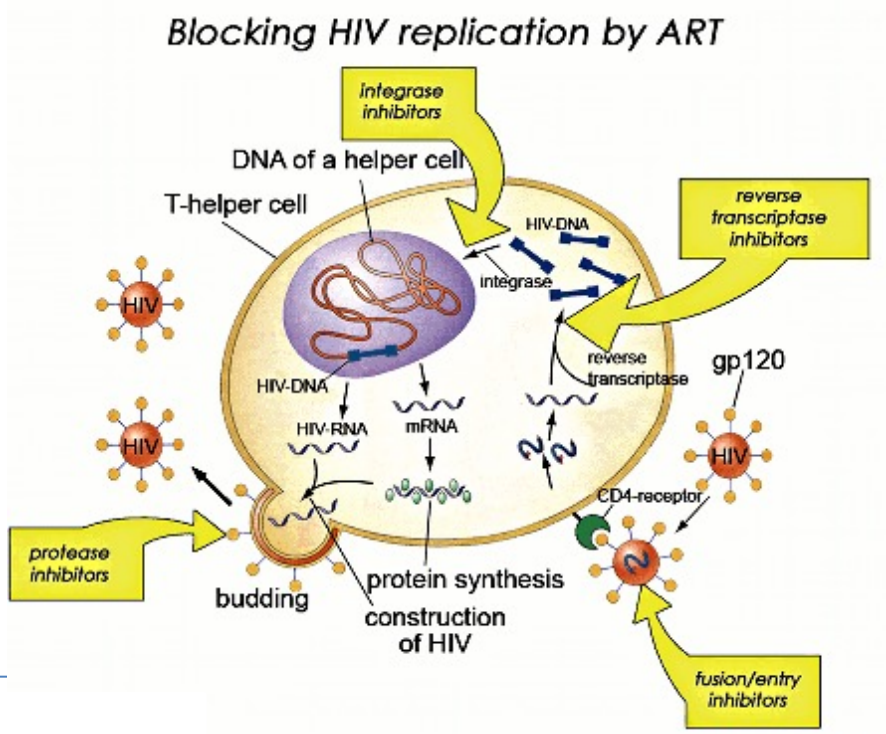
* Screening for at least chlamydia and gonorrhoea is necessary before inserting a copper-IUD/LNG-IUS

* Laboratory STI screening can be replaced in resource poor areas by syndromic screening and treatment of all STIs presenting within the certain syndrome

Ref 1-3

Classes of antiretroviral drugs

- reverse transcriptase inhibitors: non-nucleotide (NNRTIs) & nucleotide (NRTIs)
- protease inhibitors (PIs)
- fusion / entry inhibitors
- Integrase inhibitors (INSTIs)



Some of these drugs increase metabolism of hormonal contraceptives

Antiretroviral therapy (ART)

- **First-line ART for adults (WHO recommendations):**

  - two NRTIs + NNRTI or INSTI

Example: tenofovir disoproxil fumarate (TDF), lamivudine and efavirenz / nevirapine, PIs (e.g. lopinavir, atazanavir, darunavir, all boosted with ritonavir), or INSTI (e.g. dolutegravir, elvitegravir, raltegravir)

* *Fusion inhibitors (enfuvirtide), gp120 attachment inhibitor (fostemsavir), CCR5 inhibitor (maraviroc) and post-attachment inhibitor or monoclonal antibody (ibalizumab) - used in salvage therapy(for HIV-infected people who do not respond favorably to common treatment regimens)*

Ref 1

Nucleotide reverse transcriptase inhibitors

Effect on metabolism of hormonal contraceptives

- zidovudine
- stavudine
- lamivudine
- abacavir
- tenofovir disoproxil fumarate
- didanosine

renally eliminated, no CYP450 metabolism

no relevant effects on hormonal contraception

May cause pharmacodynamic interactions when used with certain drugs (e.g. tenovir co-administration with nephrotoxic agents)

Ref 1-3

Non-nucleotide reverse transcriptase inhibitors

Effect on metabolism of hormonal contraceptives

Non-nucleotide reverse transcriptase inhibitors	Effect on ethinyl oestradiol	Effect on progestin	Contraceptive efficacy
nevirapine	significant ↓	insignificant ↓	possibly decreased
efavirenz	insignificant	significant ↓	decreased for all HC
etravirine	insignificant	insignificant	not decreased
rilpivirine	insignificant	insignificant	not decreased

Ref 1-5

Protease inhibitors boosted with ritonavir/cobicistat
Effect on metabolism of hormonal contraceptives

Protease inhibitors boosted with	Effect on ethinyl - oestradiol	Effect on progestin	Contraceptive efficacy of COC	Contraceptive efficacy of POC
ritonavir	significant ↓	insignificant ↑	maintained in ≥30µg EE COC	not decreased
cobicistat	insignificant ↓	significant ↑	not decreased	not decreased

Note: Atazanavir boosted with ritonavir or cobicistat is contraindicated with drospirenone containing HC due to potential for hyperkalaemia. Other protease inhibitors boosted with cobicistat increase the risk for drospirenone-associated hyperkalaemia.

Ref 1-5

Entry inhibitors and integrase strand transfer inhibitors

Effect on metabolism of hormonal contraceptives

Entry inhibitor (Ei) / integrase strand transfer inhibitor (Insti)	Effect on ethinyl - oestradiol	Effect on progestin	Contraceptive efficacy of COC	Contraceptive efficacy of POC
Ei maraviroc	insignificant	insignificant	not decreased	not decreased
Insti elvitegravir/cobicistat	significant ↓	significant ↑	maintained in ≥30µg EE COC	not decreased
Insti raltegravir, dolutegravir, cabotegravir	insignificant	insignificant	not decreased	not decreased

Note: Stribild® (elvitegravir/cobicistat/ tenofovir/emtricitabine) may increase the risk for drospirenone-associated hyperkalaemia.

Ref 1-5

Emergency contraception and ARV

- **Levonorgestrel** – double dose (3 mg) should be given (off-label) if enzyme-inducing ARV
- **Ulipristal acetate** – enzyme-inducing ARV (efavirenz, etravirine) decrease efficacy of UPA – double dose (60 mg) should be given (off-label)
- **Copper-IUD** is an option in those cases

Ref 1-5

Pre-exposure prophylaxis (PrEP)

- Tenofovir disoproxil fumarate and emtricitabine (Truvada®) – No significant effect on efficacy of HC

Post-exposure prophylaxis (PEP)

- WHO recommended regimen: a combination of two NRTIs (tenofovir combined with either lamivudine or emtricitabine) and ritonavir-boosted lopinavir - No significant effect on efficacy of HC

Ref 1

Part 2
Hormonal contraceptives and drug interactions

Advanced slide kit complementing the
WHO training tool www.fptraining.org

Contents
Part 2 Drug - drug interactions

- Resorption of steroid contraceptive hormones
- Metabolism of steroid contraceptive hormones
- Interactions of hormonal contraception with:
  - anti-epileptic drugs
  - psychotropic drugs
  - opioids and psychostimulants
  - antibiotics
  - other drugs
  - herbal remedies
- Direct effect on the efficacy of hormonal contraception

Resorption of steroid contraceptive hormones

- **Ulipristal acetate emergency contraception -** reduced resorption by drugs that increase gastric pH *(proton pump inhibitors, antacids and H2-receptor antagonists)*
- **COC and POC** – reduced resorption of ethinyl-oestradiol (EE) and progestins by laxatives, medications inducing vomiting or diarrhoea, activated charcoal
- **EE/nestorone contraceptive vaginal ring -** reduced systemic exposure to EE and nestorone by miconazole suppositories

Ref 1-2

Metabolism of ethinyl-oestradiol and progestins

ORAL BIOAVAILABILITY:

- Ethinyl-oestradiol 20-65%
- Progestins 70-100%

METABOLISM:

- Ethinyl-oestradiol - 30% by hydroxylation (CYP3A4 and CYP2C9) and 58% by conjugation via sulphation and glucuronidation
- Progestins (variations) - hydroxylation / conjugation

Ref 1-2

Impact of hormonal contraception on the metabolism of other drugs

COMBINED ORAL CONTRACEPTIVES *(due to the effect of EE)*:

- moderate inhibitors of CYP1A2 and weak inhibitors of CYP3A4, CYP2C19 and CYP2D6 enzymes
- inducers of UGT enzymes (conjugation via glucuronidation)

PROGESTINS:

- no impact on the activity of CYP450 enzymes

Impact of hormonal contraceptive route on contraceptive efficacy with concomitant use of CYP3A4-inducing drugs

Contraceptive product	ROR (95% CI)
Ethinyl oestradiol/levonorgestrel oral	4.2 (3.0–5.7)
Levonorgestrel intrauterine device	0.9 (0.6–1.3)
Levonorgestrel implant	8.0 (5.8–11.0)
Ethinyl oestradiol/desogestrel (pro-drug) oral	0.6 (0.2–1.8)
Etonogestrel vaginal ring	1.3 (0.8–2.0)
Etonogestrel implant	4.9 (4.0–5.9)

Ref 1

Interactions between drugs and hormonal contraception

What magnitude of change in pharmacokinetics of hormonal contraception is considered

- **clinically irrelevant?** Range within 80%–125% (90% CI)*
- **clinically important?** Range <80% or >125%

* In the absence of any pharmacodynamic data to suggest otherwise

Ref 1

Antiepileptics

Antiepileptic drug (AED)	Changes in serum concentration of AED	Changes in serum concentration of ethinyl-oestradiol	Changes in serum concentration of progestin
Strong enzyme inducers			
Carbamazepine	no data	decrease	decrease
Felbamate	no data	decrease	decrease
Eslicarbazepine	no data	decrease	decrease
Oxcarbazepin	no data	decrease	decrease
Primidone	no data	decrease	decrease
Phenobarbitone	no data	decrease	decrease
Phenytoin	no data	decrease	decrease
Topiramate	no data	decrease*	none**
Perampanel	no data	none	decrease*

** dose-dependent effect*

*** possibly decrease with 75 mcg desogestrel-only POP*

Antiepileptics

Antiepileptic drug (AED)	Changes in serum concentration of AED	Changes in serum concentration of ethinyl-oestradiol	Changes in serum concentration of progestin
Weak enzyme inducers			
Lamotrigine	decrease	none	decrease
No enzyme inducers			
Valproate	decrease	none	none
Gabapentin	no data	none	none
Lacosamide	none	none	none
Levitiracetam	none	none	none
Zonisamide	none	none	none
Retigabine/ ezogabine	none	none	none
Pregabalin	no data	no data	no data
Vigabatrin	none	none	none

Ref 1-3

Example: A patient on monotherapy with lamotrigine. Can she use combined oral contraception?

COMBINED ORAL CONTRACEPTION ⇄ **LAMOTRIGINE**

7% decreased AUC of EE

19% decreased AUC of levonorgestrel (increase in FSH and LH, ovulations not detected)

App. 50% decrease in lamotrigine concentration in plasma (induced by EE)

App. a twofold increase in serum concentration of lamotrigine in hormone-free period

WHO Medical eligibility criteria category 3

Ref 1-3

Lamotrigine levels in non-oral combined hormonal contraceptive users

- VAGINAL RING – in 5 of 6 users dose - corrected lamotrigine concentrations decreased from 36% to 70%
- TRANSDERMAL PATCH - one patient had a decrease of 37% in dose - corrected lamotrigine concentration

Ref 1

Lamotrigine and combined hormonal contraception (CHC) – Role of progestin

Progestin in COC	LTG serum concentrations (ng/mL)		*p*-Value
	End of the week of inactive pill use	The third week of active pill use	
Drospirenon	3.1 ± 1.2	1.6 ± 0.7	0.018
Levonorgestrel	8.1 ± 4.7	4.2 ± 4.6	0.068
Gestoden	9.8 ± 7.9	8.6 ± 12.4	0.593

Lamotrigine does not decrease the progestin levels, there is no concern related to contraceptive efficacy.

Ref 1

Contraception in women treated with lamotrigine
Combined hormonal contraception (CHC)

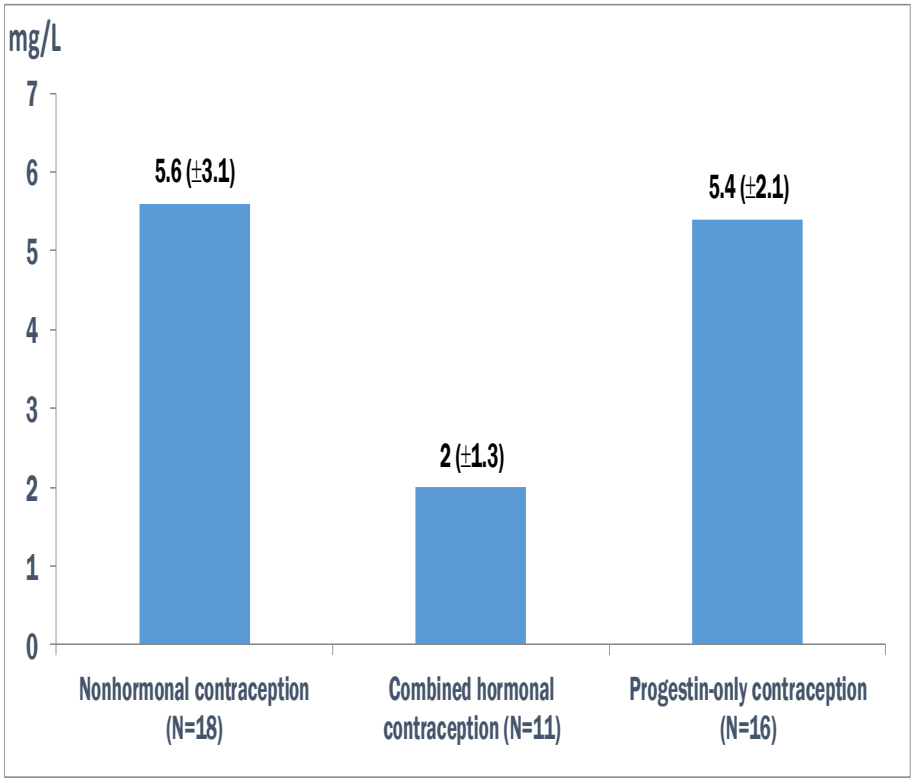
- CHC can only be used continously (long-cycle) and lamotrigine dosing has to be adapted, related to the interaction with EE (plasma level control)
- This needs collaboration with the neurologist in newstarters
- Before stopping CHC the lamotrigine dosage has to be adapted again in collaboration with the neurologist!
- It is important that the woman understands this and will not stop without contacting her doctors.

Ref 1

Contraception in women treated with lamotrigine
Progestin only contraception (POC)

- At present an interaction with POC has only been found for drospirenone*
- Continuous POC use is possible without adapting the lamotrigine dose (drospirenone is an exception!) and might be the favored option for less compliant women or, if they have no access to a neurologist surveilling plasma levels of lamotrigine.

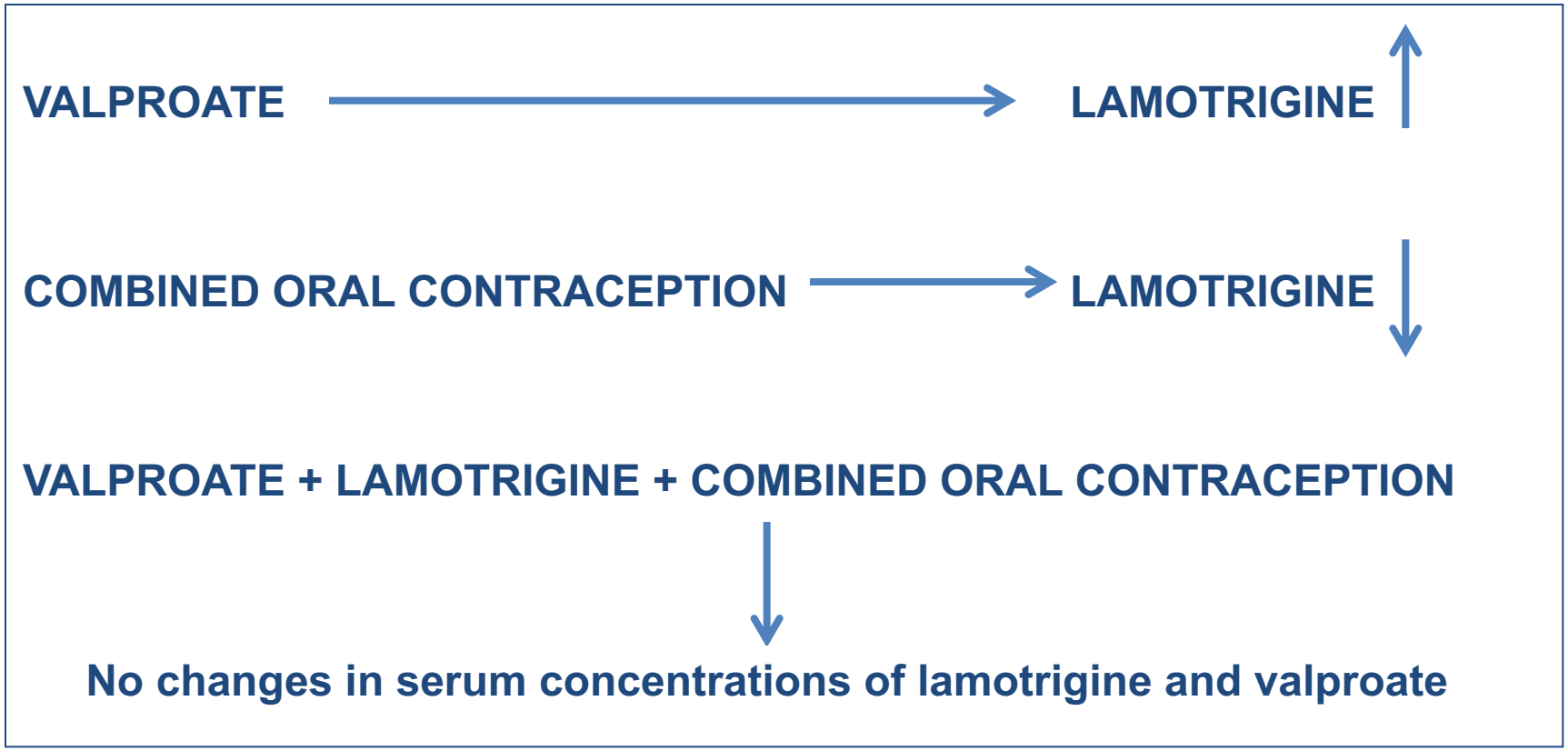
Serum concentrations of lamotrigine at identical doses



Note* Drospirenone will decrease the level or effect of lamotrigine

Ref 1-4

Example: A patient on combination therapy with valproate and lamotrigine. Can she use combined oral contraception?



YES

Contraceptive options for women taking antiepileptic drugs, which interact with CHC and POC metabolism

How to increase contraceptive efficacy of CHC :

- ≥ 30 mcg EE
- Extended regimens / continuous cycling

The most effective contraceptive options:

- DMPA, copper-IUD, LNG-IUS

Be cautious - less effective contraceptive methods:

- desogestrel-only pill, the progestin-only implant

Interactions with psychotropic drugs

The most common mental health disorders in women of reproductive age are

- **DEPRESSION**
- **ANXIETY DISORDER**

Psychotropic drugs:

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin-norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- oral benzodiazepines
- bupropion, mirtazapine, trazadone, buspirone, hydroxyzine, monoamine oxidase inhibitors (MAOIs)
- atypical antipsychotics

Interactions with psychotropic drugs (I)

Psychotropic drug	Changes in serum concentration of psychotropic drug	Changes in serum concentration of estrogen/progestin
Selective serotonin reuptake inhibitors (SSRIs)		
fluoxetine, citalopram	none	none
vortioxetine	none	decrease of EE and increase of progestin
fluvoxamine	none	increase of EE and progestin*
Tricyclic antidepressants (TCAs)		
clomipramine	none	none
imipramine	app. two - fold increase*	none
amitriptyline	app. two - fold increase*	none

* ***The increase in dose might be clinically relevant***

Ref 1

Interactions with psychotropic drugs (II)

Psychotropic drug	Changes in serum concentration of psychotropic drug	Changes in serum concentration of estrogen/progestin
Atypical antidepressant		
bupropion	modest decrease	none
Atypical antipsychotics		
ziprasidone	none	none
olanzapine	modest decrease with CHC; no changes with POC	none
lurasidone	none	none
clozapine	app. two-fold increase*	none
duloxetine	no data	no data
mirtazapine	no data	no data

** Might cause clozapine toxicity*

Ref 1-2

Interactions with psychotropic drugs (III)

Psychotropic drug	Changes in serum concentration of psychotropic drug	Changes in serum concentration of estrogen/progestin
Oral benzodiazepines		
oxazepam	decrease	no data
lorazepam	decrease	no data
temazepam	decrease	no data
triazolam	none	no data
alprazolam	increase	no data
chlordiazepoxide	increase	breakthrough bleeding*
meprobamate	no data	breakthrough bleeding*

No pregnancies were detected in a study, but reduced contraceptive efficacy can not be excluded

Ref 1-2

Interactions with opioids and psychostimulants

Drug type	Changes in serum concentration of drug	Changes in serum concentration of estrogen/progestin
Opioids		
hydrocodone	increase	none
meperidine	increase	none
oxycodone	increase	none
tramadol	increase	none
codeine	decrease	none
hydromorphone	decrease	none
morphine	decrease	none
oxymorphone	decrease	none
cannabis	no data	no data*
Psychostimulants		
modafinil	none	decrease**

** Refer to the comment in the note*

*** Efficacy of hormonal contraception reduced with modafinil*

Ref 1-4

Conclusion

Interactions with psychotropic drugs, opioids and psychostimulants

- Contraceptive efficacy of CHC and POC:
  - is reduced with modafinil
  - might be reduced with chlordiazepoxide and meprobamate
  - no data exist for cannabis
- The increase of EE/progestin in CHC users treated with fluvoxamine might be clinically relevant
- Adjustment of the therapeutic dose in users of CHC may be necessary for some tricyclic antidepressants (imipramine, amitriptyline), bupropion, olanzapine, and many opioids
- CHC users may be more sensitive to the psychomotor effects of benzodiazepines

Interactions with antibiotics (I)

Antibiotic	Changes in serum concentration of antibiotic	Changes in serum concentration of estrogen/progestin
Rifamycin		
rifamycin, rifabutin	none	decrease of EE and progestin*
Non-rifamycin antibiotics		
Penicillins and cephalosporins		
ampicillin	insignificant decrease	none
cephaloridine	insignificant decrease	none
Tetracyclines		
tetracycline	none	none for EE, increase of progestin**
doxycycline	none	none
oxtetracycline	no data	no breakthrough bleeding

**** Hormonal contraception should not be prescribed***
***** Not clinically relevant***

Ref 1-3

Interactions with antibiotics (II)

Antibiotic	Changes in serum concentration of antibiotic	Changes in serum concentration of estrogen/progestin
Fluoroquinolones		
ciprofloxacin, temafloxacin, ofloxacin	none	none
trovafloxacin, moxifloxacin	decrease	none
Macrolides		
erythromycin	no data	increase
dirithromycin	no data	decrease of EE
azithromycin	increase*	none**
clarithromycin	no data	none
roxithromycin	no data	none

**** Further investigations needed to assess if this is clinically significant***
***** According to European leaflet for azithromycin***

Ref 1-3

Interactions with other antibiotics (III)

Antibiotic	Changes in serum concentration of antibiotic	Changes in serum concentration of estrogen/progestin
metronidazole	no data	none
sulfamethoxasole/trimethoprim	no data	breakthrough bleeding*
nitrofurantoin	no data	none
dapsone	no data	increase of EE, no changes for progestin*
griseofulvin	none	decrease of EE, no changes for progestin**

** Refer to the comment in the note*
*** Possibly reduced efficacy of CHC*

Ref 1-4

Conclusion

Interactions with antibiotics

- Contraceptive efficacy of CHC and POC:

  - is reduced with rifamycin antibiotics and possibly with griseofulvin

  - is not significantly changed with other antibiotics

- Changes in serum concentration of antibiotics in CHC users may be considered as not clinically significant

Interactions with other drugs

Drug	Changes in serum concentration of drug	Changes in serum concentration of estrogen/progestin
isotretinoin	none	decrease in both EE and progestin*
aprepitant	none	decrease in both EE and progestin*
bosentan	decrease	decrease in both EE and progestin*

** Reduced contraceptive efficacy of hormonal contraception*

Ref 1-3

Interactions with antifungals and herbal remedies

Drug	Changes in serum concentration of drug	Changes in serum concentration of estrogen/progestin
Antifungals		
fluconazole **ketokonazole** **voriconazole** **posakonazole**	**increase of voriconazole**	**increase in both EE and progestin***

**** Clinically significant interactions - It is better to prescribe POC or CHC with low doses of EE in women on long-term antifungal treatment and avoid COC containing drospirenone because of the increased risk for hyperkalemia.***

Ref 1-3

Interactions with St. John's wort (*Hypericum perforatum*)

- A common therapy for depression - a strong inducer of CYP3A4 and weak inducer of CYP2C9 enzymes
- With concomitant use of St. John's wort contraceptive efficacy:

  - reduced in CHC and POC users (dose-dependent effect) - additional contraception needed

** The greatest risk for a clinically significant interaction – use of low-dose COCs or POPs and progestin implant*

** For DMPA users shortening of the injection interval may be an option*

- unchanged in users of copper-IUD and LNG-IUS – better choice

Ref 1,2

Interactions between ulipristal acetate (UPA) and hormonal contraception (I)

- Ulipristal acetate (30 mg) administered for emergency contraception in the mid to late follicular phase (within 120 hours after unprotected sexual intercourse) delays ovulation for 5 days in 97% of women.
- If desogestrel (POP) was initiated next day after UPA, ovulation occurred in 45% of women within first 5 days.
- If COC (30 μg EE/150 μg levonorgestrel) was initiated 2 days after UPA, ovulation within first 5 days occurred in 27% of women.
- If UPA is administered after missing up to three pills of COC, immediate restart significantly reduces a theoretical risk of pregnancy at any time in that cycle (before the end of the cycle ovulated 0/26 of women with immediate restart vs. 4/23 or 17.4% of women who delayed 5 days to restart COC)

Ref 1-3

Interactions between ulipristal acetate (UPA) and hormonal contraception (II)

- COC and POC decrease the efficacy of UPA if started within first five days after UPA
- Do not start CHC or POC earlier than 5 days after UPA
- *Exception: in the case of women having missed up to three pills of COC, immediate restart after UPA significantly reduces the risk of pregnancy in that cycle (or copper-IUD can be inserted as EC)*

Interactions between emergency contraception and other drugs

LEVONORGESTREL:

- Strong to moderate interaction with efavirenz, oxcarbazepine, eslicarbazepine, carbamazepine, phenytoin, weak with lamotrigine

ULIPRISTAL ACETATE:

- Increased plasma levels with erythromycin and ketoconazole
- Decreased plasma levels

- strong interaction with enzalutamide, mitotne, phenytoin, rifampicin
- moderate interaction with carbamazepine, bosentan, dabrafenib, efavirenz, etravirine, lesinurad, lumacaftor, modafinil, pentobarbital, phenobarbital, rifabutin, St. John's Wort (higher doses)
- weak interaction with armodafinil, eslicarbazepine, oxcarbazepine, pioglitazone, rufinamide, vemurafenib

Ref 1