FSRH The Faculty of Sexual & Reproductive Healthcare

Clinical Guidance: Drug Interactions Between HIV Antiretroviral Therapy (ART) and Contraception

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Drug Interactions Between HIV Antiretroviral Therapy (ART) and Contraception (February 2023)

1. Introduction

Key Information	
☑	For people who take antiretroviral therapy (ART), hormonal contraceptive options may be affected by drug-drug interactions (DDIs).
☑	Many safe and effective contraceptive options exist for people living with HIV on ART, despite some potential adverse pharmacokinetic DDIs between hormonal contraception and some antiretroviral drugs.
☑	The contraceptive effectiveness of the depot medroxyprogesterone acetate (DMPA) injectable, the levonorgestrel-releasing intrauterine device (LNG-IUD) and the copper intrauterine device (Cu-IUD) is considered to be unaffected by DDIs with ART. All offer very effective contraception.
☑	Where there are significant DDIs that prevent a person choosing their preferred method of contraception, and there is a clinically appropriate alternative ART, an ART switch should be considered.
☑	For people at-risk of sexually transmitted infections (STI), condoms are recommended for STI prevention. Condoms also reduce the risk of HIV transmission from a partner living with HIV who is not on suppressive ART.
Suggested good practice points	
☑	HIV care and contraception providers should take a detailed medication history at every visit.

HIV is a chronic, long-term, manageable condition, and people living with HIV will take antiretroviral therapy (ART) to maintain viral suppression throughout their reproductive years, and beyond. Providing safe, effective contraception that is in line with a person's contraceptive preferences is important to support a safe and fulfilling sexual and reproductive life. In addition, HIV-negative people of reproductive age may be prescribed antiretroviral drugs as part of HIV pre-exposure prophylaxis (PrEP)[1] or HIV post-exposure prophylaxis (PEP),[2] and need contraceptive advice.

This guidance is relevant to all people at risk of pregnancy and taking ART. It provides information on expected or potential drug-drug interactions (DDIs) between ART for the prevention and management of HIV infection, and contraception. Such DDIs could potentially affect exposure to contraceptive hormones, and therefore impair contraceptive effectiveness or impact contraceptive safety, or could potentially alter the effectiveness and safety of ART.

It is essential that contraceptive providers always take a careful medication history and check for potential DDIs before prescription of contraception. Where a patient is taking ART for HIV treatment or prevention, the prescribing clinician should **check for potential DDIs with each individual drug component of the ART regimen**. In addition to this FSRH CEU guidance document, it is recommended that patients and clinicians use comprehensive and regularly updated DDIs resources such as the University of Liverpool HIV Drug Interaction Checker[3] and the British National Formulary (BNF) Drug Interactions Checker.[4] A quick-reference overview of all ART-contraceptive interactions can be found on the Liverpool HIV Drug Interaction Checker under Prescribing Resources – Treatment Selector (Contraceptives).

It should be noted that the 2022 British HIV Association (BHIVA) guidelines[5] recommend many first-line ART regimens that have no DDIs with contraception. Both ART and contraceptive choice require a patient-centred, tailored approach, taking into consideration effectiveness, safety, DDIs, and patient preferences and lifestyles.

Suggested good practice points	
☑	Check for potential DDIs between contraceptives and each individual drug component of the person's ART regimen when prescribing and at each review appointment.
☑	Consult the University of Liverpool HIV Drug Interaction Checker here*, including the quick-reference guide here and the BNF Drug Interactions Checker here* for interactions between hormonal contraception and each component ART drug before prescribing.
*Search under etonogestrel, desogestrel, drospirenone, norethisterone, levonorgestrel, medroxyprogesterone, norelgestromin or ethinylestradiol, etc., as appropriate. Note: If you have a Medicines Complete login, you can search for interactions between multiple drugs at Stockley's Drug Interactions.	

This guidance document can be used in conjunction with the more general FSRH guidance on 'Drug interactions with hormonal contraception', published in May 2022.[6]

2. What information about drug-drug interactions should be provided to the user when making contraceptive decisions?

The contraceptive provider should carefully check for potential DDIs between contraceptive methods and each component of the person's ART regimen before prescribing the contraceptive method. Use the resources noted in Section 1 to check for the most up to date information on DDIs.

- Advise contraceptive users that combined hormonal contraception (ie, combined oral contraceptive pills, vaginal ring and patch), progestogen-only pills and the etonogestrel implant have the potential for interactions with prescription (including enzyme-inducing ART), non-prescription and recreational drugs, herbal preparations and dietary supplements. They should be advised to seek the advice of a healthcare professional before starting any new drugs, herbal preparations or supplements.
- Advise users of intrauterine contraception and the DMPA injectable that the contraceptive effectiveness of these methods is not expected to be affected by DDIs, and that they offer very effective contraception.

The basic steps outlined below can be used as a guide when prescribing contraception for people living with HIV on ART.

Steps for prescribing contraception to people living with HIV on ART	
1	Explain that many safe and effective contraceptive options exist for people living with HIV on ART.
2	Identify all the individual components of the patient's ART regimen.
3	Use resources to identify potential DDIs for each ART component: Liverpool HIV interactions checker and the BNF Drug Interactions Checker.
4	Use shared decision-making to decide the most appropriate method of contraception for the individual based on UK Medical Eligibility Criteria for Contraceptive Use (UK MEC), patient values and preferences, effectiveness of contraceptive method and length of use of ART (eg, shorter-term use of PEP or PrEP versus the longer-term/lifelong use of ART for people living with HIV). *If an individual is particularly keen to use a contraceptive method that is inadvisable due to a DDI, a discussion could take place with their HIV team about switching ART.* *HIV teams should always review ART regimens and contraception to assess whether there are clinically relevant interactions and, if so, to determine whether more compatible ART-contraceptive combinations are available.*

3. Evidence issues: ART and hormonal contraception

The evidence base evaluating ART and hormonal contraception DDIs is limited. The evidence that does exist is mostly from pharmacokinetic studies, with few studies assessing clinical outcomes such as rates of unintended pregnancy. Where necessary, the clinical guidance in this document extrapolate the potential effect of DDIs on contraceptive effectiveness from pharmacokinetic data.

The need to extrapolate from pharmacokinetic findings brings with it uncertainty and therefore a need for the FSRH CEU to exercise the precautionary principle. Given the significance of an unintended pregnancy, where there is the potential for an interaction between two medications that could affect contraceptive effectiveness or safety, we generally advise against giving these medications concomitantly, and advise additional or alternative effective methods of contraception.

However, contraceptive choices are personal and complex, and there may be instances where a particular contraceptive method may still be the appropriate choice for a person, despite a potential DDI. As people with a chronic, manageable condition, people living with HIV will take ART to maintain viral suppression continuously throughout their reproductive years and beyond. Therefore, considerations for appropriate contraception in long-term ART users may differ compared to people taking ARTs that interact with contraceptives over the short-term, for example, in second-line PEP regimens, etc. In addition, there are now many newer antiretrovirals that avoid DDIs with hormonal contraception, and an ART switch could be considered to suit an individual's choice of contraception, if appropriate. Providing and documenting individualised, comprehensive contraceptive discussions with a patient about their contraceptive options, including the potential risks and benefits, will help them to make an informed choice about the contraceptive method most suitable to meet their needs and preferences. This may include the need to change a person's ART regimen to suit their choice of contraception.

4. Types of drug-drug interactions between ART and hormonal contraception

The FSRH CEU guidance on 'Drug interactions with hormonal contraception'[6] contains information on types of DDIs. These include *pharmacokinetic* drug interactions, which occur when one drug alters the absorption, distribution, metabolism or excretion of another, changing its bioavailability; and *pharmacodynamic* drug interactions, which occur when the pharmacological effect of one drug affects the pharmacological effect of another drug. Most DDIs between ART and hormonal contraception are *pharmacokinetic*.

4.1 Pharmacokinetic interactions: Reduced contraceptive effectiveness

The most important pharmacokinetic interaction affecting hormonal contraceptives is with **drugs that *induce* hepatic cytochrome P450 (CYP450) enzymes (ie, enzyme-inducing drugs)** and therefore increase clearance of contraceptive hormones. This process could potentially result in reduced contraceptive effectiveness of:

- combined hormonal contraceptive methods (ie, combined oral contraceptive pills, vaginal ring, and patch)
- progestogen-only pills
- contraceptive progestogen implants, and
- oral emergency contraception.

The effectiveness of the following contraceptive methods is considered to be unaffected by enzyme-inducing drugs:

- depot medroxyprogesterone acetate (DMPA) progestogen-only injectable (achieves very high serum progestogen levels)
- levonorgestrel-releasing intrauterine device (LNG-IUD) (the local progestogen effect on endometrium is unaffected), and
- copper intrauterine device (Cu-IUD) (non-hormonal method).

The antiretrovirals most associated with cytochrome P450 enzyme-induction are certain non-nucleoside reverse transcriptase inhibitors (NNRTIs), particularly efavirenz, and ritonavir-boosted protease inhibitors (PIs). In the case of antiretrovirals, not all enzyme inducing ARTs affect contraceptive exposure to the same degree, so expert providers may wish to consider enzyme-inducing ARTs individually. See Appendix for a detailed listing of enzyme inducing and inhibiting antiretrovirals by ART drug class.

4.2 Pharmacokinetic interactions: Increased exposure to contraceptive hormones

Concomitant use of **drugs that *inhibit* cytochrome P450** with hormonal contraception could result in increased exposure to contraceptive hormones. In the case of ethinylestradiol, elevated serum levels could theoretically result in increased risk of thrombosis. The antiretrovirals associated with cytochrome P450 inhibition are protease inhibitors. See Appendix for a detailed listing of enzyme inducing and inhibiting antiretrovirals by ART drug class. All protease inhibitors in common usage are given in combination with a 'booster' to increase the active drug levels. The pharmacokinetic enhancer ritonavir, which is used to boost many PIs, inhibits CYP3A4 but induces glucuronidation enzymes. Therefore, boosting of PIs with ritonavir is expected to increase progestogen exposure but to reduce ethinylestradiol exposure (ie, through induction of glucuronidation). However, the pharmacokinetic enhancer cobicistat, which is used to boost both some PIs, has no inducing properties and is therefore expected to increase both progestogen and ethinylestradiol exposure. In the particular case of elvitegravir/cobicistat (elvitegravir is an integrase inhibitor that is also boosted with the pharmacokinetic enhancer cobicistat) levels of ethinylestradiol are decreased.

4.3 Pharmacokinetic interactions: Altered effectiveness or safety of ART

Key Information	
☑	There is no evidence to suggest that hormonal contraception reduces ART effectiveness or negatively affects progression of HIV disease or HIV clinical outcomes.
☑	There is no evidence to suggest that hormonal contraception affects the risk of transmission of HIV infection to others.

Contraceptive hormones may interact with concomitantly administered drugs, with potential loss of effectiveness of those drugs if exposure is reduced, or toxicity if exposure is increased. However, there is **no evidence to suggest that hormonal contraception reduces ART effectiveness**, including HIV viral suppression, or affects HIV-related clinical outcomes.[7–9]

4.4 Pharmacodynamic interactions: ART and contraceptive hormones

Suggested good practice points	
☑	Bone mineral density (BMD) considerations should be included in contraceptive discussions and decision-making, particularly for people who may already be at a higher risk of BMD loss or osteoporosis who are taking lifelong ART

Loss of bone mineral density (BMD) is a known adverse effect associated with use of both the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) (reversible for most on switch to alternative ART), and the DMPA progestogen-only injectable. DMPA is associated with a small loss of BMD, usually recovered after discontinuation.[10–12] A small retrospective study recently found that individuals using tenofovir disoproxil fumarate and DMPA simultaneously had increased BMD loss compared to TDF use alone.[13] Further research is required, including an evaluation of whether this translates into an increased risk of fractures. Concomitant use of drugs with bone adverse effects should be identified during contraceptive discussions, particularly for people who may already be at a higher risk of BMD loss or osteoporosis, taking lifelong ART or oral PrEP, where TDF is a key component of the regimen. The bone fracture risk assessment tool (FRAX™ score), as recommended by the BHIVA monitoring guidelines, can be used for identifying those at higher risk of osteoporotic fractures.[14,15] Tenofovir alafenamide (TAF) has less of an effect on BMD and may be considered as an alternative to TDF in people at risk of osteopenia or osteoporosis if tenofovir is required in their ART regimen.

5. Drug-drug interactions by ART class

Key Information	
☑	Enzyme-inducing drugs could potentially reduce effectiveness of all combined hormonal contraceptives (ie, combined oral contraceptive pills, vaginal ring and patch), all progestogen-only pills, the etonogestrel and levonorgestrel contraceptive implants and oral emergency contraception (levonorgestrel and ulipristal acetate).
☑	Based on pharmacokinetic studies, patients can be advised that there are no expected DDIs between the integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG), raltegravir (RAL), bictegravir (BIC) and cabotegravir (CAB) and hormonal contraception.

Suggested good practice points	
☑	People taking enzyme-inducing ART should be offered an alternative effective contraceptive method that is unaffected by the enzyme-inducer (eg, intrauterine contraception or DMPA injectable).
☑	People taking enzyme-inducing ART who require emergency contraception should be advised that the effectiveness of oral emergency contraception could be reduced. They should be offered a Cu-IUD if eligible (GPP). *If a Cu-IUD is unacceptable, unsuitable or unavailable, a double dose (3mg) of levonorgestrel or a single dose (30mg) of ulipristal acetate can be offered, with advice that effectiveness in the context of enzyme inducing antiretrovirals is unknown.*
☑	HIV teams should discuss contraception needs with their patients, and regularly review for and anticipate potential DDIs. Where DDIs exist that may prevent an individual choosing their preferred contraceptive option, HIV teams could consider ART switch if appropriate and acceptable

The following ART drug classes are covered in this document:

1. **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)**.
   Examples include tenofovir disoproxil fumarate, tenofovir alafenamide, lamivudine, emtricitabine, abacavir, zidovudine
2. **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**.
   Examples include efavirenz, nevirapine, etravirine, doravirine, rilpivirine
3. **Boosted protease inhibitors (boosted PIs).**
   Examples include atazanavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir, atazanavir/cobicistat, darunavir/cobicistat
4. **Integrase strand transfer inhibitors (INSTIs).**
   Examples include raltegravir, dolutegravir, bictegravir, cabotegravir
5. **Boosted integrase strand transfer inhibitors (boosted INSTIs).**
   Examples include elvitegravir
6. **C-C chemokine receptor 5 (CCR5) antagonists.**
   Examples include maraviroc
7. **Fusion inhibitors.**
   Examples include enfuvirtide
8. **Attachment inhibitors.**
   Examples include fostemsavir
9. **Post-attachment inhibitors.**
   Examples include ibalizumab
10. **Pharmacokinetic enhancers.**
    Examples include ritonavir, cobicistat

5.1 Drug-drug interactions: Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

NRTIs do not cause cytochrome P450 induction or inhibition at clinically relevant concentrations.[16] Therefore, **NRTIs are not expected to affect the effectiveness of any contraceptive method.**

Tenofovir disoproxil fumarate and emtricitabine are commonly used NRTI drugs in ART, PEP and PrEP regimens in the UK. The available pharmacokinetic data indicates no effect of tenofovir disoproxil fumarate/emtricitabine on exposure to contraceptive progestogens.[17] DMPA use has also been shown to not affect PrEP effectiveness.[18]

Quick reference: Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and contraception

ART Class	Contraceptive Method					
	CHC	POP	ENG-IMP	DMPA	LNG-IUD	Cu-IUD
▶ Abacavir (ABC) ▶ Emtricitabine (FTC) ▶ Lamivudine (3TC) ▶ Tenofovir disoproxil fumarate (TDF) ▶ Tenofovir alafenamide (TAF) ▶ Zidovudine (AZT)	✓	✓	✓	✓	✓	✓
	No expected effect on contraceptive effectiveness. No need for extra precautions.					

✓ No interaction: method suitable

? Potential interaction: caution required

✗ Known interaction: avoid and advise alternative method

Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; ENG-IMP, etonogestrel implant; LNG-IUD, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill

Additional information

- The most commonly used PrEP regimen contains two NRTIs, eg, tenofovir disoproxil fumarate and emtricitabine, and therefore there is **no expected interaction between PrEP and any method of contraception**.
- NRTIs are used in combination with other antiretrovirals: remember to check for DDIs between contraceptives and **all** components of the patient's ART regimen.

5.2 Drug-drug interactions: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs fall into two broad categories—those that are enzyme-inducing, and those that are not (see Appendix). The NNRTI for which most evidence exists for DDIs with hormonal contraception is the enzyme-inducing antiretroviral **efavirenz**, particularly when efavirenz-containing ART is used alongside progestogen-only implants and combined hormonal contraception administered as the pill or vaginal ring. Individuals using efavirenz-containing ART alongside both the levonorgestrel and etonogestrel progestogen-only implants had reduced progestogen pharmacokinetic values,[19–21] increased pregnancy rates compared to non-efavirenz-containing ART users,[22–25] and luteal progesterone levels suggesting ongoing ovulation,[26] consistently across studies. Pharmacogenetics may play a role in the extent of DDIs between the progestogen-only implants and efavirenz-based ART. Two studies showed that a single nucleotide polymorphism (SNP) in CYP2B6 (the main enzyme metabolising efavirenz) resulted in higher efavirenz concentrations and thereby higher enzyme inducing effect leading to lower progestogen concentrations compared with those without CYP2B6 SNPs.[27,28] However, screening for CYP2B6 polymorphisms is not undertaken in routine clinical practice.

The contraceptive effectiveness of DMPA is considered to be unaffected by DDIs with ART, including efavirenz. Individuals using efavirenz-based ART who used the DMPA injectable contraceptive had similar pregnancy rates to HIV-negative women and nevirapine-based ART users.[7,31] Two pharmacokinetic studies do suggest a greater risk of DMPA users having sub-therapeutic DMPA concentrations (ie, <0.1 ng/mL) at the end of the dosing interval in individuals with a high body mass index and in individuals co-treated with efavirenz and rifampicin.[29,30] For these specific groups, the FSRH CEU suggests that you may wish to consider advising use of intrauterine contraception, or additional use of condoms, or a reduction in the DMPA dosing interval.

Although the NNRTI **nevirapine** has some enzyme inducing activity and could theoretically reduce contraceptive hormone levels, pharmacokinetic data has shown similar levonorgestrel and etonogestrel levels in nevirapine-based ART users and HIV-negative controls not on ART.[24]

The NNRTIs **doravirine** and **rilpivirine** do not appear to induce drug metabolising enzymes and therefore they are not expected to affect contraceptive effectiveness. One pharmacokinetic study assessing single dose combined oral contraception (ethinylestradiol/levonorgestrel) and doravirine found no clinically relevant effect.[32]

Despite the evidence for significant interactions between efavirenz and hormonal contraceptives, unintended pregnancy rates reported with efavirenz and concomitant contraceptive progestogen-only implant use (etonogestrel and levonorgestrel) remain lower than those reported with ‘typical use’ of other reversible hormonal contraception methods, including oral contraceptives[16,24,26] and DMPA,[33] likely due to imperfect adherence with the latter two. If intrauterine contraception and the DMPA injectable are not acceptable in individual situations involving informed discussions, an individual may choose to use an progestogen-only implant with efavirenz but should be made aware that contraceptive effectiveness is reduced and that additional condom use is advised. The use of two implants together is **not** recommended.

HIV teams should discuss contraception needs with their patients, and regularly review for and anticipate potential DDIs. Where DDIs exist which would prevent an individual choosing their preferred contraceptive option, HIV teams should consider whether switching their ART is appropriate and acceptable.

Quick reference: Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and contraception

ART Class	Contraceptive Method					
	CHC	POP	ENG-IMP	DMPA	LNG-IUD	Cu-IUD
Enzyme inducing NNRTIs with expected effect on contraceptive effectiveness						
Efavirenz (EFV)						
	Contraceptive effectiveness could be reduced. Use not advised.			No expected effect on contraceptive effectiveness. No need for extra precautions.		
	Recommend an alternative effective method.†	Recommend an alternative effective method. ‡	Recommend an alternative effective method.*			
Enzyme-inducing NNRTIs not expected to affect contraceptive effectiveness						
Etravirine (ETR) Nevirapine (NVP)						
	Potential weak interaction but not expected to affect contraceptive effectiveness. To err on the side of caution, recommend an alternative effective method or advise additional condoms use.			No expected effect on contraceptive effectiveness. No need for extra precautions.		
Non-enzyme inducing NNRTIs						
Doravirine (DOR) Rilpivirine (RPV)						
	No expected effect on contraceptive effectiveness. No need for extra precautions.					

 No interaction: method suitable

 Potential interaction: caution required

 Known interaction: avoid and advise alternative method

Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; ENG-IMP, etonogestrel implant; LNG-IUD, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill.

*Users of efavirenz for whom alternative effective contraception is not acceptable may, in exceptional circumstances, consider use of ENG-IMP—with full and documented discussuion on the potential for DDIs and the increased risk of unintended pregnancy. Use of two implants together is **not** recommended.

†Users of efavirenz for whom alternative effective contraception is not acceptable may, in exceptional circumstances, consider use of two ethinylestradiol (EE) monophasic combined oral contraceptive pills together containing a total of 50μg of EE (30μg + 20μg). These should be used in a continuous regimen (or tricycled with a shortened hormone-free interval of 4 days). The user should be aware that contraceptive effectiveness is not guaranteed and there could be increased risk of thrombosis if exposure to EE is increased. Use of two combined contraceptive patches or two combined contraceptive rings together is **not** recommended.

‡Use of two progestogen-only pills together for users of efavirenz is **not** recommended. An alternative method should be recommended.

Additional information

- Users of efavirenz should **always** be advised to use an alternative effective contraceptive method that is not affected by enzyme induction, such as intrauterine contraceptive methods (Cu-IUD and LNG-IUD) or DMPA.
- Etravirine and nevirapine have inducing properties but, unlike efavirenz, are not expected to impair the effectiveness of CHC, POP or ENG-IMP. Check the Liverpool HIV Drug Interaction Checker for full details. However, to err on the side of caution, recommend an alternative effective contraceptive method or advise additional condoms use.
- NNRTIs are used in combination with other antiretrovirals; remember to check for DDIs between hormonal contraception and **all** components of the patient's ART regimen.

5.3 Drug-drug interactions: Boosted protease inhibitors (PIs)

Studies investigating DDIs between boosted PIs and hormonal contraception have yielded mixed results. In general, pharmacokinetic studies found that co-administration of a boosted PI and hormonal contraception mostly resulted in increased progestogen exposure and/or unchanged or decreased ethinylestradiol exposure.[34–38]

Despite these potential DDIs, studies have found no indication of reduced contraceptive effectiveness in users of PI-containing ART and concomitant hormonal contraception, presumably because contraceptive effectiveness is driven by the progestogen component which is increased by boosted PIs.[24,38,39] In two pharmacokinetic studies assessing endogenous progesterone levels as a surrogate marker of ovulation in people using ritonavir or a ritonavir-boosted PI and combined oral contraception, endogenous progesterone levels were appropriately suppressed, suggesting no evidence of ovulation.[34,38] DDI studies with boosted PIs have shown that the increase in progestogen levels did not result in serilus adverse effects, but may be more likely to cause mild adverse effects such as irregular vaginal bleeding or amenorrhoea.[40] The decrease in ethinylestradiol levels seen in these studies with ritonavir-boosted PIs due to ritonavir-induced glucuronidation may cause irregular bleeding, and thereby could potentially have an impact on acceptability of or adherence to the contraceptive method.[41] Note that boosting of PIs by cobicistat is expected to increase both progestogen and ethinylestradiol exposure. So in this case, the FSRH CEU suggests that the user should be aware that there could be increased risk of thrombosis if exposure to ethinylestradiol is increased and advises that an effective non-estrogen containing contraceptive is used.

Quick reference: Protease inhibitors (PIs) and contraception

ART Class	Contraceptive Method					
	CHC	POP	ENG-IMP	DMPA	LNG-IUD	Cu-IUD
Boosted protease inhibitors						
▶ Atazanavir/ritonavir (ATV/r) ▶ Darunavir/ritonavir (DRV/r) ▶ Lopinavir/ritonavir (LPV/r) ▶ Atazanavir/cobicistat (ATV/c)* ▶ Darunavir/cobicistat (DRV/c)*						
	Interaction that could increase progestogen exposure but not expected to affect contraceptive effectiveness.† *In case of PIs boosted with cobicistat, recommend an alternative effective method or use with caution due to increased ethinylestradiol exposure.	Potential weak interaction that could increase progestogen exposure but not expected to affect contraceptive effectiveness.† No need for extra precautions.		No expected effect on contraceptive effectiveness. No need for extra precautions.		

 No interaction: method suitable

 Potential interaction: caution required

 Known interaction: avoid and advise alternative method

Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; ENG-IMP, etonogestrel implant; LNG-IUD, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill.

*In case of PIs boosted with cobicistat, recommend an alternative effective method or use with caution due to increased ethinylestradiol exposure.

†Boosted PIs increase the progestogen component and therefore do not affect the contraceptive effectiveness of the progestogen-only pill and etonogestrel progestogen-only implant. They can therefore be used together with no need for extra precautions.

Additional information

- The pharmacological boosters ritonavir and cobicistat vary slightly in their impact on CYP450 enzymes: check the Liverpool HIV Drug Interaction Checker for full details.
- If an un-boosted PI is used on its own (eg, atazanavir alone), effects on contraceptive hormone levels may differ from the boosted PI: check the Liverpool HIV Drug Interaction Checker for individual antiretroviral drugs.
- As boosted PIs may be both inducers and inhibitors of CYP450 enzymes, the inhibition effect may increase contraceptive hormone levels and has the potential to increase the risk of side effects such as irregular vaginal bleeding, spotting or amenorrhoea, which may have an impact on contraceptive method adherence.
- Boosted PIs are used in combination with other antiretroviral drugs: remember to check for DDIs between hormonal contraception and **all** components of the patient's ART regimen.

5.4 Drug-drug interactions: integrase strand transfer inhibitors (INSTIs)

The INSTIs dolutegravir, raltegravir and bictegravir do not cause cytochrome P450 induction or inhibition at clinically relevant concentrations.[16] Therefore, there is no expected effect of these INSTIs on the effectiveness of any contraceptive method.

Evidence on potential DDIs between INSTIs and hormonal contraception is limited to pharmacologic studies. Two pharmacokinetic studies have shown no DDIs between dolutegravir and hormonal contraceptives.[19,42] One found similar etonogestrel levels above the level required for ovulation suppression in individuals living with HIV on dolutegravir-containing ART using the etonogestrel implant compared to HIV-negative individuals.[19] Another study showed dolutegravir co-administration had no effect on the pharmacokinetics or pharmacodynamics of a combined oral contraceptive.[42] No clinically important DDIs were detected in pharmacokinetic studies with combined oral contraceptives used alongside cabotegravir[43,44] or raltegravir.[45].

Boosted elvitegravir (ie, elvitegravir/cobicistat) may cause a reduction in ethinylestradiol levels through induction of CYP2C9,[46] but this reduction has been compensated for in a DDI study by increasing the ethinylestradiol dose. Available pharmacokinetic data suggest that elvitegravir/cobicistat should not be given with a low dose (ie, 20μg of ethinylestradiol) combined oral contraceptive.[47,48]

Quick reference: Integrase strand transfer inhibitors (INSTIs) and contraception						
ART Class	**Contraceptive Method**					
	CHC	**POP**	**ENG-IMP**	**DMPA**	**LNG-IUD**	**Cu-IUD**
Integrase strand transfer inhibitors (INSTIs)						
▶ Raltegravir (RAL) ▶ Dolutegravir (DTG) ▶ Bictegravir (BIC) ▶ Cabotegravir CAB)						
	No expected effect on contraceptive effectiveness. No need for extra precautions.					
Boosted INSTIs						
Elvitegravir/ cobicistat (EVG/c)						
	Potential interaction causing decreased ethinylestradiol exposure. Should not be given with a low dose (ie, 20μg ethinylestradiol) combined oral contraceptive.	No expected effect on contraceptive effectiveness. No need for extra precautions.		No expected effect on contraceptive effectiveness. No need for extra precautions.		

 No interaction: method suitable

 Potential interaction: caution required

 Known interaction: avoid and advise alternative method

Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; ENG-IMP, etonogestrel implant; LNG-IUD, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill.

Additional information

- Elvitegravir is boosted with cobicistat—elvitegravir is a modest inducer of CYP2C9 while cobicistat causes CYP450 inhibition. Overall progestogen levels are increased which means contraceptive efficacy is not altered; however, the induction of CYP2C9 may decrease ethinylestradiol levels which may cause irregular bleeding. See the Liverpool HIV Interaction Checker for more details.
- INSTIs are used in combination with other antiretroviral drugs: remember to check for DDIs between hormonal contraception and all components of the patient's ART regimen

5.5 Drug-drug interactions: Entry inhibitors: CCR5 antagonists (maraviroc), fusion inhibitors (enfuvirtide), attachment inhibitors (fostemsavir) and post-attachment inhibitors (ibalizumab)

The C-C chemokine receptor 5 (CCR5) antagonists, fusion inhibitors, attachment inhibitors and post-attachment inhibitors currently available do not cause cytochrome P450 induction or inhibition at clinically relevant concentrations. Therefore, **there is no expected effect of currently available CCR5 antagonists, fusion inhibitors, attachment inhibitors or post-attachment inhibitors on contraceptive effectiveness of any contraceptive method.**

The attachment inhibitor fostemsavir may increase ethinylestradiol levels, possibly through breast cancer resistance protein (BCRP) inhibition.[3,49] FSRH CEU advises in this case that an effective non-estrogen containing contraceptive is used. If the combined oral contraceptive is preferred by a patient on fostemsavir-containing ART, the daily ethinylestradiol dose should not exceed 30μg.[3,50]

A pharmacokinetic study in healthy volunteers found no changes in ethinylestradiol/levonorgestrel levels with concomitant maraviroc use.[51] No studies have investigated interactions between enfuvirtide or ibalizumab and hormonal contraceptives; as a monoclonal antibody, ibalizumab is not anticipated to be associated with any DDIs, including with hormonal contraception. No studies have reported pregnancy rates with concomitant CCR5 antagonist, fusion inhibitor, attachment inhibitor or post-attachment inhibitor-containing ART with hormonal contraceptive use.

Quick reference guide: Entry-inhibitors: CCR5 antagonists (maraviroc), fusion inhibitors (enfuvirtide), attachment inhibitors (fostemsavir) and post-attachment inhibitors (ibalizumab) and contraception						
ART Class	**Contraceptive Method**					
	CHC	**POP**	**ENG-IMP**	**DMPA**	**LNG-IUD**	**Cu-IUD**
CCR5 antagonists						
Maraviroc (MVC)						
	No expected effect on contraceptive effectiveness. No need for extra precautions.					
Fusion inhibitors						
Enfuvirtide (ENF)						
	No expected effect on contraceptive effectiveness. No need for extra precautions.					
Attachment inhibitors						
Fostemsavir (FTR)						
	No expected effect on contraceptive effectiveness. May increase exposure to ethinylestradiol. Recommend an alternative effective method or use with caution due to increased ethinylestradiol exposure. If a COC is given, daily ethinylestradiol dose should not exceed 30μg.	No expected effect on contraceptive effectiveness. No need for extra precautions.				
Post-attachment inhibitors						
Ibalizumab (IBA)						
	No expected effect on contraceptive effectiveness. No need for extra precautions.					

 No interaction: method suitable

 Potential interaction: caution required

 Known interaction: avoid and advise alternative method

Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; ENG-IMP, etonogestrel implant; LNG-IUD, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill.

Additional information

- Entry inhibitors are used in combination with other antiretroviral drugs: remember to check for DDIs between hormonal contraception and **all** components of the patient's ART regimen.
- The attachment inihibitor fostemsavir may increase ethinylestradiol levels; therefore if a COC is given alongside fostemsavir, the daily ethinylestradiol dose should not exceeed 30μg. See Liverpool HIV Drug Interaction Checker for more details.

6. Emergency contraception and ART

Key Information	
☑	Double dose of UPA-EC is not recommended.
Suggested good practice points	
☑	People using a known enzyme-inducing drug who require emergency contraception should be advised that effectiveness of oral emergency contraception could be reduced. They should be offered a copper intrauterine device (Cu-IUD) if indicated as first line emergency contraception.
☑	For people taking a known enzyme-inducing drug for whom the Cu-IUD is unacceptable, unsuitable or unavailable, a double dose (3mg) of levonorgestrel oral emergency contraception (LNG-EC) or a single dose (30mg) of ulipristal acetate oral emergency contraception (UPA-EC) can be offered if indicated, with advice that effectiveness is unknown.

The emergency copper intrauterine device (Cu-IUD) is the most effective method of emergency contraception and, for this reason, all those requiring emergency contraception should be offered the Cu-IUD if appropriate, regardless of DDI risk. For people for whom the emergency Cu-IUD is not suitable or acceptable, there are two currently available oral emergency contraceptive options: levonorgestrel emergency contraception (LNG-EC), and ulipristal acetate emergency contraception (UPA-EC).[52]

LNG-EC and UPA-EC predominantly work as emergency contraceptives by delaying ovulation. The metabolism of both LNG-EC and UPA-EC is increased during and for 28 days after use of drugs that induce liver enzymes.[53–55] Thus, enzyme-inducing ART has the potential to decrease the peak hormone level achieved by oral emergency contraception, which could then not be sufficient to delay ovulation. There is a lack of clinical outcome data on DDIs between antiretrovirals and either LNG-EC or UPA-EC. However, pharmacokinetic data demonstrate reduced LNG levels when co-administered with certain antiretrovirals, particularly efavirenz, which can be extrapolated to LNG-EC. An open-label study with individuals randomised to receive LNG-EC at a dose of 1.5mg or 3mg with efavirenz showed that the pharmacokinetic DDI with efavirenz can be overcome by doubling the LNG-EC dose.[56]

People taking known enzyme-inducing medications such as efavirenz should be advised to use the Cu-IUD as first line emergency contraception. The Cu-IUD has the dual advantage of being unaffected by potential DDIs, and of being the most effective form of emergency contraception. For people using enzyme-inducing ART for whom the emergency Cu-IUD is not appropriate or acceptable, consider offering a double dose LNG-EC (3mg, ie, two 1.5mg levonorgestrel tablets taken together). This is an off-label use, as recommended by the Medicines and Healthcare products Regulatory Agency (MHRA).[53] Providers should therefore explain that the effectiveness of double-dose LNG-EC in this situation is unknown. Double dose of UPA-EC is not recommended. The effectiveness of UPA-EC compared to double-dose LNG-EC is not known. The FSRH Emergency Contraception Guideline provides further information on the provision of emergency contraception.[52]

Quick reference: ART and emergency contraception			
ART Class	**LNG-EC**	**UPA-EC**	**Cu-IUD**
NRTIs			
▶ Abacavir (ABC) ▶ Emtricitabine (FTC) ▶ Lamivudine (3TC) ▶ Tenofovir disoproxil fumarate (TDF) ▶ Tenofovir alafenamide (TAF) ▶ Zidovudine (AZT)	No effect on EC effectiveness.	No effect on EC effectiveness.	No effect on EC effectiveness.
Enzyme-inducing NNRTIs			
Efavirenz (EFV)	Effectiveness of EC *could* be reduced. Offer a Cu-IUD if appropriate. If Cu-IUD not appropriate or not acceptable, offer double dose LNG-EC.	Effectiveness of EC *could* be reduced. Offer a Cu-IUD if appropriate. Double dose UPA-EC is not recommended. The effectiveness of UPA-EC compared to double-dose LNG-EC is not known.	No effect on EC effectiveness.
▶ Nevirapine (NVP) ▶ Etravirine (ETR)	Effectiveness of EC *could* be reduced. Offer a Cu-IUD if appropriate. If Cu-IUD not appropriate or not acceptable, offer double dose LNG-EC.	Effectiveness of EC *could* be reduced. Offer a Cu-IUD if appropriate. Double dose UPA-EC is not recommended. The effectiveness of UPA-EC compared to double-dose LNG-EC is not known.	No effect on EC effectiveness.
Non-enzyme inducing NNRTIs			
▶ Doravirine (DOR) ▶ Rilpivirine (RPV)	No effect on EC effectiveness.	No effect on EC effectiveness.	No effect on EC effectiveness.
Boosted PIs			
▶ Atazanavir/ritonavir (ATV/r) ▶ Darunavir/ritonavir (DRV/r) ▶ Lopinavir/ritonavir (LOP/r) ▶ Atazanavir/cobicistat (ATV/c) ▶ Darunavir/cobicistat (DRV/c)	No effect on EC effectiveness but progestogen levels may be *increased.*	No effect on EC effectiveness but ulipristal levels may be *increased.*	No effect on EC effectiveness.

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Quick reference: ART and emergency contraception (continued)			
ART Class	**LNG-EC**	**UPA-EC**	**Cu-IUD**
INSTIs			
▶ Bictegravir (BIC) ▶ Cabotegravir (CAB) ▶ Dolutegravir (DTG) ▶ Raltegravir (RAL) ▶ Elvitegravir/cobicistat (EVG/c)	No effect on EC effectiveness.	No effect on EC effectiveness.	No effect on EC effectiveness.
Entry inhibitors			
▶ **CCR5 antagonists** Maraviroc (MVC) ▶ **Fusion inhibitors** Enfuvirtide (ENF) ▶ **Attachment inhibitors** Fostemsavir (FTR) ▶ **Post-attachment inhibitors** Ibalizumab (IBA)	No effect on EC effectiveness.	No effect on EC effectiveness.	No effect on EC effectiveness.

No interaction: method suitable

Potential interaction: caution required

Known interaction: avoid and advise alternative method

Contraceptive methods: Cu-IUD, copper intrauterine contraceptive device; EC, emergency contraception; LNG, levonorgestrel; UPA, ulipristal acetate.

ART drug class: CCR5, cysteine-cysteine chemokine receptor 5; INSTIs, integrase strand transfer inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; PIs, protease inhibitors.

Additional information

- Enzyme-inducing ART, particularly efavirenz, may affect the effectiveness of oral EC. The Cu-IUD is the most effective method of EC overall, and particularly so for people using enzyme-inducing drugs, as it is not affected by CYP450 enzyme induction.
- If the Cu-IUD is not appropriate or not acceptable, the pharmacokinetic DDI with efavirenz and LNG-EC can be overcome by giving a double dose of LNG-EC (2x 1.5mg LNG tablets taken together).[56]
- Use of double dose UPA-EC is not recommended for people using enzyme-inducing drugs. The effectiveness of UPA-EC compared to that of double dose (3mg) LNG-EC in this situation is unknown.

7. Frequently asked questions

Q: Does PrEP (HIV pre-exposure prophylaxis) interact with any methods of contraception?

A: The most commonly used oral PrEP regimen contains the NRTIs tenofovir disoproxil fumarate and emtricitabine. These NRTIs do not cause cytochrome P450 induction or inhibition at clinically relevant concentrations[16] and therefore do not reduce the effectiveness of any contraceptive method.

However, one recent study[13] has suggested that BMD loss is exacerbated by concomitant use of the intramuscular DMPA contraceptive injectable and tenofovir disoproxil fumarate, a key component of PrEP and many ART regimens. Contraceptive providers should be aware of this and consider an alternative contraceptive method, particularly for people at high risk of BMD loss or osteoporosis.

There is no evidence to suggest any methods of hormonal contraception reduce the effectiveness of PrEP.[18,57]

Q: Does PEP (HIV post-exposure prophylaxis) interact with any methods of contraception?

A: The 2021 UK *British Association of Sexual Health and HIV* (BASHH)/BHIVA guideline for first-line PEP is a 28-day ART course containing two NRTIs, tenofovir disoproxil fumarate and emtricitabine, with the INSTI raltegravir.[2] With this first-line PEP regimen, no DDIs are expected with hormonal contraception.

Alternative second-line PEP regimens, prescribed in a very small number of scenarios including known drug reactions or an HIV contact with known resistance, may rarely contain antiretrovirals that have the potential for DDIs with hormonal contraception.[2] Always check DDIs between hormonal contraception and each individual component of PEP that is prescribed using the resources provided in this document. **People using the etonogestrel implant, progestogen-only pill or combined hormonal contraceptives who are prescribed a PEP regimen containing enzyme-inducing ART should be advised to use an additional contraceptive precautions for the duration of PEP and for 28 days after completion of treatment, or to switch to the DMPA injectable of intrauterine contraception for this period.** As PEP is only a short-term treatment, patients could be advised about the risk of DDIs reducing contraceptive effectiveness and could choose to use a barrier method in addition to their chosen contraceptive method for the duration of treatment and for 28 days after stopping, to prevent an unintended pregnancy.

Q: What advice should be given to someone who wants to use the etonogestrel (ENG) implant but is taking efavirenz as part of their ART regimen?

A: Explain that the contraceptive effectiveness of the ENG implant could be reduced and that use is not advised. Recommend alternative effective methods of contraception not affected by enzyme induction or switching to a non-interacting ART regimen if possible. Users of efavirenz, for whom alternative effective contraception is not acceptable, may, in exeptional circumstances, consider use of an ENG implant; with full and documented discussions on the potential for DDIs and the increased risk of unintended pregnancy with this method when compared to people not using enzyme-inducing ART. There is no evidence to support the use of two implants together and this is not recommended.

Q: What emergency contraception should be recommended to someone using efavirenz-containing ART?

A: If emergency contraception is required, FSRH CEU suggests that a Cu-IUD should always be offered as first-line EC if the individual is clinically eligible. If a Cu-IUD is not appropriate or is not acceptable, oral LNG-EC at a double dose can be offered. This is an off-label use, as recommended by the MHRA, and effectiveness is unknown.[53] This strategy is supported by data from an open-label study of individuals randomised to receive LNG-EC at a dose of 1.5mg or 3mg with efavirenz which showed that the pharmacokinetic DDI with efavirenz can be overcome by doubling the LNG-EC dose.[56] Use of double dose UPA-EC is not recommended. The effectiveness of UPA-EC compared to double dose LNG-EC for people using enzyme-inducing ART is not known. The FSRH Emergency Contraception Guideline provides further information on the provision of emergency contraception.[52]

Q: Does any method of hormonal contraception reduce ART effectiveness?

Several pharmacokinetic studies have shown that there may be slightly reduced concentrations of some antiretrovirals when used in conjunction with hormonal contraception, but none are clinically significant reductions.[9,21,35–37,44,58,59] There is no evidence to suggest that hormonal contraception reduces ART effectiveness, reduces HIV viral suppression or affects HIV clinical outcomes.[7,9]

Appendix

Enzyme inducing and inhibiting HIV drugs by ART drug class		
ART class	**ART drug(s)**	**Cytochrome P450 (CYP450) enzyme induction/inhibition**
NRTIs (nucleoside/nucleotide reverse transcriptase inhibitors)	Tenofovir disoproxil fumarate (TDF) Tenofovir alafenamide (TAF) Lamivudine (3TC) Emtricitabine (FTC) Abacavir (ABC) Zidovudine (AZT)	**No expected inhibition or induction** of cytochrome P450 enzymes at clinically relevant concentrations
NNRTIs (non-nucleoside reverse transcriptase inhibitors)	Efavirenz (EFV) Nevirapine (NVP) Etravirine (ETR)	**Induces** cytochrome P450 (CYP3A4); however, NVP and ETR do not appear to markedly decrease contraceptive hormone exposure
	Doravirine (DOR) Rilpivirine (RPV)	**No expected inhibition or induction** of cytochrome P450 enzymes at clinically relevant concentrations
Boosted PIs (boosted protease inhibitors)	Atazanavir/ritonavir (ATV/r) Lopinavir/ritonavir (LPV/r) Darunavir/ritonavir (DRV/r) Atazanavir/cobicistat (ATV/c) Darunavir/cobicistat (DRV/c)	**Induces and inhibits** cytochrome P450

Table continues on next page

Enzyme inducing and inhibiting HIV drugs by ART drug class (continued)		
ART class	**ART drug(s)**	**Cytochrome P450 (CYP450) enzyme induction/inhibition**
INSTIs (integrase strand transfer inhibitors)	Raltegravir (RAL) Dolutegravir (DTG) Bictegravir (BIC) Cabotegravir (CAB)	**No expected inhibition or induction** of cytochrome P450 enzymes at clinically relevant concentrations
Boosted INSTIs	Elvitegravir/cobicistat (EVG/c)	**Induces and inhibits** cytochrome P450.
Entry inhibitors		
▶ CCR5 antagonists	Maraviroc (MVC)	**No expected inhibition or induction** of cytochrome P450 enzymes at clinically relevant concentrations
▶ Fusion inhibitors	Enfuvirtide (ENF)	**No expected inhibition or induction** of cytochrome P450 enzymes at clinically relevant concentrations
▶ Attachment inhibitors	Fostemsavir (FTR)	**No expected inhibition or induction** of cytochrome P450 enzymes at clinically relevant concentrations May increase ethinylestradiol levels through another mechanism (breast cancer resistance protein (BCRP) inhibition)
▶ Post-attachment inhibitors	Ibalizumab (IBA)	**No expected inhibition or induction** of cytochrome P450 enzymes at clinically relevant concentrations
Pharmacokinetic enhancers	Ritonavir (/r; RIT) Cobicistat (/c; COBI)	Ritonavir **inhibits** some cytochrome P450 enzymes and **induces** others. Cobicistat **inhibits** cytochrome P450.
ART drug class: CCR5, cysteine-cysteine chemokine receptor 5; INSTIs, integrase strand transfer inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; PIs, protease inhibitors;		
Expected or known DDIs between ART and hormonal contraceptives adapted from https://www.hiv-druginteractions.org/checker		

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Comments and feedback on published guidance document

All comments on this published guidance document can be sent directly to the Clinical Effectiveness Unit (CEU) of the Faculty of Sexual & Reproductive Healthcare (FSRH) via the FSRH website (www.fsrh.org). The CEU may not respond individually to all feedback. However, the CEU will review all comments and provide an anonymised summary of comments and responses, which are reviewed by the Clinical Effectiveness Committee and any necessary amendments made subsequently.

References

1. British HIV Association and British Association for Sexual Health and HIV. BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018. Availabe from: https://www.bhiva.org/PrEP-guidelines
2. British HIV Association and British Association for Sexual Health and HIV. UK guideline for the use of HIV post-exposure prophylaxis 2021. Available from: https://www.bhiva.org/PEP-guidelines
3. University of Liverpool. Liverpool HIV Drug Interactions Checker [Internet]. Available from: https://www.hiv-druginteractions.org/checker
4. National Institute for Clinical Excellence. British National Formulary Online [Internet]. Available from: https://bnf.nice.org.uk/interactions/
5. British HIV Association. BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022. Available from: https://www.bhiva.org/hiv-1-treatment-guidelines
6. Faculty of Sexual and Reproductive Healthcare (FSRH). Clinical Guidance: Drug Interactions with Hormonal Contraception (May 2022). Available from: https://www.fsrh.org/standards-and-guidance/documents/ceu-clinical-guidance-drug-interactions-with-hormonal/
7. Patel RC, Baeten JM, Heffron R, Hong T, Davis NL, Nanda K, *et al*. Brief report: hormonal contraception is not associated with reduced ART effectiveness among women initiating ART: evidence from longitudinal data. *J Acquir Immune Defic Syndr* 2017;75:91–6.
8. Morrison CS, Hofmeyr GJ, Thomas KK, Rees H, Philip N, Palanee-Phillips T, *et al*. Effects of depot medroxyprogesterone acetate, copper intrauterine devices, and levonorgestrel implants on early HIV disease progression. *AIDS Res Hum Retroviruses* 2020;36:632–40.
9. Todd CS, Jones HE, Langwenya N, Hoover DR, Chen P-L, Petro G, *et al*. Safety and continued use of the levonorgestrel intrauterine system as compared with the copper intrauterine device among women living with HIV in South Africa: a randomized controlled trial. *PLoS Med* 2020;17:e1003110.
10. Kaunitz AM, Arias R, McClung M. Bone density recovery after depot medroxyprogesterone acetate injectable contraception use. *Contraception*. 2008;77:67–76.
11. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006;20:2165–74.
12. National Institute for Health and Care Excellence (NICE). Long-acting reversible contraception (update) [Internet]. 2019. Available from: https://www.nice.org.uk/guidance/cg30
13. Kiweewa Matovu F, Kiwanuka N, Nabwana M, Scholes D, Musoke P, Glenn Fowler M, et al. Intramuscular depot medroxyprogesterone acetate accentuates bone loss associated with tenofovir disoproxil fumarate-containing antiretroviral therapy initiation in young women living with HIV (the BONE: CARE study): a prospective cohort study in Uganda. *Lancet Glob Heal* 2022;10:e694–704.
14. University of Sheffield. Fracture risk assessment tool (FRAX) [Internet]. 2008. Available from: https://frax.shef.ac.uk/FRAX/tool.aspx
15. British HIV Association. BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals 2016 (2019 interim update). Available from: https://www.bhiva.org/monitoring-guidelines
16. Nanda K, Stuart GS, Robinson J, Gray AL, Tepper NK, Gaffield ME. Drug interactions between hormonal contraceptives and antiretrovirals. *AIDS* 2017;31:917–52.
17. Nanda K, Callahan R, Taylor D, Wang M, Agot K, Jenkins D, *et al*. Medroxyprogesterone acetate levels among Kenyan women using depot medroxyprogesterone acetate in the FEM-PrEP trial. *Contraception* 2016;94:40–7.
18. Heffron R, Mugo N, Were E, Kiarie J, Bukusi EA, Mujugira A, *et al*. Preexposure prophylaxis is efficacious for HIV-1 prevention among women using depot medroxyprogesterone acetate for contraception. *AIDS* 2014;28:2771–6.

19. Bishop IJ, Gertz AM, Simon B, Tawe L, Lechiile K, Liu S, *et al*. Etonogestrel concentrations among contraceptive implant users in Botswana using and not using dolutegravir-based antiretroviral therapy. *Contraception* 2020;102:174–9.
20. Patel RC, Stalter RM, Thomas KK, Tamraz B, Blue SW, Erikson DW, *et al.* A pharmacokinetic and pharmacogenetic evaluation of contraceptive implants and antiretroviral therapy among women in Kenya and Uganda. *AIDS* 2019;33:1995–2004.
21. Chappell CA, Lamorde M, Nakalema S, Chen BA, Mackline H, Riddler SA, *et al*. Efavirenz decreases etonogestrel exposure: a pharmacokinetic evaluation of implantable contraception with antiretroviral therapy. *AIDS* 2017;31:1965–72.
22. Okoboi S, Eunice A, Oceng R, Etukoit B. Correlation between co-therapy of efavirenz-based ART among HIV-positive women on hormonal contraceptive implants at tASO Tororo-Uganda: a retrospective review. *J AIDS Clin Res* 2018;9:2.
23. Patel RC, Jakait B, Thomas K, Yiannoutsos C, Onono M, Bukusi EA, *et al*. Increasing body mass index or weight does not appear to influence the association between efavirenz-based antiretroviral therapy and implant effectiveness among HIV-positive women in western Kenya. *Contraception* 2019;100:288–95.
24. Patel RC, Amorim G, Jakait B, Shepherd BE, Mocello AR, Musick B, *et al*. Pregnancies among women living with HIV using contraceptives and antiretroviral therapy in western Kenya: a retrospective, cohort study. *BMC Med* 2021;19:178.
25. Scarsi KK, Darin KM, Nakalema S, Back DJ, Byakika-Kibwika P, Else LJ, *et al*. 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; 15;62:675–82. Available from: https://pubmed.ncbi.nlm.nih.gov/26646680
26. Patel RC, Morroni C, Scarsi KK, Sripipatana T, Kiarie J, Cohen CR. Concomitant contraceptive implant and efavirenz use in women living with HIV: perspectives on current evidence and policy implications for family planning and HIV treatment guidelines. *J Int AIDS Soc* 2017;20:21396.
27. Neary M, Lamorde M, Olagunju A, Darin KM, Merry C, Byakika-Kibwika P, *et al*. The effect of gene variants on levonorgestrel pharmacokinetics when combined with antiretroviral therapy containing efavirenz or nevirapine. *Clin Pharmacol Ther* 2017;102:529–36.
28. Neary M, Chappell CA, Scarsi KK, Nakalema S, Matovu J, Achilles SL, *et al*. Effect of patient genetics on etonogestrel pharmacokinetics when combined with efavirenz or nevirapine ART. *J Antimicrob Chemother* 2019;74:3003–10.
29. Mngqibisa R, Kendall MA, Dooley K, Wu XS, Firnhaber C, Mcilleron H, *et al*. Pharmacokinetics and pharmacodynamics of depot medroxyprogesterone acetate in African women receiving treatment for human immunodeficiency virus and tuberculosis: potential concern for standard dosing frequency. *Clin Infect Dis* 2020;71:517–24.
30. Francis J, Mngqibisa R, McIlleron H, Kendall MA, Wu X, Dooley KE, *et al*. A semimechanistic pharmacokinetic model for depot medroxyprogesterone acetate and drug-drug interactions with antiretroviral and antituberculosis treatment. *Clin Pharmacol Ther* 2021;110:1057–65.
31. Zia Y, Tang JH, Chinula L, Tegha G, Stanczyk FZ, Kourtis AP. Medroxyprogesterone acetate concentrations among HIV-infected depot-medroxyprogesterone acetate users receiving antiretroviral therapy in Lilongwe, Malawi. *Contraception* 2019;100:402–5. Available from: https://pubmed.ncbi.nlm.nih.gov/31374188
32. Khalilieh SG, Yee KL, Sanchez RI, Fan L, Anderson MS, Sura M, *et al*. Doravirine and the potential for CYP3A-mediated drug-drug interactions. *Antimicrob Agents Chemother* 2019;63:e02016-18.
33. Patel RC, Onono M, Gandhi M, Blat C, Hagey J, Shade SB, *et al*. Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study. *Lancet HIV* 2015;2:e474-82.

34. Barcellos T, Natavio M, Stanczyk FZ, Luo D, Jusko WJ, Bender NM. Effects of ritonavir-boosted protease inhibitors on combined oral contraceptive pharmacokinetics and pharmacodynamics in HIV-positive women. *Contraception*. 2019;100:283–7.
35. Elliot ER, Bisdomini E, Penchala SD, Khoo S, Nwokolo N, Boffito M. Pharmacokinetics (PK) of ethinylestradiol/levonorgestrel co-administered with atazanavir/cobicistat. *HIV Res Clin Pract* 2019 Jul;1–10.
36. Majeed SR, West S, Ling KH, Das M, Kearney BP. Confirmation of the drug-drug interaction potential between cobicistat-boosted antiretroviral regimens and hormonal contraceptives. *Antivir Ther* 2019;24:557–66.
37. Kreitchmann R, Stek A, Best BM, Capparelli E, Wang J, Shapiro D, *et al*. Interactions between etonogestrel-releasing contraceptive implant and 3 antiretroviral regimens. *Contraception* 2022;105:67–74.
38. Kancheva Landolt N, Bunupuradah T, Kosalaraksa P, Ubolyam S, Thammajaruk N, Cremers S, *et al*. High variability of hormonal levels and no clinically relevant interaction between ethinyl estradiol, desogestrel and lopinavir/ritonavir in a small sample of HIV-positive adolescents. *J Acquir Immune Defic Syndr* 2016;72:507–12.
39. Pfitzer A, Wille J, Wambua J, Stender SC, Strachan M, Ayuyo CM, *et al*. Contraceptive implant failures among women using antiretroviral therapy in western Kenya: a retrospective cohort study. *Gates open Res* 2019;3:1482.
40. Ragazini CS, Bahamondes MV, Prandini TRR, Brito MB, Amaral E, Bahamondes L, *et al*. Bleeding patterns of HIV-infected women using an etonogestrel-releasing contraceptive implant and efavirenz-based or lopinavir/ritonavir-based antiretroviral therapy. *Eur J Contracept Reprod Heal care* 2016;21:285–9.
41. Scarsi KK, Darin KM, Chappell CA, Nitz SM, Lamorde M. Drug-drug interactions, effectiveness, and safety of hormonal contraceptives in women living with HIV. *Drug Saf* 2016;39:1053–72.
42. Song IH, Borland J, Chen S, Wajima T, Peppercorn AF, Piscitelli SC. Dolutegravir has no effect on the pharmacokinetics of oral contraceptives with norgestimate and ethinyl estradiol. *Ann Pharmacother* 2015;49:784–9. Available from: https://pubmed.ncbi.nlm.nih.gov/25862012
43. Blair CS, Li S, Chau G, Cottle L, Richardson P, Marzinke MA, *et al*. Brief report: hormonal contraception use and cabotegravir pharmacokinetics in HIV-uninfected women enrolled in HPTN 077. *J Acquir Immune Defic Syndr* 2020;85:93–7.
44. Trezza C, Ford SL, Gould E, Lou Y, Huang C, Ritter JM, *et al*. Lack of effect of oral cabotegravir on the pharmacokinetics of a levonorgestrel/ethinyl oestradiol-containing oral contraceptive in healthy adult women. *Br J Clin Pharmacol* 2017;83:1499–505.
45. Anderson MS, Hanley WD, Moreau AR, Jin B, Bieberdorf FA, Kost JT, *et al*. Effect of raltegravir on estradiol and norgestimate plasma pharmacokinetics following oral contraceptive administration in healthy women. *Br J Clin Pharmacol* 2011;71:616–20.
46. Food and Drug Administration (FDA). Stribild (Elvitegravir/cobicistat/emtricitabine/tenofovir) [Internet]. [cited 2022 Nov 2]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203100Orig1s000ClinPharmR.pdf
47. German P. Pharmacokinetic interactions between norgestimate/ethinyl estradiol and stribild STR. 12th International Workshop on Clinical Pharmacology of HIV Therapy 2011. Abstract 0_17. 2011.
48. British HIV Association. BHIVA/BASHH/FSRH guidelines for the sexual and reproductive health of people living with HIV - consultation open. 2017. Available from: https://www.bhiva.org/srh-guidelines-consultation
49. Muccini C, Canetti D, Castagna A, Spagnuolo V. Efficacy and safety profile of fostemsavir for the treatment of people with human immunodeficiency virus-1 (HIV-1): current evidence and place in therapy. *Drug Des Devel Ther* 2022;16:297–304.
50. Nwokolo N, Post E, Mageau AS, Shah R, Magee M, Mannino F, *et al*. Fostemsavir and ethinyl

estradiol drug interaction: clinical recommendations for co-administration. *HIV Med* 2022; Nov 13. doi: 10.1111/hiv.13442.
51. Abel S, Russell D, Whitlock LA, Ridgway CE, Muirhead GJ. Effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and ethinyloestradiol/levonorgestrel in healthy volunteers. *Br J Clin Pharmacol* 2008;65 (Suppl 1):19–26.
52. Faculty of Sexual and Reproductive Healthcare (FSRH). FSRH Clinical Guideline: Emergency Contraception (March 2017, amended December 2020). Available from: https://www.fsrh.org/documents/ceu-clinical-guidance-emergency-contraception-march-2017/
53. Medicines and Healthcare Products Regulatory Agency. Levonorgestrel-containing emergency hormonal contraception: advice on interactions with hepatic enzyme inducers and contraceptive efficacy [Internet]. 2016. Available from: https://www.gov.uk/drug-safety-update/levonorgestrel-containing-emergency-hormonal-contraception-advice-on-interactions-with-hepatic-enzyme-inducers-and-contraceptive-efficacy
54. Electronic Medicines Compendium (eMC). Summary of Product Characteristics: ellaOne 30 mg.
55. Electronic Medicines Compendium (eMC). Summary of Product Characteristics: Levonelle 1500 microgram tablet.
56. Scarsi KK, Smeaton LM, Podany AT, Olefsky M, Woolley E, Barr E, *et al*. Pharmacokinetics of dose-adjusted levonorgestrel emergency contraception combined with efavirenz-based antiretroviral therapy or rifampicin-containing tuberculosis regimens. *Contraception* 2023 Jan;109951.
57. Tarleton J, Chen BA, Meyn LA, Hendrix CW, Marzinke MA, Achilles SL. Pharmacokinetic and pharmacodynamic impacts of depot medroxyprogesterone acetate use on HIV pre-exposure prophylaxis in women. *J Acquir Immune Defic Syndr* 2020;85:182–8.
58. Scarsi KK, Cramer YS, Rosenkranz SL, Aweeka F, Berzins B, Coombs RW, *et al*. Antiretroviral therapy and vaginally administered contraceptive hormones: a three-arm, pharmacokinetic study. *Lancet HIV* 2019;6:e601–12.
59. Thurman AR, Schwartz JL, Brache V, Clark MR, McCormick T, Chandra N, *et al*. Randomized, placebo controlled phase I trial of safety, pharmacokinetics, pharmacodynamics and acceptability of tenofovir and tenofovir plus levonorgestrel vaginal rings in women. *PLoS One* 2018;13:e0199778.

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