

**Combined Oral Contraceptive (COC) and Antiretroviral (ARV)
Drug Interactions**

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Nucleotide Reverse Transcriptase Inhibitor			
Tenofovir (Viread®)	Minimal systemic metabolism. Not substrate of CYP 450 enzymes. Renal elimination.	No effect on norgestimate (NGM)-ethinyl estradiol (EE) levels after taking tenofovir 300mg daily for 7 days. ¹	No specific action required.
Protease Inhibitors			
Atazanavir (Reyataz®)	<u>Metabolism:</u> CYP3A4 substrate <u>Enzyme Inhibition:</u> Inhibits CYP3A4	↑ 48% AUC of EE and ↑ 110% AUC of norethindrone (NE) after taking atazanavir 400mg daily for 2 weeks. ² ↓ 19% AUC, ↓ 16% C _{max} of EE; ↑ 85% AUC, ↑ 68% C _{max} of NGM with atazanavir 300mg/ritonavir 100mg for 14 days. Authors concluded that 35 µg EE + ATV/RTV is expected to produce EE exposures similar to EE 25 µg without ATV/RTV. ³	Atazanavir/Ritonavir: Use OC with minimum 30 µg ethinyl estradiol (manufacturer recommendation). <u>Atazanavir:</u> Use OC with no more than 30 µg ethinyl estradiol (manufacturer recommendation). Monitor for side effects of increased progesterone levels (including acne, and ↓ HDL and ↑ insulin resistance esp. in diabetic women). Use of other hormonal products (i.e. patch/ring/injectable) not recommended. ⁴
Darunavir (Prezista®)	<u>Metabolism:</u> CYP3A4 substrate <u>Enzyme Inhibition:</u> Inhibits CYP3A4	↓ 44% AUC, ↓ 62% C _{min} of EE and ↓ 14% AUC, ↓ 30% C _{min} of NE after taking darunavir/ ritonavir 600/100mg bid for 2 weeks. ⁵	Use alternate/additional methods of contraception (latex condom) secondary to loss of OC efficacy.
Fos/amprenavir (Telzir®)	<u>Metabolism:</u> CYP3A4 substrate <u>Enzyme Induction:</u> Induces CYP3A4 <u>Enzyme Inhibition:</u> Inhibits CYP3A4	<u>Amprenavir studies:</u> ↓ 22% AUC, ↓ 20% C _{min} of amprenavir; ↑ 32% C _{min} of EE; ↑ 45% C _{min} , ↑ 18% AUC of NE with oral contraceptives containing EE 0.035 mg/NE 1mg. ⁶ May lead to loss of virologic response and possible resistance to amprenavir. <u>Fosamprenavir</u>	Use alternate/additional non-hormonal methods of contraception (latex condom).

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

		<p><u>studies:</u> No change pk of amprenavir; ↓ 28% C_{max}, ↓ 37% AUC of EE; ↓ 38% C_{max}, ↓ 34% AUC, ↓ 26% C_{min} norethisterone after fosamprenavir 700 mg/ritonavir 100mg bid for 21 days.⁶ Significant hepatic enzyme elevations and increased ritonavir levels also seen when boosted fosamprenavir used with COC.⁶</p>	
Indinavir (Crixivan®)	<p><u>Metabolism:</u> CYP3A4 substrate</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4</p>	<p>↑ 24% AUC of EE; ↑ 26% AUC of NE.⁷</p>	No specific action required.
Lopinavir (Kaletra®)	<p><u>Metabolism:</u> CYP3A4 substrate</p> <p><u>Enzyme Induction:</u> Induces GT and possibly CYP1A2, 2C19, 2C</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4>2D6</p>	<p>↓ 42% AUC, ↓ 41% C_{max}, ↓ 58% C_{min} of EE and ↓ 17% AUC, ↓ 16% C_{max}, ↓ 32% C_{min} of NE.⁸</p>	<p>Use alternate/additional methods of contraception (latex condom) secondary to loss of OC efficacy. Use Progestin based contraceptives (Depo-Provera®). However, delavirdine, lopinavir/ritonavir, nelfinavir, and ritonavir might ↑ concentration of progestin-based contraceptives (metabolized by CYP 3A4). Monitor for the development of adverse effects with Depo-Provera®.⁹</p>
Nelfinavir (Viracept®)	<p><u>Metabolism:</u> CYP3A4>2C19</p> <p><u>Enzyme Induction:</u> Induces CYP2B6, 2C8 and 2C9</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4</p>	<p>↓ 47% AUC, ↓ 28% C_{max} of EE; ↓ 18% AUC of NE after nelfinavir 750mg q8h for 7 days. C_{max} NE unchanged.¹⁰</p>	<p>See Lopinavir See DMPA chart</p>
Ritonavir (Norvir®)	<p><u>Metabolism:</u> CYP3A4>2D6</p> <p><u>Enzyme Induction:</u></p>	<p>↓ 40% AUC, ↓ 32% C_{max} of EE after ritonavir 500mg</p>	See Lopinavir

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	Induces glucuronyl transferases (GT), CYP1A2, 2B6, 2C9, 2C19 <u>Enzyme Inhibition:</u> CYP3A>2D6>2C9, 2C19>>2A6, 2E1	q12h for 16 days. ¹¹	
Saquinavir (Invirase®)	<u>Metabolism:</u> CYP3A4 substrate <u>Enzyme Inhibition:</u> Weak inhibitor of CYP3A4	Single dose saquinavir levels were not affected by combined low-dose OC (0.03 mg EE, 0.075 mg gestodene). ¹²	Due to use of saquinavir in combination with ritonavir, use alternate/additional methods of contraception (latex condom).
Tipranavir (Aptivus®)	<u>Metabolism:</u> CYP3A4, p-glycoprotein (Pgp) substrate <u>Enzyme Induction:</u> Induces CYP3A4, GT, Pgp>CYP1A2>2C9 <u>Enzyme Inhibition:</u> Inhibits CYP2D6 Note: When given with ritonavir, net effect is CYP3A inhibition.	↓ 50% AUC and C _{max} of single dose EE; no change in NE after tipranavir 500mg/ritonavir 100mg twice daily. ¹³	Use alternate/additional methods of contraception (latex condom) secondary to loss of OC efficacy. ¹³
CCR5 Antagonist			
Maraviroc (Celsentri®)	<u>Metabolism:</u> CYP3A4, Pgp substrate	No change in C _{max} or AUC of oral contraceptives (30mcg EE/150 mcg levonorgestrel (LNG)) with low dose maraviroc (100mg twice daily) ¹⁴	No specific action required. More research needed with full dose maraviroc (300mg twice daily).
Integrase Inhibitor			
Raltegravir (Isentress®)	<u>Metabolism:</u> UGT1A1-mediated glucuronidation	↓ 12% AUC of EE; ↑ 14% AUC of norelgestromin (NGMN). ¹⁵ ↓ 2% AUC, ↑ 6% C _{max} of EE; ↑ 14% AUC, ↑ 29% C _{max} of NGMN when taken with raltegravir 400mg twice daily for 21 days. ¹⁶	No specific action required.

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<p>Elvitegravir (GS-9137) Quad tablet (elvitegravir/cobicistat/emtricitabine/tenofovir)</p>	<p><u>Metabolism:</u> combination of oxidative (CYP3A) and glucoronidation pathways</p> <p><u>Enzyme Induction:</u> moderate inducer of CYP3A</p>	<p>↓ 25% AUC of EE; ↑ 2-fold AUC/C_{max} of NGM-active metabolite with stable OrthoTri-Cyclen Lo (EE 25 µg/NGM 180/215/250 µg) and Quad tablet daily for 14 days. No change progesterone level, similar ↓ FSH, larger ↓ LH during co-administration with Quad versus EE/NGM alone.¹⁷</p>	<p>Authors recommend using oral contraceptive with minimum of 30 µg EE.</p>
<p>Non-nucleoside Reverse Transcriptase Inhibitors</p>			
<p>Delavirdine (Rescriptor®)</p>	<p><u>Metabolism:</u> CYP3A4>>2D6 substrate</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4, 2C9,2C19</p>	<p>Clinically significant interaction is unlikely.¹⁸</p>	<p>No specific action required.</p>
<p>Efavirenz (Sustiva®)</p>	<p><u>Metabolism:</u> CYP3A4, 2B6 substrate</p> <p><u>Enzyme Induction:</u> Induces CYP3A4</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4, 2C9, 2C19</p>	<p>↑ 37% AUC of EE 50 µg after 10 days of efavirenz (EFV) 400mg.¹⁹</p> <p>However, EFV found to interfere with the estradiol ELISA assay. This may artificially elevate estradiol levels if ELISA assay used.²⁰</p> <p>No change EE level (LC-MS/MS assay); ↓ 64% AUC of NGM and ↓ 83% AUC of LNG (active metabolite of NGM) after EFV 600mg for 14 days.²¹</p> <p>↓ 56% AUC of LNG (0.75 mg single dose for emergency contraception) after EFV 600mg for 14 days.²²</p>	<p>Potential for failure of progesterone component. May need to increase progesterone dose when used for daily or emergency contraception (i.e. use third generation progesterone such as desogestrel or gestodene which have higher affinity for progesterone receptor). Alternative methods of contraception (latex condom) recommended.</p>

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

Etravirine (Intelligence®)	<u>Metabolism:</u> CYP 3A4, 2C9, 2C19 substrate <u>Enzyme Induction:</u> Induces CYP3A4 <u>Enzyme Inhibition:</u> Inhibits CYP2C9, 2C19, mildly inhibits Pgp	↑ 22% AUC of EE; no change in AUC of NE after 15 days of ETV 200mg twice daily. ²³	No specific action required.
Nevirapine (Viramune®)	<u>Metabolism:</u> CYP3A4>>2B6 substrate <u>Enzyme Induction:</u> Induces CYP3A4, 2B6	↓ 20 % AUC of EE; ↓ 19% AUC, ↓ 16% C _{max} of NE. ²⁴ ↓ 29% AUC EE; ↓ 18% AUC of NE. ²⁵ Steady-state kinetics of COC (EE 30 µg and norgestrel 300 µg for at least 6 weeks) were studied in 3 groups of women: Group 1: HIV-positive on nevirapine (plus 3TC/d4T) for 90 days minimum Group 2: HIV-positive <u>not</u> on ARVs Group 3: HIV-negative Group 1: Highest AUC of EE; Highest AUC, C _{min} of LNG; ovulation suppressed. Conflicting evidence from previous studies, further study needed. ²⁶	Use alternate/additional methods of contraception (latex condom) secondary to loss of OC efficacy. Use Progestin based contraceptives (Depo-Provera®). See DMPA chart.
Rilpivirine	<u>Metabolism:</u> CYP3A4> CYP2C19, 1A2, 2C8/9/10 (minor). <u>Enzyme Induction:</u> CYP2C19,> CYP1A2, 2B6, 3A4. (unlikely clinically relevant)	↑ 17% C _{max} of EE; pK of NE unaffected after 15 days of rilpivirine 25mg daily. ²⁷	No specific action required.

COC metabolism:

Ethinyl Estradiol:GT, sulphatase, substrate CYP3A4 > 2C9; Inhibits CYP1A2, 3A
Progestins: if contain ethinyl group-may inhibit CYP enzymes

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

Transdermal Contraceptive and Antiretroviral (ARV) Drug Interactions

Name	Ingredients
Evra®	Ethinyl estradiol 35 µg/norelgestromin 200 µg once a week for 3 weeks out of 4

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Protease Inhibitors			
Lopinavir (Kaletra®)	<p><u>Metabolism:</u> CYP3A4 substrate</p> <p><u>Enzyme Induction:</u> Induces GT and possibly CYP1A2, 2C19, 2C</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4>2D6</p>	<p>Transdermally delivered EE and NGMN was studied in 8 HIV positive women on stable Kaletra® (LPV/r) compared to 24 women not on ARVs. Also, EE AUC after a single dose of a COC pill (EE/NE) was measured before patch placement and was compared with patch EE AUC in both groups.</p> <p>↓ 45% AUC EE patch; ↓ 55% AUC EE pill in women on LPVr vs. controls (p=0.064 and p=0.003, respectively). ↑ 83% AUC NGMN in LPVr group vs. controls (p=0.036).²⁸</p>	<p>The investigators concluded that although the kinetics of EE and NGMN were significantly altered in the presence of LPV/r, the contraceptive efficacy of the patch was likely to be maintained due to the increased NGMN levels.</p> <p>The manufacturer recommends alternative/additional contraception with the contraceptive patch.⁸</p>

Implantable Contraceptive and Antiretroviral (ARV) Drug Interactions

Name	Ingredients
Implanon®	Etonogestrel 68 µg <i>*not available in Canada</i>

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Non-nucleoside Reverse Transcriptase Inhibitors			
Efavirenz (Sustiva®)	<p><u>Metabolism:</u> CYP3A4, 2B6 substrate</p> <p><u>Enzyme Induction:</u> Induces CYP3A4</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4, 2C9, 2C19</p>	<p>Etonogestrel exposure may be decreased (although not studied) due to postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.^{29,30}</p>	<p>Use alternate/additional methods of contraception (latex condom) secondary to loss of OC efficacy.</p>

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

Depo-medroxyprogesterone (DMPA) and Antiretroviral Drug Interactions

Name	Ingredients
Depo-Provera®	depo-medroxyprogesterone 150 µg IM every 3 months

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Protease Inhibitors			
Nelfinavir (Viracept®)	<p><u>Metabolism:</u> CYP3A4>2C19,2D6 substrate</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4</p>	In 21 HIV patients, no change in AUC of nelfinavir 4 weeks after DMPA administered. After 12 weeks, no pregnancies, no women appeared to ovulate based on progesterone levels. ³¹ No affect on CD4 or HIV RNA levels. ³²	DMPA appears effective and safe in patients on nelfinavir. ³¹
Atazanavir (Reyataz®)	<p><u>Metabolism:</u> CYP3A4 substrate</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4</p>	Not studied.	Manufacturer does not recommend use of injectable contraceptives. ⁴
Non-nucleoside Reverse Transcriptase Inhibitors			
Efavirenz (Sustiva®)	<p><u>Metabolism:</u> CYP3A4, 2B6 substrate</p> <p><u>Enzyme Induction:</u> Induces CYP3A4</p> <p><u>Enzyme Inhibition:</u> Inhibits CYP3A4, 2C9, 2C19</p>	In 17 HIV patients, no change in AUC of efavirenz 4 weeks after DMPA administered. After 12 weeks, no pregnancies, no women appeared to ovulate based on progesterone levels. ³¹ No affect on CD4 or HIV RNA levels. ³² In 30 HIV+ women, pK of DMPA similar with women on ARVs (EFV/AZT/3TC) versus no ARVs. ³³	DMPA appears effective and safe in patients on efavirenz. ³¹
Nevirapine (Viramune®)	<p><u>Metabolism:</u> CYP3A4>>2B6 substrate</p> <p><u>Enzyme Induction:</u> Induces CYP3A4, 2B6</p>	In 16 HIV patients, small increase in nevirapine AUC 4 weeks after DMPA administered. After 12 weeks, no pregnancies, no women appeared to ovulate based on progesterone levels. ³¹ No affect on CD4 or HIV RNA levels. ³²	DMPA appears effective and safe in patients on nevirapine. Increased nevirapine levels do not appear to be clinically significant. ³¹

DMPA metabolism:
CYP3A4 substrate

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

Levonorgestrel-releasing Intrauterine System (LNG-IUS) and Antiretroviral Drug Interactions

Name	Ingredients
Mirena®	Intrauterine system /levonorgestrel 52 mg
Nova-T®	Intrauterine copper

Drug	Interaction	Suggestion
HAART (Nine different combinations of reverse transcriptase inhibitors and protease inhibitors)	In a study of 12 HIV + women, 83% on HAART, LNG levels slightly decreased over the 12 month study period. Estradiol levels remained in the follicular-phase range (>70 pmol/l). No pregnancies were reported. No affect on CD4 or HIV RNA levels. ³⁴	More research on interactions with specific antiretrovirals needed. Currently use of LNG-IUS and copper IUD recommended by CDC.³⁵

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

Canadian Contraceptives Overview

Oral Contraceptives

Low Dose EE	Ingredients
Alesse® Aviane®	Ethinyl estradiol 20 µg/levonorgestrel 100 µg
Linessa®	Ethinyl estradiol 25 µg/desogestrel 100/125/150 µg
Minestrin®	Ethinyl estradiol 20 µg/norethindrone acetate 1mg
Tri-Cyclen Lo®	Ethinyl estradiol 25 µg/ norgestimate 180/215/250 µg
Yaz®	Ethinyl estradiol 20 µg/ drospirenone 3 mg
High Dose EE	Ingredients
Cyclen®	Ethinyl estradiol 35 µg/norgestimate 250 µg
Ovral®	Ethinyl estradiol 50 µg/norgestrel 250 µg
Tri-Cyclen®	Ethinyl estradiol 35 µg/norgestimate 180/215/250 µg
Brevicon 0.5/35® Ortho 0.5/35®	Ethinyl estradiol 35 µg/norethindrone 0.5mg
Brevicon 1/35® Ortho 1/35®	Ethinyl estradiol 35 µg/norethindrone 1mg
Synphasic®	Ethinyl estradiol 35 µg/norethindrone 0.5/1/0.5mg
Ortho 7/7/7®	Ethinyl estradiol 35 µg/norethindrone 0.5/0.75/1 mg

Third Generation Progestones

Name	Ingredients
Apri®	Ethinyl Estradiol 30 µg/ desogestrel 150 µg
Linessa®	Ethinyl estradiol 25 µg/ desogestrel 100/125/150 µg
Marvelon®	Ethinyl Estradiol 30 µg/ desogestrel 150 µg
Ortho-Cept®	Ethinyl Estradiol 30 µg/ desogestrel 150 µg

Transdermal Contraceptives

Name	Ingredients
Evra®	Ethinyl estradiol 35 µg/norelgestromin 200 µg once a week for 3 weeks out of 4

Implantable Contraceptives-not available in Canada

Name	Ingredients
Implanon®	Etonogestrel 68 µg

Injectable Contraceptives

Name	Ingredients
Depo-Provera®	depo-medroxyprogesterone 150 µg IM every 3 months

Intrauterine Contraceptives

Name	Ingredients
Mirena®	Intrauterine system /levonorgestrel 52 mg
Nova-T®	Intrauterine copper

Abbreviations: COC=combined oral contraceptive, EE= ethinyl estradiol, LNG= levonorgestrel, NE= norethindrone, NGM= norgestimate, NGMN= norelgestromin

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