Interactions between Antiretrovirals (ARVs) and Hormonal Contraceptives

This document consists of the following sections:

1. Metabolism Characteristics of Hormonal Contraceptives

Hormone	Metabolism
Desogestrel	Rapidly and completely metabolized by hydroxylation in the intestinal mucosa and on first pass through the liver via CYP2C9 to etonogestrel, its biologically active metabolite.
Drospirenone	Extensively metabolized after oral administration, but CYP3A4 is involved only to a minor extent.
Ethinyl Estradiol	Extensively metabolized. Substrate of CYP3A4, 2C9, and UGT. Inhibitor of CYP2C19, CYP3A4 and CYP2B6. Induces UGT.
Etonogestrel	Substrate of CYP3A4.
Levonorgestrel	Substrate of CYP3A4. Undergoes glucuronidation to a minor extent.
Medroxyprogesterone acetate	Substrate of CYP3A4.
Norelgestromin	Metabolized to norgestrel which is a substrate of CYP3A4
Norethindrone	Extensively metabolized, substrate of CYP3A4
Norgestimate	Metabolized to norelgestromin
Norgestrel	Substrate of CYP3A4.

Legend: The information in this table is compiled from review articles summarizing available published literature.[1-4]

2. ARV and Combined Oral Contraceptive (COC) 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.[5]	**No specific action required.**

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

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Protease Inhibitors			
Atazanavir (Reyataz®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Inhibits CYP3A4	↑ 48% AUC of EE and ↑ 110% AUC of norethindrone (NE) after taking atazanavir 400mg daily for 2 weeks.[6] ↓ 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.[7] In this study, atazanavir AUC 20% ↑ and Cmax 11% ↑ compared to historical controls, but these differences were not considered clinically significant.	Atazanavir/Ritonavir: Use OC with **minimum 30 µg ethinyl estradiol** (manufacturer recommendation). Atazanavir: 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.[8] Atazanavir/cobicistat: No data are available to make recommendations; alternative nonhormonal forms of contraception should be considered (manufacturer recommendation).
Darunavir (Prezista®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: 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.[9]	Darunavir/ritonavir and darunavir/cobicistat: **Use alternate/additional methods of contraception** (latex condom) secondary to loss of OC efficacy.
Fos/amprenavir (Telzir®)	Metabolism: CYP3A4 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP3A4	Amprenavir studies: ↓ 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.[10] May lead to loss of virologic response and possible resistance to amprenavir. Fosamprenavir studies: No change pk of amprenavir; ↓ 28% C_{max},	**Use alternate/ additional non-hormonal methods of contraception** (latex condom). Use of fosamprenavir alone with ethinyl estradiol/norethindrone may lead to loss of virologic response.

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		↓ 37% AUC of EE; ↓ 38% C_{max}, ↓ 34% AUC, ↓ 26% C_{min} norethisterone after fosamprenavir 700 mg/ritonavir 100mg bid for 21 days[10] Significant hepatic enzyme elevations and increased ritonavir levels also seen when boosted fosamprenavir used with COC.[10]	
Indinavir (Crixivan®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Inhibits CYP3A4	↑ 24% AUC of EE; ↑ 26% AUC of NE.[11]	**No specific action required.**
Lopinavir (Kaletra®)	Metabolism: CYP3A4 substrate Enzyme Induction: Induces GT and possibly CYP1A2, 2C19, 2C Enzyme Inhibition: Inhibits CYP3A4>2D6	↓ 42% AUC, ↓ 41% C_{max}, ↓ 58% C_{min} of EE and ↓ 17% AUC, ↓ 16% C_{max}, ↓ 32% C_{min} of NE.[12]	**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®.[13]
Nelfinavir (Viracept®)	Metabolism: CYP3A4>2C19 Enzyme Induction: Induces CYP2B6, 2C8 and 2C9 Enzyme Inhibition: Inhibits CYP3A4	↓ 47% AUC, ↓ 28% C_{max} of EE; ↓ 18% AUC of NE after nelfinavir 750mg q8h for 7 days. C_{max} NE unchanged.[14]	**See Lopinavir** **See DMPA chart**
Ritonavir (Norvir®)	Metabolism: CYP3A4>2D6 Enzyme Induction: Induces glucuronyl transferases (GT), CYP1A2, 2B6,	↓ 40% AUC, ↓ 32% C_{max} of EE after ritonavir 500mg q12h for 16 days.[15]	**See Lopinavir**

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
	2C9, 2C19 Enzyme Inhibition: CYP3A>2D6>2C9, 2C19>>2A6, 2E1		
Saquinavir (Invirase®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Weak inhibitor of CYP3A4	Single dose saquinavir levels were not affected by combined low-dose OC (0.03 mg EE, 0.075 mg gestodene).[16]	Due to use of saquinavir in combination with ritonavir, use **alternate/ additional methods of contraception** (latex condom).
Tipranavir (Aptivus®)	Metabolism: CYP3A4, p-glycoprotein (Pgp) substrate Enzyme Induction: Induces CYP3A4, GT, Pgp>CYP 1A2>2C9 Enzyme Inhibition: 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.[17]	Use **alternate/ additional methods of contraception** (latex condom) secondary to loss of OC efficacy.[17]
CCR5 Antagonist			
Maraviroc (Celsentri®)	Metabolism: 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).[18]	**No specific action required**. **More research needed** with full dose maraviroc (300mg twice daily).
Integrase Inhibitors			
Dolutegravir (Tivicay®)	Metabolism: substrate of UGT1A1 (primary pathway) and CYP3A4 (10-15%).	In a randomized, 2-period, double-blind, placebo-controlled, crossover study conducted within a single menstrual cycle, healthy female subjects received Ortho-Cyclen (ethinyl estradiol [EE] 0.035 mg and norgestimate 0.25 mg) and dolutegravir 50 mg BID or placebo for 10 days followed by Ortho-Cyclen only on day 11. From days 12 to 21,	**Oral contraceptives can be co-administered with dolutegravir 50 mg once or twice daily without dose adjustment.**

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		subjects who had taken DTG were switched to placebo, and subjects who had taken placebo were switched to DTG, which subjects took every 12 hours with food. Luteinizing hormone, follicle stimulating hormone, and progesterone levels were collected on days 1, 10, 11, 21, and 22. The PK of EE and norelgestromin (NGMN) were not altered by concomitant dolutegravir and there were no clinically relevant differences in pharmacodynamic measures.[19]	
Elvitegravir (Stribild®: elvitegravir/cobicistat/ emtricitabine/tenofovir)	Metabolism: combination of oxidative (CYP3A) and glucoronidation pathways Enzyme Induction: moderate inducer of CYP3A	↓ 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.[20]	**Authors recommend using oral contraceptive with minimum of 30 µg EE.**
Raltegravir (Isentress®)	Metabolism: UGT1A1-mediated glucuronidation	↓ 2% AUC, ↑ 6% Cmax of EE; ↑14% AUC, ↑ 29% C_{max} of NGMN when taken with raltegravir 400mg twice daily for 21 days.[21]	**No specific action required**.
Non-nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (Rescriptor®)	Metabolism: CYP3A4>>2D6 substrate Enzyme Inhibition: Inhibits CYP3A4, 2C9,2C19	Concentrations of ethinyl estradiol may increase. However, the clinical significance is unknown.[22]	**No specific action required.**

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Efavirenz (Sustiva®)	<u>Metabolism:</u> CYP3A4, 2B6 substrate <u>Enzyme Induction:</u> Induces CYP3A4 <u>Enzyme Inhibition:</u> Inhibits CYP3A4, 2C9, 2C19	↑ 37% AUC of EE 50 µg after 10 days of efavirenz (EFV) 400mg.[23] However, EFV found to interfere with the estradiol ELISA assay. This may artificially elevate estradiol levels if ELISA assay used.[24] 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.[25] Low efavirenz concentrations in the presence of COC (Marvelon: 0.150 mg desogestrel/0.03 mg ethinyl estradiol) were noted in one study.[26] In HIV-positive women (n=16) on stable efavirenz-based therapy, coadministration of Marvelon (0.150 mg desogestrel/0.03 mg ethinyl estradiol) for 2 cycles led to a 61% reduction in the expected GM C24 of ENG and no significant changes in the EE2 C24 compared with healthy controls. Possible signs of ovulation were detected in 19% of the subjects based on single endogenous progesterone measurement. Therefore, **use of DSG/ENG-containing hormonal contraception in women on EFV-based therapy should be avoided** due to possible contraceptive	**Potential for failure of progesterone component.** May need to increase progesterone dose when used for 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.**

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		failure.[27]	
Etravirine (Intelence®)	Metabolism: CYP 3A4, 2C9, 2C19 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP2C9, 2C19, mildly inhibits Pgp	↑ 22% AUC of EE; no change in AUC of NE after 15 days of ETV 200mg twice daily.[28]	**No specific action required.**
Nevirapine (Viramune®)	Metabolism: CYP3A4>>2B6 substrate Enzyme Induction: Induces CYP3A4, 2B6	↓ 20 % AUC of EE; ↓ 19% AUC, ↓ 16% C_{max} of NE.[29] ↓ 29% AUC EE; ↓ 18% AUC of NE.[30] 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 not 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.[31]	Some studies suggest preservation of COC efficacy with nevirapine coadministration.[26, 31, 32] Alternate/additional methods of contraception may still be considered. **Progestin-based contraceptives (Depo-Provera®) may be used**. **See DMPA chart.**

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Rilpivirine	Metabolism: CYP3A4> CYP2C19, 1A2, 2C8/9/10 (minor). Enzyme Induction: CYP2C19,> CYP1A2, 2B6, 3A4. (unlikely clinically relevant)	↑ 17% C_{max} of EE; pK of NE unaffected after 15 days of rilpivirine 25mg daily.[33]	**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

3. Progesterone-Only Oral Contraceptive

Name	Ingredients
Micronor®	Norethindrone 0.35 mg

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Protease Inhibitors			
All	Metabolism: CYP3A4 *Ritonavir:* Enzyme Induction: Induces glucuronyl transferases (GT), CYP1A2, 2B6, 2C9, 2C19 Enzyme Inhibition: CYP3A>2D6>2C9, 2C19>>2A6, 2E1	In an open-label, prospective, nonrandomized trial to characterize the steady-state pharmacokinetics of norethindrone 0.35 mg once daily for 21 days in HIV-infected women receiving PI therapy (n=10 on atazanavir/rtv, n=1 on atazanavir, n=3 on darunavir/ritonavir, n=2 on lopinavir/ritonavir) compared with a control group of HIV-infected women not receiving PIs, serum norethindrone AUC was 50% higher in the women on concomitant PI compared to women not on PI therapy (p=0.004). The investigators concluded that this increase was not a concern for	Coadministration of PI inhibits NET metabolism as shown by higher serum NET area under the curve levels, a surrogate marker for therapeutic contraceptive efficacy. This study supports the increased utilization of progestin-only pills in HIV-infected women receiving certain PI regimens.

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		toxicity and did not warrant dose reduction.[34] Norethindrone (NET) serum concentrations were significantly higher in HIV-infected women taking a PI compared with controls (P = 0.004). The ratio of the geometric mean NET area under the curve in the PI group compared with controls was 1.5 (90% confidence interval: 1.21 to 1.86).[35]	

4. Emergency Contraception Drug Interactions

Name	**Ingredients**
Plan B®	Levonorgestrel 0.75 mg (two tablets within 72 hours of unprotected sexual intercourse)

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Non-Nucleoside Reverse Transcriptase Inhibitors			
Efavirenz (Sustiva®)	Metabolism: CYP3A4, 2B6 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP3A4, 2C9, 2C19	↓ 56% AUC of LNG (0.75 mg single dose for emergency contraception) after EFV 600mg for 14 days.[36]	**Potential for failure of progesterone component.** May need to increase progesterone dose when used for emergency contraception (i.e. use third generation progesterone such as desogestrel or gestodene which have higher affinity for progesterone receptor).

5. ARV-Transdermal Contraceptive 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

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Protease Inhibitors			
Lopinavir/ritonavir (Kaletra®)	Metabolism: CYP3A4 substrate Enzyme Induction: Induces GT and possibly CYP1A2, 2C19, 2C Enzyme Inhibition: Inhibits CYP3A4>2D6	**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. ↓ 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).[37]	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. **The manufacturer recommends alternative/additional contraception with the contraceptive patch.**[12] Similar recommendations apply to all ritonavir-containing regimens.[38]

6. ARV-Implantable Contraceptive Drug Interactions

Name	**Ingredients**
Implanon®	Etonogestrel 68 µg ***not available in Canada***
Jadelle®	Levonorgestrel 75 mg ***not available in Canada***

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Protease Inhibitors			
Lopinavir/ritonavir (Kaletra®)	Metabolism: CYP3A4 substrate Enzyme Induction: Induces GT and possibly CYP1A2, 2C19, 2C Enzyme Inhibition: Inhibits CYP3A4>2D6	Etonogestrel: In a prospective, non-randomized pharmacokinetic study, the kinetics of etonogestrel (ENG) were assessed in women on stable lopinavir/r therapy (n=15), efavirenz-based therapy (n=15) or not on any ART (n=15). PK	Combination is not anticipated to impair the efficacy of etonogestrel or levonorgestrel implant.

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		parameters were measured at baseline and 2, 4, 6, 8, 10, 12, 16, 20, and 24 weeks after implant placement. Etonogestrel exposures were increased in the lopinavir/r group (ENG AUC ↑ 52%, Cmax ↑ 61% and Cmin ↑ 34%) compared to the non-ART group.[39] <u>Levonorgestrel</u>: In a retrospective analysis of 570 HIV-infected women in Swaziland using the Jadelle implant, 16 women (2.8%) became pregnant while using the Jadelle implant. 347 women were on ARVs at the time of implant insertion (n=208 on nevirapine, n=121 on efavirenz and n=18 on lopinavir/ritonavir). Antiretroviral regimen at the time of pregnancy correlated with pregnancy outcomes (P<0.001). None of the women on nevirapine or lopinavir/ritonavir-based regimens became pregnant, whereas 15 women on efavirenz (n=121; 12.4%) became pregnant.[40]	
Non-nucleoside Reverse Transcriptase Inhibitors			

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Efavirenz (Sustiva®)	Metabolism: CYP3A4, 2B6 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP3A4, 2C9, 2C19	Etonogestrel: In a prospective, non-randomized pharmacokinetic study, the kinetics of etonogestrel (ENG) were assessed in women on stable lopinavir/r therapy (n=15), efavirenz-based therapy (n=15) or not on any ART (n=15). PK parameters were measured at baseline and 2, 4, 6, 8, 10, 12, 16, 20, and 24 weeks after implant placement. Etonogestrel exposures were decreased in the efavirenz group (ENG AUC ↓ 63%, Cmax ↓ 54% and Cmin ↓ 70%) compared to the non-ART group.[39] Several postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.[41-45] Levonorgestrel: In a retrospective analysis of 570 HIV-infected women in Swaziland using the Jadelle implant, 16 women (2.8%) became pregnant while using the Jadelle implant. 347 women were on ARVs at the time of implant insertion (n=208 on nevirapine, n=121 on efavirenz and n=18 on	**Use alternate/additional methods of contraception** (latex condom) secondary to loss of OC efficacy. The levonorgestrel implant may be used with nevirapine-based therapy.

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		lopinavir/ritonavir). Antiretroviral regimen at the time of pregnancy correlated with pregnancy outcomes (P<0.001). None of the women on nevirapine or lopinavir/ritonavir-based regimens became pregnant, whereas 15 women on efavirenz (n=121; 12.4%) became pregnant.[40] In a prospective pharmacokinetic study, levonorgestrel concentrations were assessed in 60 HIV-positive women receiving a sub-dermal levonorgestrel implant: 20 initiating efavirenz-based therapy, 20 initiating nevirapine-based therapy, and 20 not yet eligible for ART. After adjusting for body weight, levonorgestrel levels in the nevirapine group were 32-39% higher compared to controls over 24 weeks, while levonorgestrel levels were 40-54% lower in the efavirenz group versus controls, and in 3 cases fell below the minimum recommended concentration for contraceptive efficacy.[46] In the final, 48-week analysis, 3 women in the efavirenz group (15%) became pregnant between weeks 36 and 48. At the last study visit, 15 subjects	

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		(75%) of the women in the efavirenz group had levonorgestrel concentrations below 303 pg/mL versus none in the control group. The efavirenz study arm was halted, and the researchers concluded that alternative contraception should be offered to women on efavirenz-based antiretroviral therapy.[47] Levonorgestrel concentrations were inversely related to efavirenz concentrations, but even in women with efavirenz concentrations within the therapeutic range (1-3 ug/mL), suboptimal levonorgestrel exposure was common. These results suggest that even if a lower efavirenz dose were used (e.g. 400 mg daily), a clinically significant interaction would still remain.[48]	
Nevirapine (Viramune®)	Metabolism: CYP3A4>>2B6 substrate Enzyme Induction: Induces CYP3A4, 2B6	Levonorgestrel: In a retrospective analysis of 570 HIV-infected women in Swaziland using the Jadelle implant, 16 women (2.8%) became pregnant while using the Jadelle implant. 347 women were on ARVs at the time of implant insertion (n=208 on nevirapine, n=121 on efavirenz and n=18 on lopinavir/ritonavir).	Preliminary data suggest that combination is not anticipated to impair the efficacy of levonorgestrel implant. Alternate/additional methods of contraception may still be considered until further data available.

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
		Antiretroviral regimen at the time of pregnancy correlated with pregnancy outcomes (P<0.001). None of the women on nevirapine or lopinavir/ritonavir-based regimens became pregnant, whereas 15 women on efavirenz (n=121; 12.4%) became pregnant.[40] In a prospective pharmacokinetic study, levonorgestrel concentrations were assessed in 60 HIV-positive women receiving a sub-dermal levonorgestrel implant: 20 initiating efavirenz-based therapy, 20 initiating nevirapine-based therapy, and 20 not yet eligible for ART. After adjusting for body weight, levonorgestrel levels in the nevirapine group were 32-39% higher compared to controls over 24 weeks, while levonorgestrel levels were 40-54% lower in the efavirenz group versus controls, and in 3 cases fell below the minimum recommended concentration for contraceptive efficacy. The researchers concluded that the levonorgestrel implant should be used with nevirapine-based rather than efavirenz-based antiretroviral therapy.[46]	

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7. ARV-Depo-medroxyprogesterone (DMPA) Drug Interactions

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

Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Nucleotide Reverse Transcriptase Inhibitor			
Tenofovir/emtricitabine (Truvada®)	Minimal systemic metabolism. Not substrate of CYP 450 enzymes. Renal elimination.	In a secondary analysis of data from a randomized, placebo-controlled trial of daily tenofovir and tenofovir/emtricitabine among serodisordant heterosexual couples, PrEP efficacy was similar among women using DMPA and those using no hormonal contraception. Similarly, PrEP efficacy for HIV-uninfected men did not differ between those whose partners used DMPA versus those who did not use hormonal contraception.[49]	**No specific action required.**
Protease Inhibitors			
Atazanavir (Reyataz®)	Metabolism: CYP3A4 substrate Enzyme Inhibition: Inhibits CYP3A4	Not studied.	Manufacturer does not recommend use of injectable contraceptives.[8]
Lopinavir/ritonavir (Kaletra®)	Metabolism: CYP3A4 substrate Enzyme Induction: Induces GT and possibly CYP1A2, 2C19, 2C Enzyme Inhibition: Inhibits CYP3A4>2D6	In a prospective assessment of DMPA in HIV-positive women, MPA exposures were significantly higher (46% higher AUC) in women taking lopinavir/ritonavir versus HIV-infected women not on ARVs or on NRTIs alone. Levels of LPV and RTV were not altered by depot MPA and there was no evidence of ovulation through week 12. Depot MPA was well-tolerated.[50]	The standard dose of DMPA (150 mg every 3 months) may be used in women taking lopinavir/ritonavir 400/100 mg BID.

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Drug	ARV Kinetic Characteristics	Interaction	Suggestion
Nelfinavir (Viracept®)	Metabolism: CYP3A4>2C19,2D6 substrate Enzyme Inhibition: Inhibits CYP3A4	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.[51] No effect on CD4 or HIV RNA levels.[52]	DMPA appears effective and safe in patients on nelfinavir.
Non-nucleoside Reverse Transcriptase Inhibitors			
Efavirenz (Sustiva®)	Metabolism: CYP3A4, 2B6 substrate Enzyme Induction: Induces CYP3A4 Enzyme Inhibition: Inhibits CYP3A4, 2C9, 2C19	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.[51] No effect on CD4 or HIV RNA levels.[52] In 30 HIV+ women, pK of DMPA similar with women on ARVs (EFV/AZT/3TC) versus no ARVs.[53]	DMPA appears effective and safe in patients on efavirenz.
Nevirapine (Viramune®)	Metabolism: CYP3A4>>2B6 substrate Enzyme Induction: Induces CYP3A4, 2B6	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.[51] No affect on CD4 or HIV RNA levels.[52]	DMPA appears effective and safe in patients on nevirapine. Increased nevirapine levels do not appear to be clinically significant.

DMPA metabolism: CYP3A4 substrate

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

8. ARV-Levonorgestrel-releasing Intrauterine System (LNG-IUS) Drug Interactions

Name	Ingredients
Jaydess®	Intrauterine system/levonorgestrel 13.5 mg
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 effect on CD4 or HIV RNA levels.[54]	**More research on interactions with specific antiretrovirals needed. Currently use of LNG-IUS and copper IUD recommended by CDC.[55, 56]**

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Canadian Contraceptives Overview

1) Combined Oral Contraceptives

Low Dose EE	**Ingredients**
Alesse® Alysena® Aviane®	Ethinyl estradiol 20 µg/levonorgestrel 100 µg
Linessa®	Ethinyl estradiol 25 µg/desogestrel 100/125/150 µg
Lolo®	Ethinyl estradiol 10 µg/norethindrone acetate 1mg, ethinyl estradiol 10 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	
Cyclen®	Ethinyl estradiol 35 µg/norgestimate 250 µg
Demulen 30®	Ethinyl estradiol 30 µg/ethynodiol diacetate 2 mg
Brevicon 0.5/35® Ortho 0.5/35®	Ethinyl estradiol 35 µg/norethindrone 0.5mg
Brevicon 1/35® Ortho 1/35® Select 1/35®	Ethinyl estradiol 35 µg/norethindrone 1mg
Loestrin®	Ethinyl estradiol 30 µg/norethindrone 1.5 mg
Ortho 7/7/7®	Ethinyl estradiol 35 µg/norethindrone 05/0.75/1 mg
Ovral®	Ethinyl estradiol 50 µg/norgestrel 250 µg
Portia® Seasonale®	Ethinyl estradiol 30 µg/levonorgestrel 150 µg
Synphasic ®	Ethinyl estradiol 35 µg/norethindrone 0.5/1/0.5mg
Tri-Cyclen®	Ethinyl estradiol 35 µg/norgestimate 180/215/250 µg
Third Generation Progesterones	
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

2) Progesterone Only Oral Contraceptive

Name	**Ingredients**
Micronor®	norethindrone 0.35 mg

3) Emergency Contraception

Name	**Ingredients**
Plan B®	Levonorgestrel 0.75 mg (two tablets within 72 hours of unprotected sexual intercourse)

4) Transdermal Contraceptives

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

5) Implantable Contraceptives-not available in Canada

Name	**Ingredients**
Implanon®	Etonogestrel 68 µg
Jadelle®	Levonorgestrel 75 mg

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

6) Injectable Contraceptives

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

7) Intrauterine Contraceptives

Name	Ingredients
Jaydess®	Intrauterine system/levonorgestrel 13.5 mg
Mirena®	Intrauterine system /levonorgestrel 52 mg
Nova-T®	Intrauterine copper

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

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