

## Supplementary materials

**Table S1** Detailed summary of pharmacokinetic studies

Author	Sample	Regimens used	Effect on HC pharmacokinetic parameters	Effect on ART pharmacokinetic parameters	Adverse events
<b>Nucleoside Reverse Transcriptase Inhibitors</b>					
<i>Tenofovir (Viread)</i>					
Kearney & Mathias (2009) <sup>1</sup>	20 HIV uninfected women	EE/ NGM NGM 0.18mg, EE 35 mcg x 7 days NGM 0.215mg, EE 35 mcg x 7 days NGM 0.25mg, EE 35 mcg x 7 days  TDF  EE/NGM alone x 3 mos EE/NGM alone x 3 weeks EE/NGM+TDF 300 mg qd contraceptive days 15-21 (peak NGM dose)	AUC <sub>t</sub> unchanged Half-life unchanged	AUC consistent with historical data	Well-tolerated.
Viread package label <sup>2</sup>			No clinically significant drug interactions observed between tenofovir and oral contraceptives.		
<b>Non-Nucleoside Reverse Transcriptase Inhibitors</b>					
<i>Nevirapine (Viramune)</i>					
Landolt et al. (2013) <sup>3</sup>	18 HIV infected women	EE 30mcg/DSG 0.150mg (1 pill per day for 2 consecutive cycles) + NVP +NRTI backbone	No evidence of ovulation	Plasma concentration 12 hours after administration: Baseline (without EE/DSG) vs Day 44 p=0.1. 6 of 18 subjects showed ↓ NVP levels.	Mild side effects.
Landolt et al. (2014) <sup>4</sup>	18 HIV infected women on NVP-based ART 14 HIV negative women	EE 30mcg/DSG 0.150mg (1 pill per day for 2 consecutive cycles) + NVP +NRTI backbone  Vs EE 30mcg/DSG 0.150mg (1 pill per day for 2 consecutive cycles)	EE: 58% reduction in levels 24 hours after pill intake DSG metabolites not significantly different	Not assessed	Not assessed
Mildvan et al. (2002) <sup>5</sup>	10 HIV infected women	Single dose administration of EE/NET days 0 and 1 Oral NVP 200 mg QD (days 2-15) followed by Oral NVP 200 mg BID (days	EE AUC↓29% (p=0.014) Half life: ↓ (p=0.010)	NVP ↔	8 subjects had at least 1 adverse event (57%). 33 AEs were reported, all mild or moderate in

		16-29) added to potent background therapy. Background regimens included: 3TC/d4T/IDV 3TC/ZDV/IDV 3TC ZDV/NFV 3TC/d4T/NFV ddI/d4T/IDV 3TC/ZDV/SQV 3TC/ZDV/ddC/IDV/RTV ddI/d4T	NET AUC↓ 18% Half life: ↓(not significant)		severity.
Viramune Package Label <sup>6</sup>	10	EE 35 mcg/NET 1 mg +Viramune 200 mg QD x 14 days followed by Viramune 200 mg BID x 14 days	EE AUC ↓20% NET AUC ↓19%	No information	No information
Stuart et al. (2011) <sup>7</sup>	9 women: 3 HIV+ on ART 3 HIV+ no ART 3 HIV-	EE 30mcg/NGST 300 mg + NVP 200mg+d4T 30mg+ 3TC 150 mg BID (if on ART)	Comparing HIV+ women to HIV- EE: AUC↑ LNG* : AUC ↑	Two women had NVP levels 2-4 fold higher than the third: genetic variation in CYP 450	No information
Watts et al. (2008) <sup>8</sup>	16 HIV+ on NVP-based regimen 16 HIV+ on NRTI only or no ART	DMPA 150 mg IM at study entry Stable ART regimen containing NVP	Progesterone levels were undetectable after DMPA administration. No pregnancies occurred.	No new information in this study	No AEs judged r/t study treatment. No significant changes in HIV-RNA seen after DMPA administration.
Cohn et al. (2007) <sup>9</sup>	16 HIV+ on NVP-based regimen 16 HIV+ on NRTI only or no ART	DMPA 150 mg IM at study entry Stable ART regimen containing NVP	No significant changes in AUC 0-12 weeks, or half-life. All progesterone levels <1.6ng/mL from week 2-12.	Drug exposure to NVP was increased at 4 weeks after DMPA.	No significant changes in CD4 count. Proportion with HIV-RNA<400 copies/mL did not change with DMPA
<b>Efavirenz (Sustiva)</b>					
Landolt et al. (2013) <sup>3</sup>	16 HIV+ women	EE 30mcg/DSG 0.150mg (1 pill per day for 2 consecutive cycles) + EFV +NRTI backbone	4 subjects had serum progesterone > 1.0 ng/mL. Could indicate ovulation	Plasma concentration 12 hours after administration: Baseline: (without EE/DSG) vs Day 44 (with EE/DSG) P=0.03. 3 had plasma EFV <1.0 mg/L (target threshold). 5 of the 16 experienced a slight increase in EFV plasma concentration 12 hours after	9 (56%) experienced mild adverse events

				administration.	
Landolt et al. (2014) <sup>4</sup>	16 HIV infected women on EFV-based ART 14 HIV negative women	EE 30mcg/DSG 0.150mg (1 pill per day for 2 consecutive cycles) + EFV +NRTI backbone Vs EE 30mcg/DSG 0.150mg (1 pill per day for 2 consecutive cycles)	EE: no significant change. ENG**: 61% reduction in levels 24 hours after pill intake p<0.0001	Not assessed	Not assessed
Sevinsky et al. (2011) <sup>10</sup>	19 HIV-	Period 1: EE 0.025 mg+NGM 0.18 mg days 1-7 EE 0.025 mg + NGM 0.215 mg days 8-14 EE 0.025 mg + NGM 0.25 mg days 15-21 Period 2: EE 35 mcg + NGM 0.25 mg Period 3: EE 35 mcg + NGM 0.25 mg+ 600 mg po QD x 14 days	EE : AUC ↔ NGMN***: AUC↓64% LNG***: AUC decreased 80-86%	Cmax, AUC, Cmin for EFV all comparable to historical controls	No deaths or discontinuations because of AEs. Most AEs were mild-moderate.
Sustiva Package Label <sup>11</sup>	21	EE 35 mcg/NGM 0.25 mg + EFV 600 mg QD x 14 days  Implant: etonogestrel	EE AUC ↔  Norelgestromin AUC↓64%  Levonorgestrel AUC↓83%  ↓etonogestrel	Not assessed	Not assessed
Carten et al. (2012) <sup>12</sup>	21 HIV-	LNG (Plan B) 0.75 mg at time 0 and 12 hours prior to starting EFV and after steady state EFV dosing (day 17). Subjects were started on EFV 600 mg 72 hours after visit 1 for 14 days.	LNG AUC↓56% Half-life ↓34%	No significant change in EFV geometric mean	Most common: Headache Abdominal pain Diarrhea Menstrual cycle changes
Vieira et al. (2014) <sup>13</sup>	15 HIV+ EFV/ZDV/3TC 15 HIV+ no ART	ENG implant EFV QD AZT+3TC BID	Progesterone levels: possible evidence of ovulation ENG: AUC: ↓63.4% compared to controls	Not assessed	All with HIV-RNA< 50 copies/mL at wk 24 in EFV group
Cohn et al. (2007) <sup>9</sup>	17 HIV+ on EFV-based regimen 16 HIV+ on NRTI only or no ART	DMPA 150 mg IM at study entry Stable ART regimen containing EFV	No effect.	No effect on AUC or half-life	See Cohn et al above.
Watts et al. (2008) <sup>8</sup>	17 HIV+ on EFV-based regimen 16 HIV+ on NRTI only or no ART	DMPA 150 mg IM at study entry Stable ART regimen containing EFV	No effect	Not assessed	See Watts et al above.
Nanda et al. (2008) <sup>14</sup>	30 HIV+ 15 on ART	DMPA 150 mg IM at study entry EFV/AZT/3TC	Mean plasma MPA concentrations were	No difference by group.	No difference by group.

	15 not on ART		similar in both groups.		
<b>Etravirine (Intelence)</b>					
Schoeller-Gyuere et al. (2009) <sup>15</sup>	30 HIV negative women	EE 35 mcg/NET 1 mg followed by a pill free week x 2 cycles. ETR 200 mg BID during the first 15 days of cycle 3.	EE: AUC: 22% higher with ETR than without.  NET: AUC: unchanged	Comparison with historical controls: Cmin, Cmax and AUC were all higher when ETR was taken with EE/NET than without	9 volunteers discontinued the trial due to adverse events. Rash: 7 – only reported in the coadministration phase. HSV: 1 Fever: 1
Intelence Package Label <sup>16</sup>	16	EE 35 mcg/NET 1mg qd	EE (mean ratio) AUC 1.22 (1.13, 1.31)  NET (mean ratio) AUC 0.95 (0.90, 0.99)	Not assessed	Not assessed
<b>Rilpivirine (Edurant)</b>					
Crauwels et al. (2013) <sup>17</sup>	15 HIV negative women	EE 35 mcg/NET 1 mg qd x 21 days RPV 25 mg qd x 15 days	EE: AUC unaffected  NET: AUC unaffected	Cmax, AUC, Cmin unaffected	No grade 3 or 4 adverse events
Edurant Package Label <sup>18</sup>	15 (impact on RPV) 17 (impact on EE/NET)	EE 35 mcg/NET 1 mg qd + RPV 25 mg QD	EE (mean ratio) AUC 1.14 (1.10, 1.19)  NET (mean ratio) AUC 0.89 (0.8f4, 0.94)	Cmax, AUC, Cmin unaffected	Not assessed
<b>Protease inhibitors</b>					
Atrio et al. (2014) <sup>19</sup>	33 HIV+ 16 taking PI-based regimens 17 taking other ART or no ART	0.35 mg NET ART including any PIs (ATV/r, ATV, DAR/r, LPV/r)	NET AUC: 37.8 ng.h/mL in PI group and 25.2 ng.h/mL in controls p=0.004 Half-life: 22.5 vs 24.3 p=0.28	Not assessed	Not assessed
<b>Ritonavir (Norvir)</b>					
Ouellet et al. (1998) <sup>20</sup>	23 HIV -	EE 50 mcg/ethynodiol diacetate 1 mg on day 1 and day 29 of the cycle Ritonavir days 15- 30, 300 mg BID day 15 400 mg BID day 16 500 mg BID days 17-30	EE AUC ↓41% (p<0.001) RTV explained 23% of the variability observed in EE AUC ratios.	Not assessed	Most were mild.
<b>Saquinavir (Inverase)</b>					
Froehlich et al. (2004) <sup>21</sup>	8 HIV -	EE 30 mcg + GSD: 0.075 mg 600 mg SQV (Invirase) prior to taking COC, and 600 mg SQV after 19 <sup>th</sup> dose of COC	Intake of COC resulted in statistically significant decrease in 17β-estradiol, progesterone, FSH and	No effect of COC on SQV pharmacokinetics	Not assessed

			LH and a significant increase in SHBG serum concentrations.		
<b>Nelfinavir (Viracept)</b>					
Cohn et al. (2007) <sup>9</sup>	21 HIV+ on NFV-based regimen 16 HIV+ on NRTI only or no ART	DMPA 150 mg IM at study entry Stable ART regimen containing NFV	No effect	No significant change in AUC. Slight decrease in half-life	See Cohen et al above.
Watts et al. (2008) <sup>8</sup>	21 HIV+ on NFV-based regimen 16 HIV+ on NRTI only or no ART	DMPA 150 mg IM at study entry Stable ART regimen containing NFV	No effect	Not assessed	See Watts et al above.
<b>Lopinavir/ritonavir (Kaletra)</b>					
Vieira et al. (2014) <sup>13</sup>	15 HIV+ LPV/r/ZDV/3TC 15 HIV+ no ART	Etonogestrel implant Stable ART regimen containing LPV/r or no ART	No evidence of ovulation. ENG: AUC ↑ 52% in LPV/r users than in controls.	Not assessed	13/15 adhered to ART regimen. 12 had HIV-RNA< 50 copies/mL at wk 24, 1 had unsatisfactory HIV-RNA reduction during the study period.
Vogler et al. (2010) <sup>22</sup>	8 HIV+ on LPV/r-based regimen (only 4 contributed PK data) 24 HIV+ not on ART	5-7 days after start of first menses since study entry both groups received a single dose OCP (EE 35mcg/NET 1mg) Started on OrthoEvra (EE 35 mcg/day and Norelgestromin 150 mcg/day) 48 hours later. LPV/r (400 mg/100 mg BID)-based regimen	EE Patch Median AUC ↓45% (p=0.064)  NGMN Patch AUC↑ 83% (p=0.036) Cmin↑134%  EE Pill AUC↓55% (p=0.003)  Median progesterone dropped for all subjects.	LPV when patch used AUC ↓19% (p=0.156)  RTV when patch used AUC↓24% (p=0.031)	A single Grade 3 symptom, others were mild.
Kaletra Package Label <sup>23</sup>	12 participants	EE 35 mcg/NET 1 mg QD x 21 days + Lopinavir/ritonavir 400/100 BID x 14 days	EE AUC 0.58 (0.54, 0.62)  NET AUC 0.83 (0.73, 0.94)	Not assessed	Not assessed
<b>Atazanavir (Reyataz)</b>					
Zhang et al. (2011) <sup>24</sup>	20 HIV- 13 with complete data	EE 35 mcg/NGM 0.18/0.215/0.25 mg from days 1-28. Then EE 35 mcg/NGM 0.18/0.215/0.25 mg + ATV/r 200/100 mg qd on days 29-42	EE+ATV/r AUC↓19%  NGM+ ATV/r AUC↑85%	ATV Cmax 6,770 ng/ml AUC 68,712 ng*h/mL Cmin 1,739 ng/mL  RTV Cmax 1480 ng/mL	Most frequent AEs Headache 16% Diarrhea 11% LPV/r+ ee/NGM Headache 38% Rash 38% Vomiting 19%

				AUC 10,471 ng*h/mL Cmin 69 ng/mL	All were mild or moderate. No deaths or serious AEs
DuBois et al. (2014) <sup>25</sup>	10 HIV+ on ATV/r 17 HIV+ on other ART not known to interact with NET	NET 0.35 mg ATV/r 300/100 x 22 days	NET+ATV/r AUC: ↑50% controls	Not assessed	Not assessed
Reyataz Package Label. <sup>26</sup>	19 participants  14 participants	EE 35 mcg/NET (days 1-29) + ATV 400 mg QD (days 16-29)  EE 35 mcg/NGM (days 1-28) then EE 35 mcg/NGM (days 29-42) + ATV 300 mg QD/RTV 100 mg QD (days 29-42)	EE AUC 1.48 (1.31, 1.68)  NET AUC 2.10 (1.68, 2.62)  EE AUC 0.81 (0.75, 0.87)  NET AUC 1.85 (1.67, 2.05)	Not assessed	Not assessed
<b>Darunavir (Prezista)</b>					
Sekar et al. (2008) <sup>27</sup>	19 HIV-	Session 1: EE 35 mcg NET 1.0 mg days 1-21 Session 2: EE 35 mcg NET 1.0 mg days 1-21 + DRV/r days 1-14	EE+DRV/r AUC↓44%  NET+DRV/r AUC↓14%	Not assessed	5 participants discontinued the study due to grade 2 cutaneous events
Prezista Package Label. <sup>28</sup>	11 participants	EE 35 mcg/NET 1mg + Prezista/ritonavir 600/100 BID	EE AUC 0.56 (0.50-0.63)  NET AUC 0.86 (0.75-0.98)	Not assessed	Not assessed
<b>Tipranavir (Aptivus)</b>					
Aptivus Package Label. <sup>29</sup>	21 participants	EE 35 mcg/NET 1.0 mg (1 dose) + Tipranavir/r 500/100 mg BID (21 doses)	EE (mean ratio) AUC 0.98 (0.88, 1.11)  NET (mean ratio) AUC 0.98 (0.90, 1.07)		
<b>Fosamprenavir (Lexiva)</b>					
Lexiva Package Label. <sup>30</sup>	25 participants	EE/NET+Lexiva (without RTV) EE 35 mcg/NET 0.5 mg qd x 21 days + Lexiva 700 mg BID/RTV 100 mg BID x 21 days	↓EE EE AUC↓37 (↓21, ↓35)  NET AUC↓34 (↓30, ↓37)	↓Lexiva Amprenavir AUC ↔	

<b>Integrase Inhibitors</b>					
<b>Raltegravir (Istentress)</b>					
Anderson et al. (2011) <sup>31</sup>	19 HIV-	EE 35 mcg/NGM 0.180mg/0.215mg/0.25mg 1 full cycle, Then received EE 35 mcg/NGM 0.180mg/0.215mg/0.25mg 400 mg + Raltegravir 400 mg or matching placebo BID on days 1-21	No meaningful differences in the AUC of either EE or NGMN	Not assessed	Well-tolerated No serious clinical or laboratory adverse events were reported.
<b>Tivicay (Dolutegravir)</b>					
Tivicay Package Insert <sup>32</sup>	15 participants	EE 35 mcg/NGMN 0.25 mg QD + Tivicay 50mg BID	EE AUC 1.03 (0.96 to 1.11)  NGMN AUC 0.98 (0.91 to 1.04)		
<b>CCR5 Entry Inhibitors</b>					
<b>Maraviroc (Selzentry)</b>					
Abel et al (2008) <sup>33</sup>	15 HIV-	EE 30 mcg/LNG 0.150 mg taken days 2-8 MRV 100 mg or placebo BID days 1-10 and AM dose day 11 7 day washout period EE 30 mcg/LNG 0.150 mg taken days 2-8 MRV 100 mg or placebo BID days 1-10 and AM dose day 11 (alternative treatment)	No significant differences in AUC for EE or LNG	Not explored	No serious AEs.
Selzentry Package Label. <sup>34</sup>			Maraviroc had no clinically relevant effect on the pharmacokinetics of the oral contraceptives		
<b>Vicriviroc</b>					
Kasserra et al. (2011) <sup>35</sup>	27 HIV-	Cycle 1: EE 35 mcg/NET 1mg Cycle 2: Days 1-20: EE 35 mcg/NET 1mg +vicriviroc OR ritonavir; Days 11-21 EE 35 mcg/NET 1mg + vicriviroc + ritonavir	No significant differences in AUC for either EE or NET when vicriviroc alone was used.  RTV alone: EE AUC estimates 71%  NET AUC estimates 93%  RTV+Vicriviroc		No severe AE.

			EE AUC estimates 71%  NET AUC estimates 83%		
Combination ART					
Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)					
Stribild Package Label <sup>36</sup>	13	EE 25 mcg/NGM 0.180/0.215.0.250 QD + Elvitegravir 150 QD + Cobicistat 150 QD	EE AUC 0.75 (0.69,0.81)  NGM AUC 2.26 (2.15,2.37)		

**Abbreviations:** AUC: area under the time-concentration curve; T½: half-life; EE: ethinyl estradiol; NET: norethindrone; DSG: desogestrel; GSD: gestodene; NGM: norgestimate; NG: norgestrel; NGMN: norelgestromin; LNG: levonorgestrel; DMPA: depot medroxyprogesterone acetate; ETG: etonogestrel; NRTI: nucleoside/tide reverse transcriptase inhibitor; TDF: tenofovir; NNRTI: non-nucleoside reverse transcriptase inhibitor; NVP: nevirapine; EFV: efavirenz; ETV: etravirine; RPV: rilpivirine; PI: protease inhibitor; RTV: ritonavir; NFV: nelfinavir; LPV/r: lopinavir/ritonavir; ATV: atazanavir; ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; TPV/r: tipranavir/ritonavir; FPV: fosamprenavir; FPV/r: fosamprenavir/ritonavir; INSTI: integrase inhibitor; RAL: raltegravir; DTG: dolutegravir; MVC: maraviroc; VCV: vicriviroc; AUC: area under the concentration-time curve; T½: half-life; Cmax: maximum concentration; Cmin: minimum concentration; SHBG: sex hormone binding globulin.

\*Norgestrel is a racemic mixture of levonorgestrel and dextronorgestrel. Assays done for LNG.

\*\*ENG is the active metabolite of DSG

\*\*\*LNG and NGMN are the active metabolites of norgestimate

**Table S2** Case studies

Authors	Number of cases	ART regimens	HC regimens	Pregnancy Outcomes	Timing of ART, implanton insertion, and pregnancy	Country
Leticee N. 2012 <sup>37</sup>	2	Efavirenz Lamivudine Zidovudine; Efavirenz Truvada;	Etonogestrel (Implanon)	Intrauterine pregnancy  Intrauterine pregnancy	ART initiation: 11/2002 Implanon insertion: 01/2004 Pregnancy: 04/2006 (conception likely 12/2005)  Implanon insertion: 07/2005 ART initiation 04/2007 Pregnancy: 10/2007	France
Lakhi N. and Govind A. 2010 <sup>38</sup>	2	Efavirenz Truvada;  Efavirenz Lopinavir	Etonogestrel (Implanon)	Intrauterine pregnancy  Intrauterine pregnancy	Implanon insertion: 07/2004 ART initiation: 01/2007 Pregnancy: 05/2007  No information provided	United States/United Kingdom
Matiluko AA et al., 2007 <sup>39</sup>	1	Efavirenz Lamivudine Zidovudine	Etonogestrel (Implanon)	Ectopic pregnancy	Implanon insertion: 02/2003 ART initiation: 03/2004 Pregnancy: 08/2005	United Kingdom
McCarty EJ et al., 2011 <sup>40</sup>	1 woman, two pregnancies	Efavirenz Lamivudine Zidovudine	Etonogestrel (Implanon)	Two ectopic pregnancies	ART initiation: 08/2005 Implanon insertion: 11/2005 1 <sup>st</sup> Pregnancy: 04/2008 2 <sup>nd</sup> Pregnancy: 01/2009	United Kingdom

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