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Nevirapine-Containing ART and Combined Oral Contraceptive (COC) Effectiveness: Results from South Africa and Uganda

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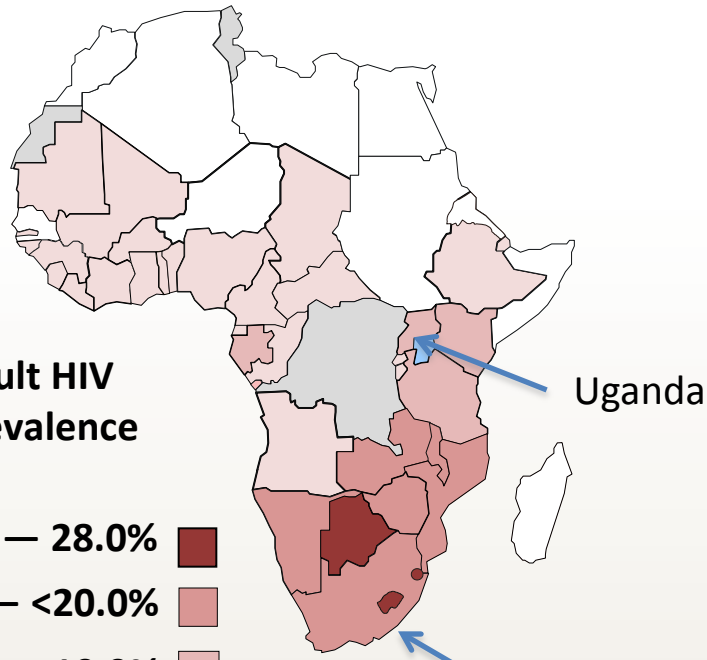
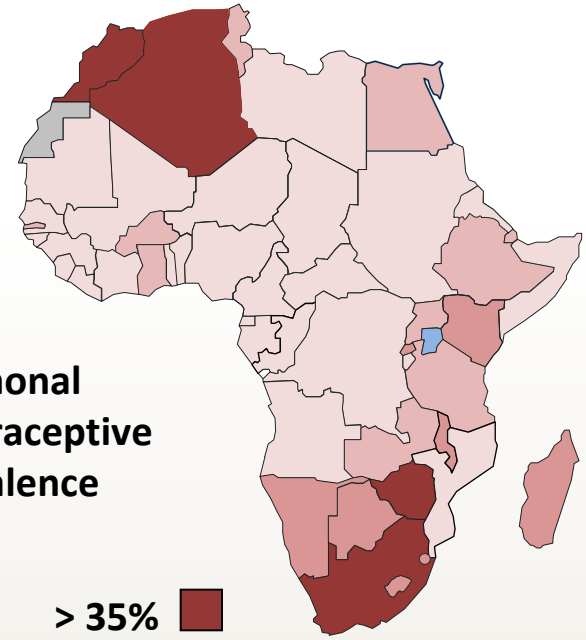
Hormonal Contraception and HIV Prevalence



Adult HIV Prevalence

- 20% — 28.0%
- 10% — <20.0%
- 5% — <10.0%
- 1% — <5.0%
- 0% — 0.9%

Sources: UNAIDS, 2011



Hormonal Contraceptive Prevalence

- > 35%
- 20 — 35%
- 10 — 20%
- <10%

Sources: UN World Contraceptive Use, 2011; represents married or in union

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Overview

- Effective contraception essential for family planning and prevention of mother-to-child HIV transmission
- Potential for drug interactions and reduced contraceptive efficacy for HIV-positive women receiving ART and contraception
- Little research on clinical outcomes (such as ovulation) in these women

Overview

- This study measured the impact of nevirapine-containing ART on COC effectiveness
- Nevirapine associated with ~30% decrease in contraceptive hormone levels in pK studies
- Nevirapine commonly included in WHO first-line ART regimens

Study Objectives

- **Primary objective**: to compare ovulation rates in women taking COCs administered concurrently with nevirapine-containing ART and COCs alone
- **Secondary objectives:**
  - to compare pregnancy rates between the two groups
  - to evaluate the safety of concurrent administration of COC and nevirapine-containing ART

Study Design

- Non-randomized trial among HIV-positive women June 2009 – May 2011:
  - Johannesburg, South Africa: University of Witwatersrand (PI: Dr. Sinead Delany-Moretlwe)
  - Kampala, Uganda: Makerere University (PI: Dr. Florence Mirembe)
- Study approved by relevant ethical committees and written informed consent obtained

Study design

- Key eligibility criteria:
  - age 18 – 35, sexually active
  - regular menses
  - BMI 18-30
  - HIV infected
  - on stable nevirapine-containing ART for least three months (ART group only)
  - CD4 ≥350 (non-ARV group only)
  - no contraindications to COC use
  - not breastfeeding
  - no enzyme inducers (other than ART)

Statistical methods

- Sample size of 360 provided 80% power
- Progesterone ≥10nmol/L considered presumptive evidence of ovulation
- Primary analysis based on a per cycle comparison of ovulation rates between treatment arms
- Used Generalized Estimating Equations (GEE) with identify link function and independent working correlation, adjusting for the pre-specified covariates to account for heterogeneity due to multiple test cycles contributed by each participant

Study procedures

- All women treated with COCs containing 30 mcg of ethinyl estradiol and 300 mcg of norgestrel
  - participants took COCs for at least one cycle before ovulation assessment

- Weekly visits for 8 weeks
  - tested for presumed ovulation in first 2 treatment cycles using weekly serum progesterone

Follow up Procedures

- Monthly visits for 24 weeks:
  - urine pregnancy testing
  - collected and followed up adverse events
  - collected concomitant medication information
  - distributed COCs and condoms as needed

Results

- Enrollment:
  - 196 women taking nevirapine-containing ART
  - 207 women ineligible for ART as a COC-only control group
- Of the 350 women in the effectiveness population:
  - 316 women completed the study; 13 were LFU; 21 discontinued early
  - 191 women-years (WY) of follow up data

Table 1: Baseline Characteristics

Characteristic	COC with ARV (n=196) n (%)	COC alone (n=206) n (%)	Total (n=402) n (%)
Age: Median (Q1 – QR3)	30 (27 – 33)	28 (24 – 30)	29 (26 – 32)
Marital status			
married, cohabiting	68 (34.7)	71 (34.5)	139 (34.6)
married, not cohabiting	20 (10.2)	10 (4.9)	30 (7.5)
not married, cohabiting	33 (16.8)	35 (17.0)	68 (16.9)
not married, not cohabiting	75 (38.3)	90 (43.7)	165 (41.0)
BMI			
<18.5	2 (1.0)	2 (1.0)	4 (1)
18.5-24.9	116 (59.2)	119 (57.8)	235 (58.5)
25.0-25.9	64 (32.7)	77 (37.4)	141 (35.1)
>=30	14 (7.2)	8 (3.9)	22 (5.5)
Prior pregnancy	191 (97.5)	195 (94.7)	386 (96.0)
Using COCs	35 (17.9)	45 (21.8)	80 (19.9)
Previous unplanned pregnancy	96 (49.0)	91 (44.2)	187 (46.5)

Results

- **Ovulation rates** similar between groups:
  - 26% of ARV and 16% of COC-only ovulated in cycle 1
  - 18% of ARV and 19% of COC-only ovulated in cycle 2
  - 11% of ARV and 12% of COC-only ovulated in both cycles
- Unadjusted odds ratio for ovulation in ARV group compared with COC only group 1.4 (95% CI 0.85 - 2.18)
- Women using COCs at baseline 62% less likely to ovulate during follow up

Table 2: Risk Factors for Ovulation

Variable	OR	95% CI	p-value
ART group *Reference: COC only group*	1.47	0.85 – 2.55	0.17
Site: Johannesburg *Reference: Kampala*	0.28	0.16 – 0.46	<0.0001*
Age (*Reference: 33+)*			
18-24	1.17	0.53 – 2.60	0.70
25-28	0.66	0.33 – 1.33	0.24
29-32	0.51	0.27 – 0.98	0.04*
Using COCs at baseline	0.38	0.20 – 0.70	0.002*

Results continued

- **9 pregnancies in each group:** pregnancy rates 10 per 100 WY (95% CI 5-19) for each group
- Women who missed 3 or more pills consecutively 17 times more likely to get pregnant
- **Adverse events** did not differ between group; 3 unrelated SAEs, all in COC only group
- No difference in vaginal bleeding patterns between groups
- No difference in self-reported pill adherence or condom use between groups

Table 3: Risk Factors for Pregnancy

Variable	HR	95% CI	P-value
ART group *Reference: COC only group*	1.08	0.41 – 2.88	0.87
Site: Johannesburg *Reference: Kampala*	0.72	0.25 – 2.07	0.54
Age (*Reference: 33+)*			
18-24	1.15	0.22 – 6.06	0.87
25-28	0.90	0.19 – 4.30	0.89
29-32	1.29	0.31 – 5.34	0.73
Missed 3+ pills in a row	16.76	3.15 – 89.24	0.001*

Conclusions

- Though ovulation and pregnancy rates were relatively high overall, nevirapine-containing ART did not reduce contraceptive effectiveness of COCs
- No difference in self-reported pill adherence between groups; therefore, the additional pill burden for women taking ART did not appear to affect pill adherence
- Additional studies needed for other contraceptive methods and ARVs

Acknowledgements

Study Participants

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