Effect of hormonal contraceptive use on time-to-death in female HIV seroconverters in Rakai, Uganda

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For HIV+ women who wish to prevent pregnancy, contraception helps…

- Avoid unintended pregnancies, pregnancy complications, and adverse birth outcomes

- Maintain access to a wider selection of antiretroviral drugs

- Avoid pregnancy/breastfeeding, which may accelerate HIV disease progression
Contraception has been called “The best kept secret in PMTCT”

- Prevention of vertical perinatal and lactational HIV transmission
  - As cost-effective* as ART prophylaxis
  - Avoids concerns about viral mutation and resistance

- Reduction in number of AIDS orphans

* Reynolds 2006 Sexually Transmitted Diseases
Why focus on hormonal contraception?
Can HIV+ women safely use hormonal contraception?
A randomized controlled trial caused concern, but had **limitations**...

- High crossover
- High dropout rate
- Not based on a priori hypothesis
- No control for baseline differences

**FIGURE 6**
Time to either CD4$^+$ cell count falling to below 200 cells/uL or death by randomization arm

HR: **1.6**  
(1.04-2.3)

- At Risk
  - IUD: 296
  - Hormonal: 303
- Time (Months)
  - IUD: 192, 150, 111, 86, 37
  - Hormonal: 258, 245, 229, 192, 150

Stringer 2007, AJOG
What other evidence exists on the effect of HC on HIV progression?

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Number of Studies</th>
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<tbody>
<tr>
<td>HC accelerates HIV progression</td>
<td>3 observational studies (+ RCT)</td>
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<tr>
<td>HC has no effect on HIV progression</td>
<td>6 observational studies</td>
</tr>
<tr>
<td>HC is protective against HIV progression</td>
<td>1 observational study</td>
</tr>
<tr>
<td>Effect of HC depends on time</td>
<td>1 observational study</td>
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</table>
Rakai data **overcomes many limitations of previous studies**

- Population-based
- Largest sample of incident HIV seroconverters ever analyzed (n=625)
- Over 10 years of follow-up time
- Yearly information on contraceptive use
- Well-established research infrastructure
- Information available immediately to address a pressing issue
Population & main analyses

- 625 incident seroconverters observed between 1994 and 2006

- Kaplan-Meier and Cox regression compared women by HC use on survival

- Used time-varying exposure information
Comparison groups & sub-analyses

- **HC users compared against:**
  - (1) All women not using HC
  - (2) Contraceptors using non-hormonal methods
  - (3) Non-contraceptors

- **Sub-analyses**
  - Considered OCs and DMPA separately
  - Lagged exposure (HC use at previous round)
HC use potentially associated with reduced mortality in K-M analysis.

Survival by HC use (time-varying), Rakai, Uganda

- Median survival: 7.06 years (IQR 4.86-9.55)
- P-value for logrank: 0.067
In multivariate analyses…HC was not associated with hazards of death

- HC users vs. all non-users of HC
  - HR: 0.72 (0.39-1.32), p=0.293
  - vs. non-contraceptors
    - HR: 0.68 (0.36-1.27), p=0.222
  - vs. non-hormonal contraceptors
    - HR: 0.72 (0.33-1.59), p=0.419

Analyses controlled for education, number of sex partners, breastfeeding, and time period
Sub-analyses supported main findings

- Lagged exposure did not suggest time-dependent confounding

- Neither OCs nor injectables were significantly associated with mortality

- No evidence of self-selection of healthier women into contraceptive use
  - No significant differences in baseline CD4 counts in never vs. ever users
Conclusions and implications

- Our findings do not support the concern that HC accelerates HIV progression
  - HC users and non-users had similar hazards of mortality

- Given high unmet need for FP in HIV+ women, we need to help HIV+ women find safe, effective methods they will use
Thank you!

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**Rakai cohort participants**
Supplementary slides
Trends in HC use in Rakai, 1994-2006

Use of hormonal contraception by HIV status and round

Span of years within round

Percent using method

94-95 96-97 97-98 99-00 00-01 01-02 02-03 03-04 05-06

Injectable OCPs Implant
Proportion of unintended pregs to HIV+ women is on the rise...

Pregnancy intention among HIV+ women in Rakai, 2000-06

*Among HIV+ women asked about intention of current or last pregnancy
Theorized biological mechanisms

- Hormones may promote viral replication \(\rightarrow\) viral diversity \(\rightarrow\) faster progression
- Hormones may upregulate cervical CCR5 coreceptors \(\rightarrow\) more target cells susceptible
- Potential immunosuppressive effect of HC
- Potential association of HC with increased risk of STIs and genital tract infections (Chlamydia, herpes, cervicitis) \(\rightarrow\) increased viral load
Does pregnancy influence HIV progression?

- Early studies suggested yes, but poorly conducted
- Systematic review found weak association, potential for bias too great to draw conclusions
- Most studies (developed world) find no effect or a protective effect (but...fertility, health care, adherence?)
- Pregnancy’s potential protective effect may be lost in developing world, burden of maternal mortality/morbidity
- 5 studies in developing countries, 3 found no effect, 2 found acceleration
- Also need to consider effects of breastfeeding on HIV progression in developing countries
Does breastfeeding influence HIV progression?

- Nduati 2001 suggested detrimental impact of breastfeeding on maternal health
- Several subsequent studies & a meta-analysis suggested no impact (Taha, Couttsoudis, Kuhn, Sedgh)
- Recent study (Otieno 2007) suggested BMI and CD4 deteriorated faster in breastfeeding women, but no difference in VL or mortality
- *Probably no significant effect*