Progestins and HIV acquisition
The association of injectable progestin-only contraceptives and endogenous progestins with HIV target cell frequency in the cervix and HIV acquisition risk

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Background
- Injectable progestin-only contraceptives (IPCs), including Depo Provera (DMPA) and norethisterone, are highly effective and commonly used in South Africa and other areas of high HIV incidence
- Association between IPCs and HIV acquisition has been observed epidemiologically but it is unclear whether this association is causal
- A causal biological mechanism linking IPCs and HIV has not been found
- The luteal phase is associated with the highest progesterone of the menstrual cycle
- Some evidence for increased HIV susceptibility during the luteal phase
- Progestins have been shown to have many immune-modulating properties in vitro

Methods
- Observational prospective cohort study, FRESH (Females Rising through Education, Support and Health):
  - HIV-negative women ages 18-23
  - Living in Umlazi, South Africa
  - At high risk of acquiring HIV
  - Non-pregnant, anticipated staying in Umlazi for duration of study, willing and able to participate in data and sample collection
- 2x/week small group classes on empowerment, job search and preparation, and HIV prevention
- HIV-1 testing 2x/week: demographic and behavioral data collection, blood and cervical sample collection every 3 months
- FACS sorting of fresh endocervical cytobrush samples for cell counts
- Measurement of plasma progesterone concentration

Results
1. FRESH participants stratified by use of IPC or no long-term contraceptive. Few differences between groups that were both statistically significant and large in magnitude.

2. IPC users had a significantly higher HIV incidence than women using no long-term contraceptive.

3. IPC users had a higher frequency of HIV target cells (CD4+CCR5+ T cells) in the cervix but not peripheral blood, compared to women using no-long term contraceptive with low plasma progesterone (<3.9ng/mL).

4. (A) In IPC users, more cervical CD4+ T cells were CCR5+ positive and (B) cervical CD4+ T cells had higher CCR5 MFI. Again, no difference was observed in the peripheral blood.

5. In women who were naturally cycling, using no long-term contraceptive, the luteal phase was associated with an increased frequency of HIV target cells in the cervix as well as increased CCR5 expression on CD4+ T cells. The luteal phase is defined by plasma progesterone concentration ≥1.2ng/mL.

Conclusions
- IPCs are associated with increased risk of acquiring HIV in this cohort of young women that, while small, is drawn from the same community and a narrow age range.
- IPC use is associated with a higher frequency of HIV target cells in the cervix, the site of HIV exposure in most heterosexual women who become infected.
- In naturally cycling women using no long-term contraceptives, the luteal phase of the menstrual cycle, which is characterized by high plasma progesterone, is similarly associated with increased HIV target cell frequency in the cervix.
- Cellular correlates of IPC use or progesterone level were observed in the cervix but not the blood, suggesting tissue-specific hormonal regulation of the immune environment.
- Increased HIV target cell frequency in the cervix may provide greater risk of systemic HIV infection upon exposure.
- We present a plausible biological mechanism for the observed increase in HIV acquisition risk for women using IPCs.

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References