An Immunologic Mechanism for Increased Risk of HIV Acquisition in Healthy Postmenopausal Compared to Premenopausal Women

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Proportion of New HIV Infections in U.S. by Sex, Race and Age, 2006

Men

Women

% New HIV-1 Infections 2006

Age at diagnosis

n = 54,230
Increased Rate of New HIV Infections in Older U.S. Women

Espinoza, Am J Public Health 2007;97:144-9
Aging of the U.S. Population

Percentages of HIV/AIDS Cases among Female Adults and Adolescents, by Transmission Category 2007—34 States

- High-risk heterosexual contact*: 83%
- Injection drug use: 16%
- Other/not identified†: 1%

Note: Data include persons with a diagnosis of HIV infection regardless of their AIDS status at diagnosis. Data from 34 states with confidential name-based HIV infection reporting since at least 2003. Data have been adjusted for reporting delays and missing risk-factor information.

*Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
†Includes blood transfusion, perinatal exposure, and risk factor not reported or not identified.
Majority of HIV-Infections in Women over 50 Attributed to Heterosexual Transmission

Over 50 Years

- Heterosexual: 69%
- Unknown: 26%
- IVDU: 5%

13–49 Years

- Heterosexual: 71%
- Unknown: 22%
- IVDU: 7%

Data from NYC Dept. of Health and Mental Hygiene, 9/08
Older Adults are Having Sex

% Sexual Activity in 12 Months

Age

- 57-64
- 65-74
- 75-85

Women
Men

n=3,005

Proposed Behavioral HIV-Risk Factors for Menopausal Women

- Less frequent condom use
- Lack of awareness of risk
- Difficulty discussing sex with partner

Linsk NL. AIDS Read 2000;10:430-40
Effects of Menopause and/or Age on the Female Genital Tract

• Anatomy
• Immunologic milieu
  – HIV co-receptors
  – Immune activation (HLA-DR, CD38)
Anatomic Changes in the Female Reproductive Tract with Menopause

- Thinning of cervical mucosa with loss of sex hormones and age (Linsk NL. AIDS Read 2000;10:430-40)

- Cervix is primary site of male to female HIV transmission (Science 1999;286:1353)
CD4+ T cells are Primary Targets for HIV
CCR5 expression on CD4+ cells is correlated with infection in vitro and in vivo (J Virol 1998;72:2855–64)
HIV Susceptibility is Linked to Immune Activation

- Percentages of HLA-DR+CD38+CD4+ T cells are correlated with susceptibility to infection
- In an ex vivo cervical tissue model, CD38+ CD4+ T cells are preferentially infected

Effects of Aging and/or Menopause on Factors Linked to HIV Susceptibility

• CCR5 Gene Expression in CD4+ T cells
  – Higher in older men and women than younger
    (Yung, J Interferon & Cytokine Research 2003; 23:575)
  – Increased in mice with surgical menopause after treating with estrogen
    (Mo, J Immunol. 2005 May 15;174(10):6023-9)

• HLA-DR and CD38 expression on T cells may be higher in older vs. younger healthy individuals
Hypothesis

CCR5 and HLA-DR (DR) and CD38 (38) expression will be higher in cervical CD4+ T cells of healthy postmenopausal women compared to premenopausal women.
Methods

• Prospective Cohort of Healthy Women
  – Samples: whole blood and cervical brush
  – Recruitment criteria
    • Negative HIV ELISA
    • Postmenopausal: no menstrual cycle 1 year, high FSH
    • Premenopausal: menstrual cycles 27-31 days (ovulation confirmed with detection of luteinizing hormone), samples collected in the follicular phase
    • Exclusion: hormone therapy, IVDU, or presence of a vaginal infection

• Fresh whole blood and cervical cells were stained for HLA-DR, CD38, CCR5, CD4 and CD3 and analyzed by flow cytometry. QuantiBRITE™ beads were used to estimate number of CCR5 molecules.

• CCR5 Genotype for 32-base pair deletion.
## Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Postmenopausal (n=24)</th>
<th>Premenopausal (n=21)</th>
<th>P value</th>
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<tbody>
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<td>Age, median years (range)</td>
<td>55 (50-65)</td>
<td>34 (23-49)</td>
<td>&lt;0.001</td>
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<td>Race/Ethnicity</td>
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<tr>
<td>White</td>
<td>82%</td>
<td>86%</td>
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<tr>
<td>Nonwhite</td>
<td>18%</td>
<td>14%</td>
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<td>CCR5 delta32 heterozygote</td>
<td>11%</td>
<td>23%</td>
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<td>Number of subjects with cervical sample</td>
<td>7</td>
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Activated CD4+ T cells are Enriched in the Cervix Compared to Whole Blood
Percent Activated CD4+ T cells was Not Significantly Different in Post-vs. Premenopausal Women

Whole Blood

Cervix

\[ \text{\% DR}^+38^+ \text{ CD4+ T Cells} \]

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\[ p=0.5 \]

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\[ p=0.2 \]
CCR5 Expression was Higher on Blood CD4+ and Activated CD4+ T Cells in Post- vs. Premenopausal Women

CD4+ T cells

DR+38+ CD4+ T cells
CCR5 Expression was Higher on Cervical CD4+ and Activated CD4+ T Cells in Post- vs. Premenopausal Women

CD4+ T cells

DR+38+ CD4+ T cells

p=0.005

p=0.05
Number of CCR5 Molecules on **Cervical CD4+ T cells** in Post- vs. Premenopausal Women

**CD4+ T cells**

- **Mean number CCR5 Molecules on CD4+ T cells**
  - Post: 4000
  - Pre: 6000
  - **p=0.6**

**DR+38+ CD4+ T cells**

- **Mean number of CCR5 molecules on DR+38+CD4+ T cells**
  - Post: 3000
  - Pre: 2000
  - **p=0.02**
CCR5 Expression on CD4+ and Activated CD4+ T cells Correlated with Age

Peripheral Blood

Cervix

CD4+ T cells

DR+38+CD4+ T cells

% CCR5+CD4+ T Cells

% CCR5+DR+38+CD4+ T Cells

r=0.5
p<0.001

r=0.58
p=0.004

r=0.6
p=0.011
Summary

• Post- vs. premenopausal women
  – No difference in percentage of activated (DR+38+) CD4+ T cells in peripheral blood or cervix
  – Higher CCR5 expression on CD4+ and activated CD4+ T cells from peripheral blood and cervix

• CCR5 expression on CD4+ and activated CD4+ T cells from peripheral blood and cervix positively correlated with age
Limitations

• Small sample size

• Lack of racial diversity

• Phenotypic observations
Conclusions

• Elevated percentages of CCR5+ CD4+ T cells in cervix may increase the risk for HIV acquisition in post- vs. premenopausal women.

• The correlation between age and cervical expression of CCR5 may be due to an age- or hormone-related effect on CCR5 expression.
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Age won't protect you from AIDS

More than 8,000 New Yorkers over 50 years old have been diagnosed with AIDS.

To prevent HIV infection:
- Use a condom every time you have sex.
- Don’t shoot drugs. Sharing works can spread AIDS.

It's not how old you are... it's what you do that matters.

HIV prevention is a lifelong job.

To learn more, call 1-800-541-AIDS

New York State Health Department