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

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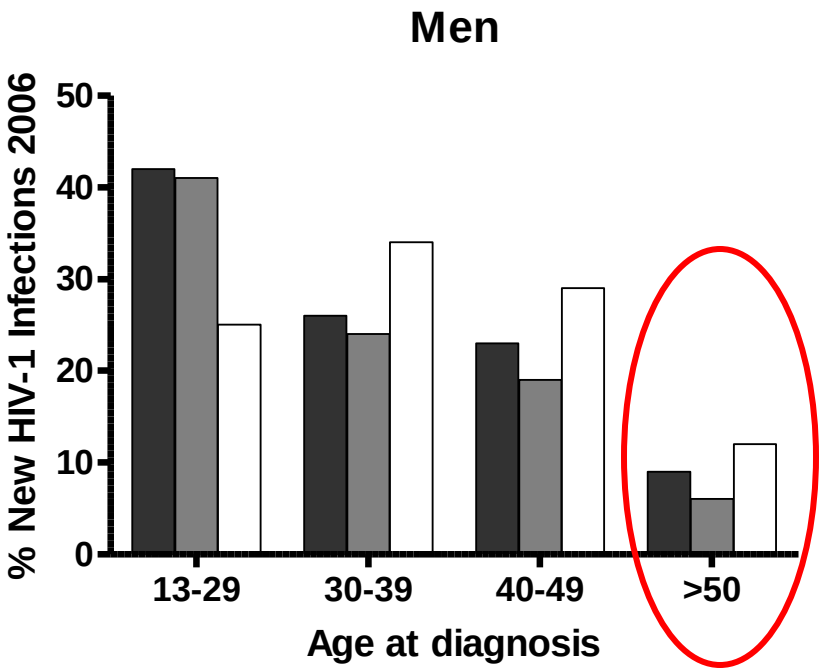
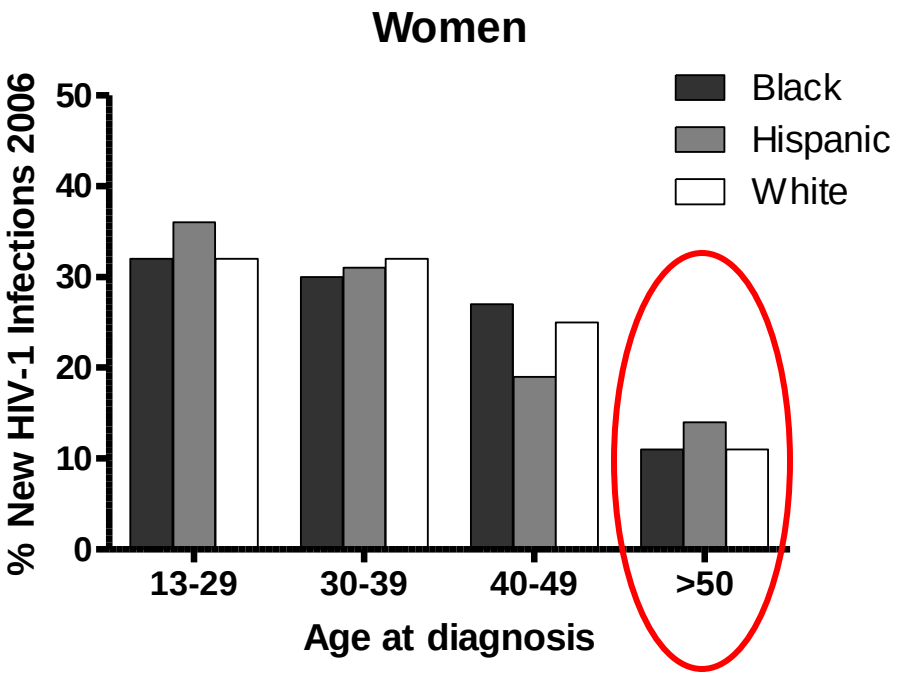
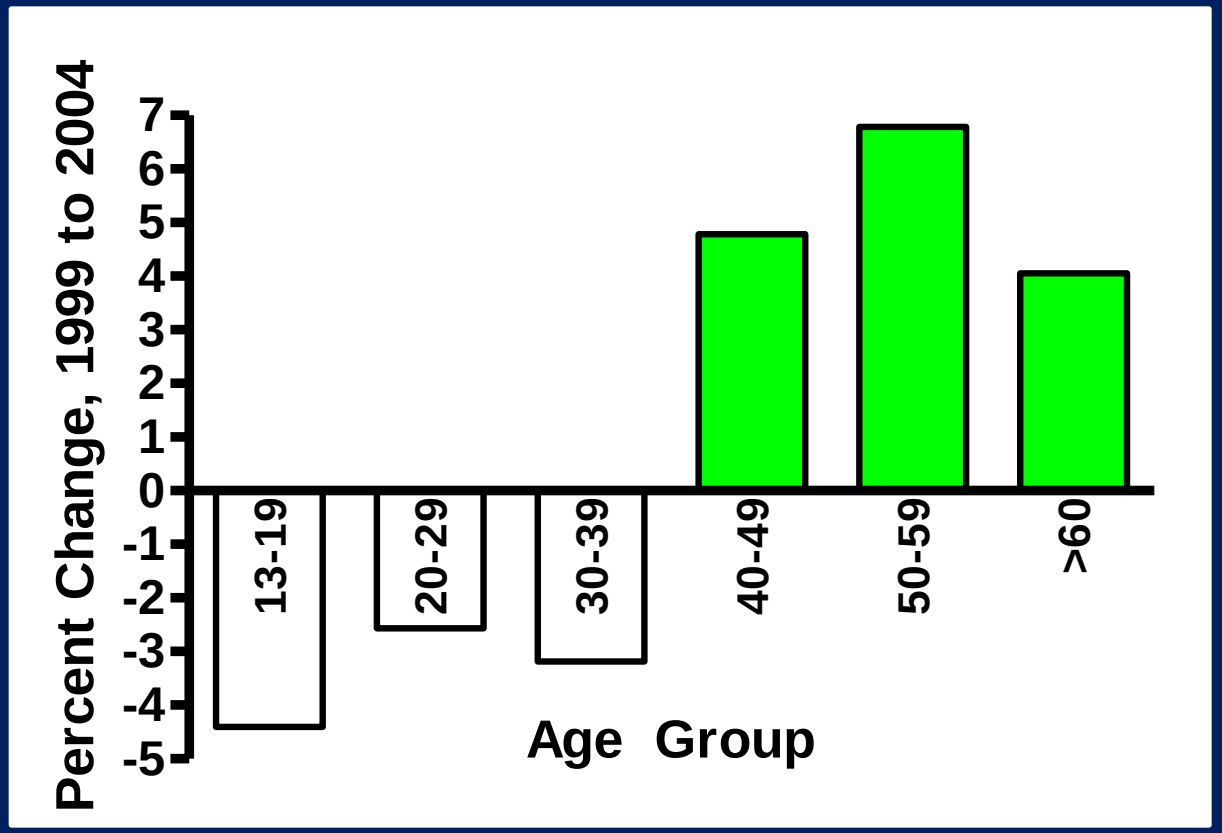
Proportion of New HIV Infections in U.S. by Sex, Race and Age, 2006





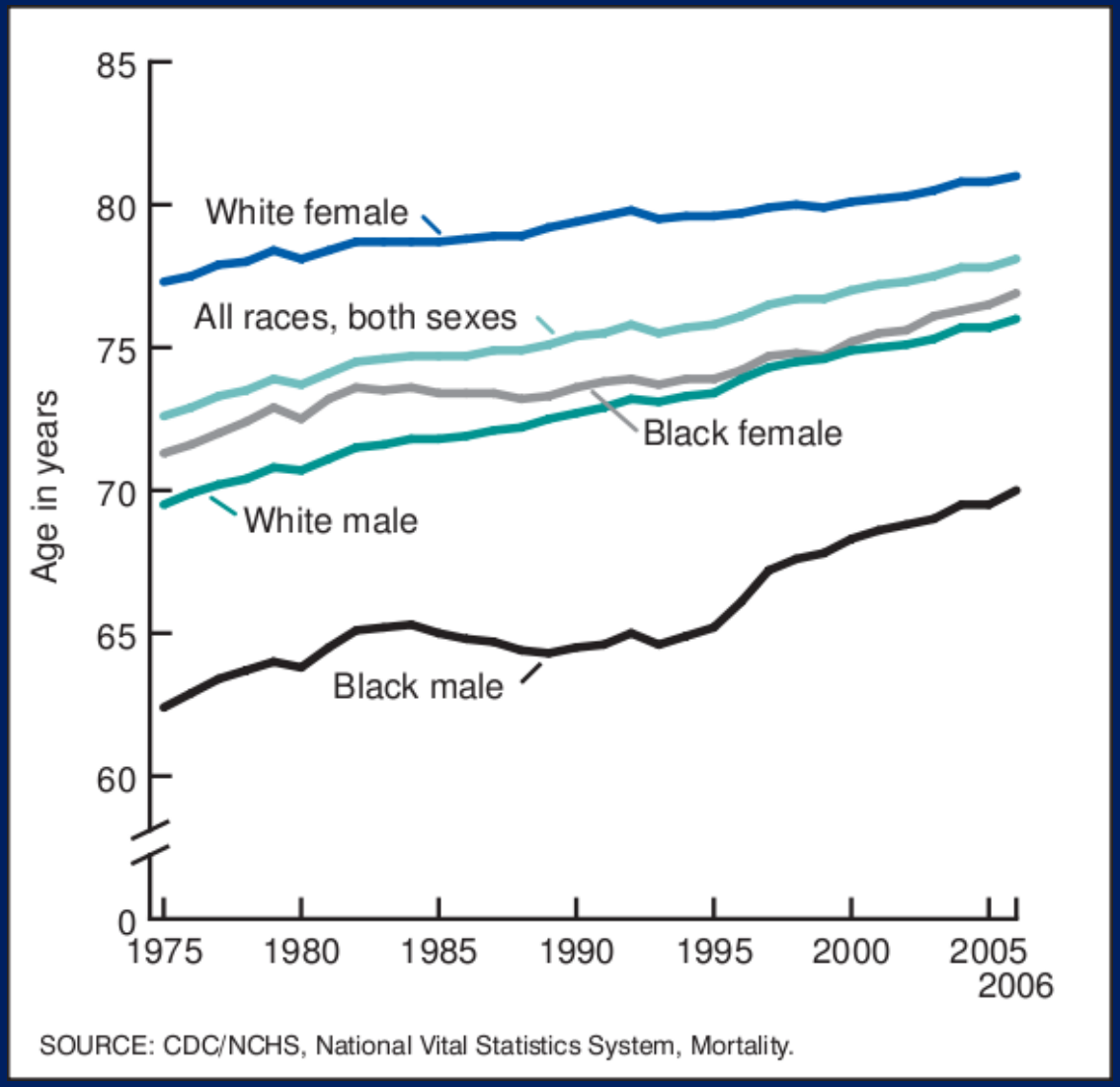
n =54,230

Increased Rate of New HIV Infections in Older U.S. Women

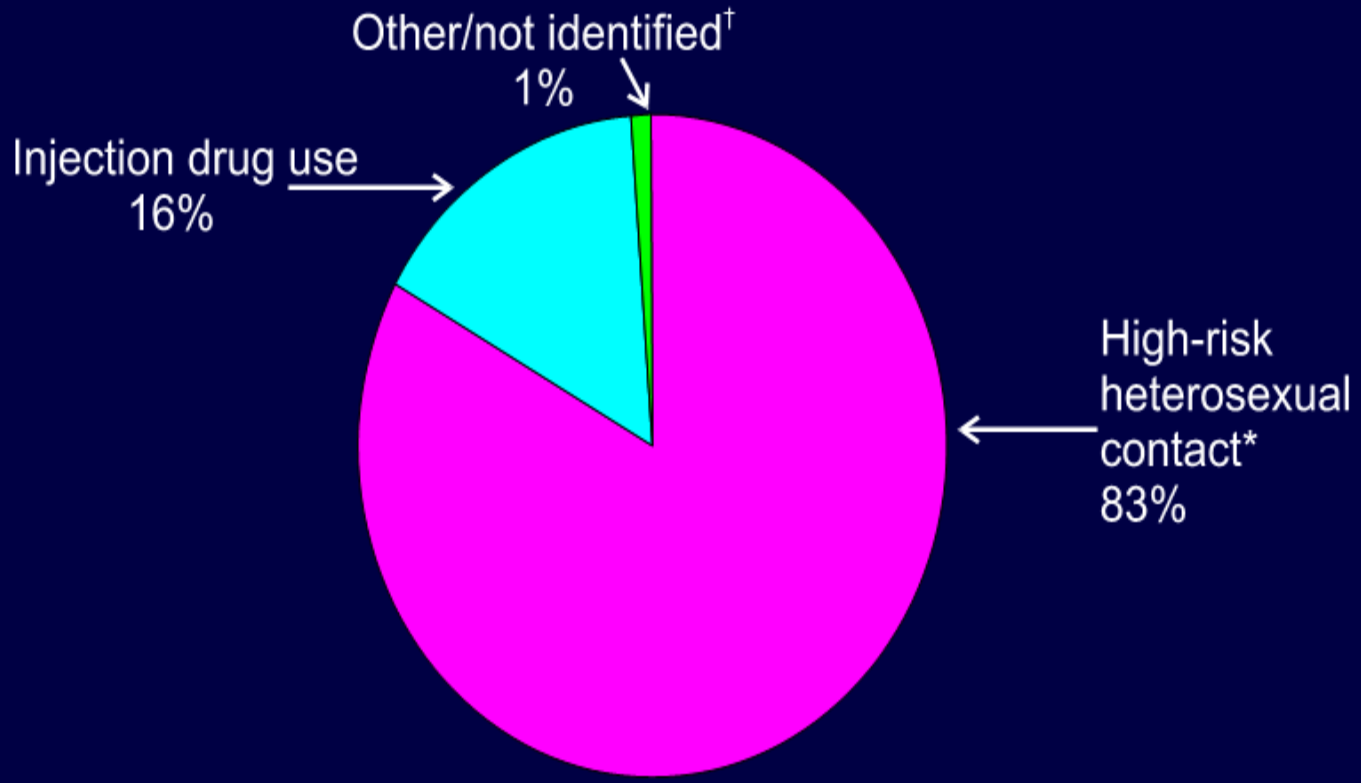


Espinoza, Am J Public Health 2007;97:144-9

Aging of the U.S. Population

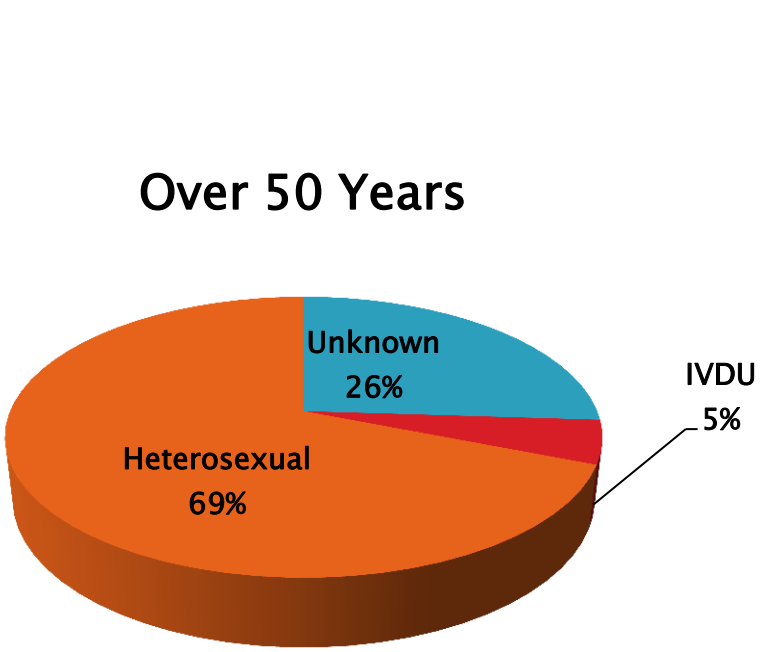


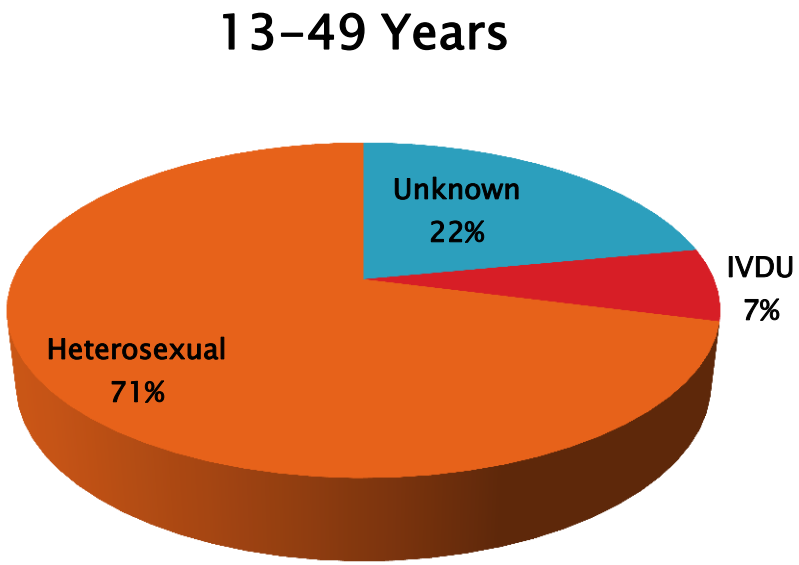
Percentages of HIV/AIDS Cases among Female Adults and Adolescents, by Transmission Category 2007—34 States



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.

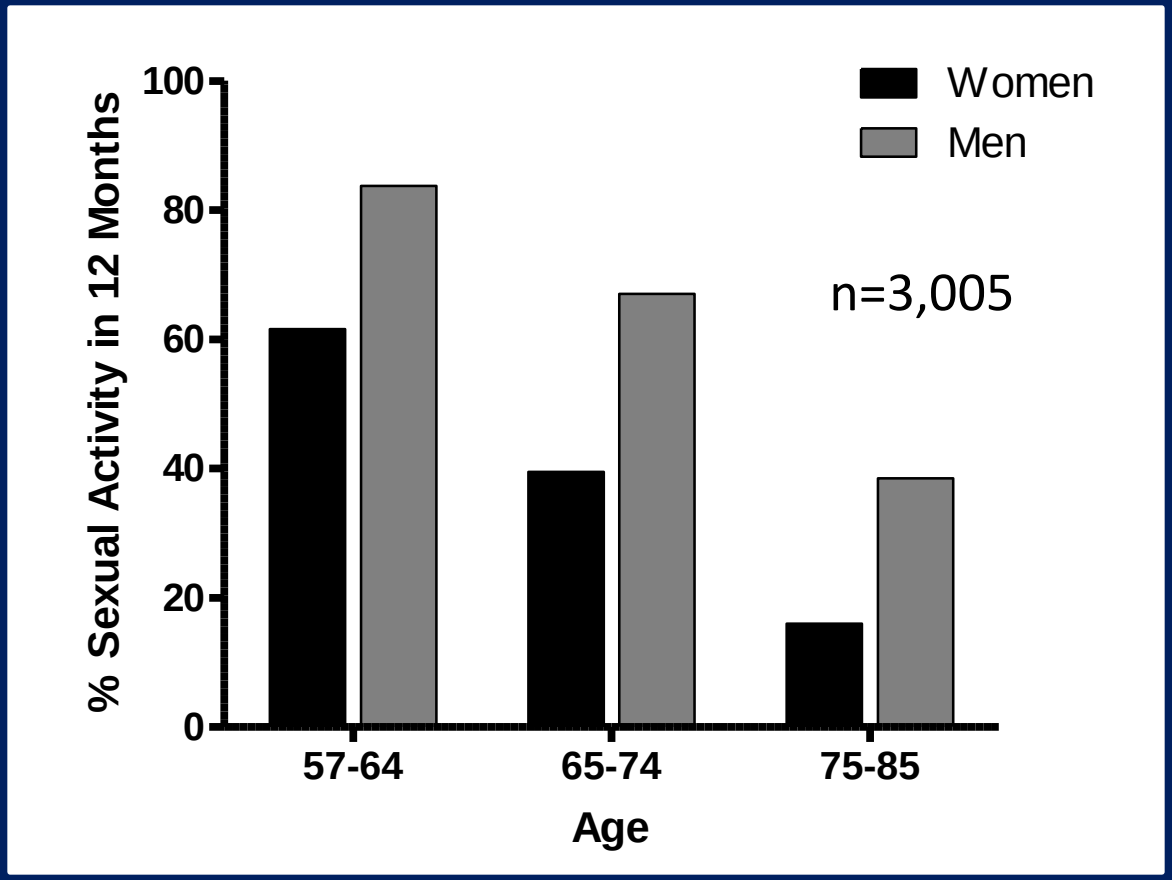
Majority of HIV-Infections in Women over 50 Attributed to Heterosexual Transmission





Data from NYC Dept. of Health and Mental Hygiene, 9/08

Older Adults are Having Sex



N Engl J Med 2007;357:762-74.

Proposed Behavioral HIV-Risk Factors for Menopausal Women

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

Lindau J Womens Health 2006;15:747-53
Linsk NL. AIDS Read 2000;10:430-40
www.cdc.gov/hiv/topics/surveillance/resources/slides/women/index.htm (2008)

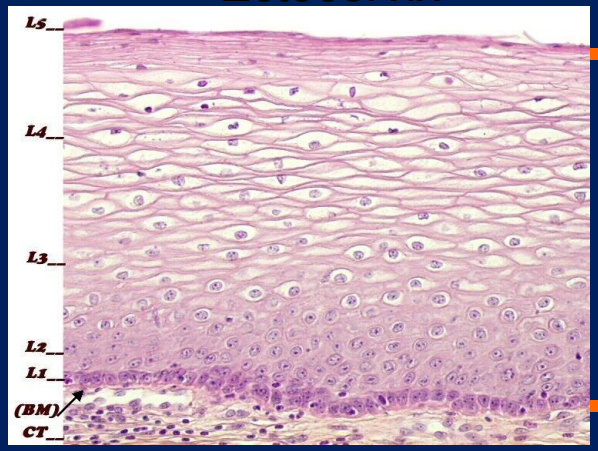
Effects of Menopause and/or Age on the Female Genital Tract

- Anatomy
- Immunologic milieu
  - HIV co-receptors
  - Immune activation (HLA-DR, CD38)

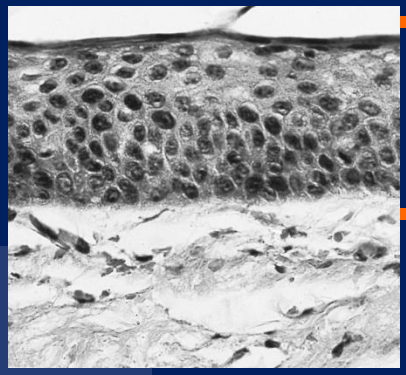
Anatomic Changes in the Female Reproductive Tract with Menopause

- 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)

Ectocervix

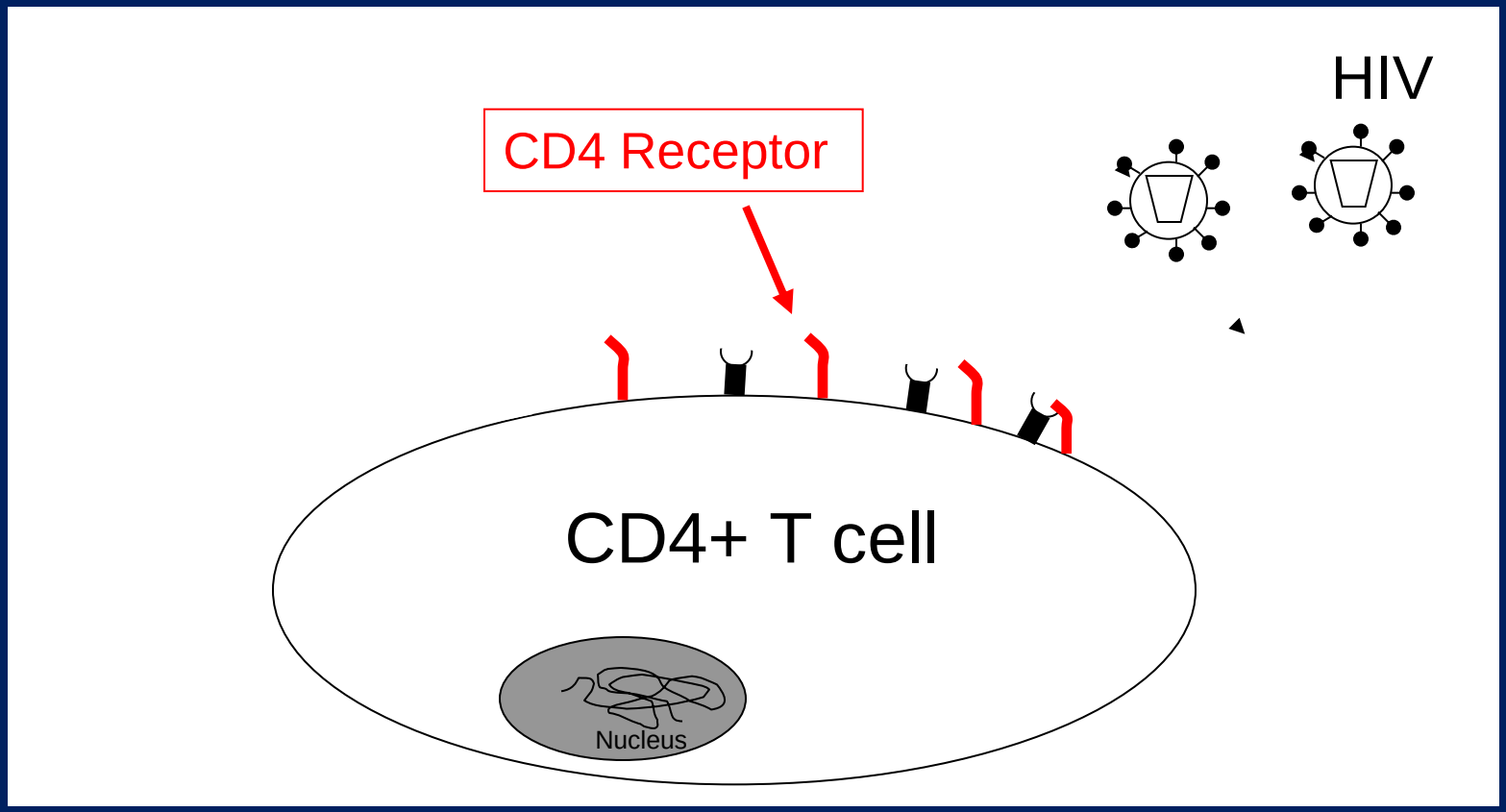


Reproductive age



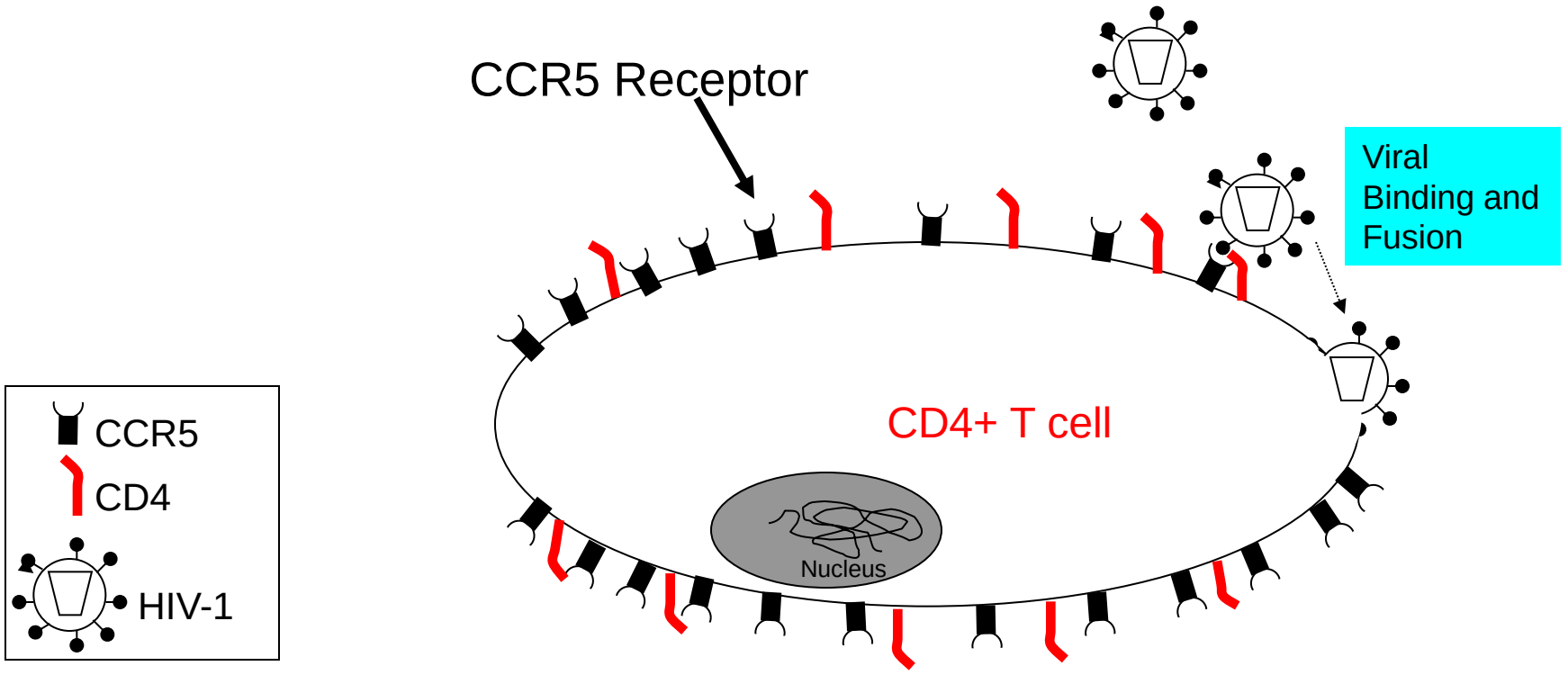
Postmenopausal

CD4+ T cells are Primary Targets for HIV



Schuitemaker H. J Virol 1992;66

CCR5 Required for Viral Binding and Fusion and Linked to HIV Susceptibility



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**

Begaud E, *Retrovirology* 2006,**3**:35
Koning FA, *J Immunol* 2005,**175**:6117-6122
Saba, *Mucosal Immunol* 2010,**3**:280-290

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** (Effros, et al. Clin Inf Dis 2008; 47:5432-5)

Hypothesis

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

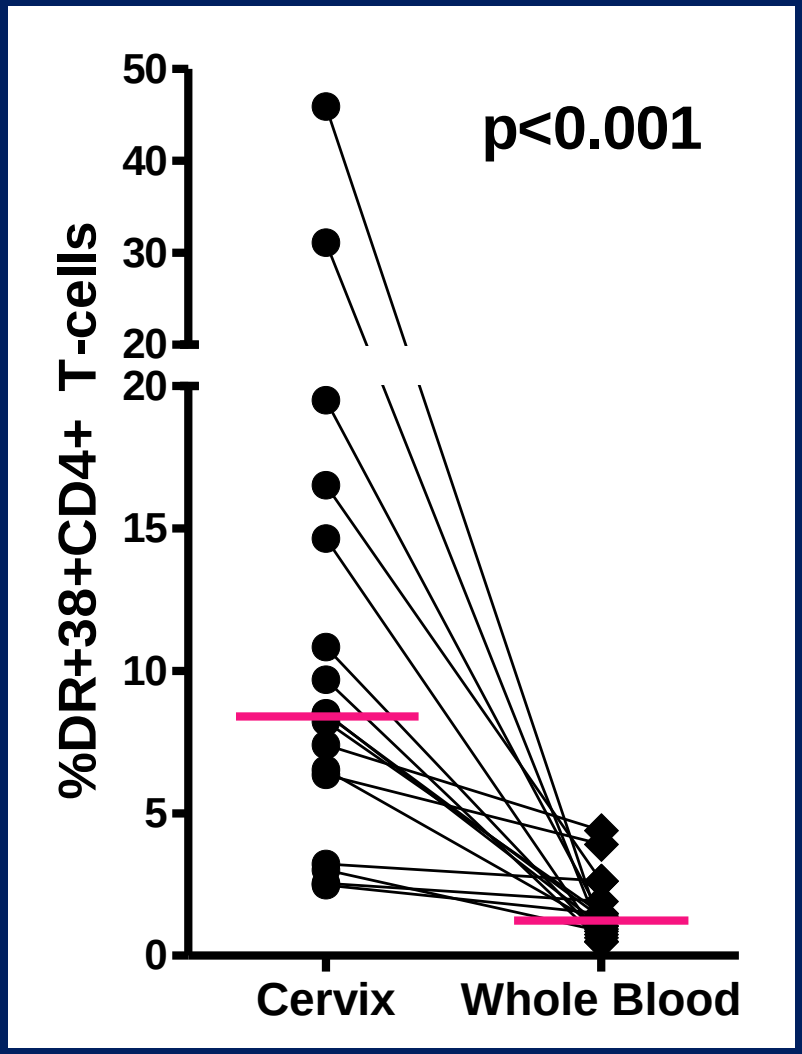
Methods

- **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

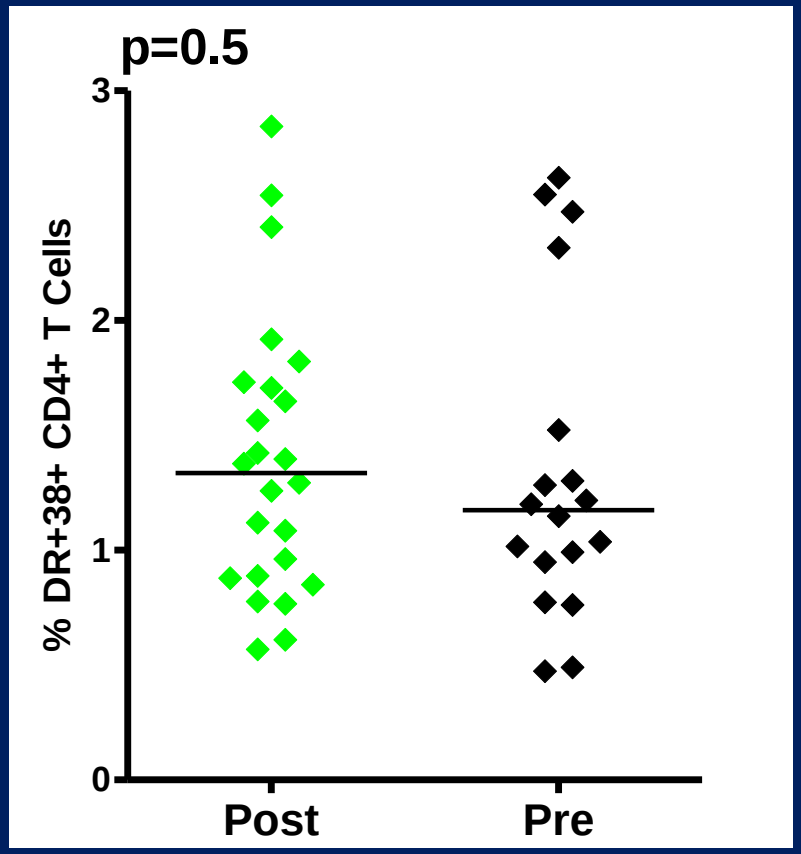
Characteristics	Postmenopausal (n=24)	Premenopausal (n=21)	*P* value
Age, median years (range)	55 (50-65)	34 (23-49)	<0.001
Race/Ethnicity			1.0
White	82%	86%	
Nonwhite	18%	14%	
CCR5 delta32 heterozygote	11%	23%	0.26
Number of subjects with cervical sample	7	18	

Activated CD4+ T cells are Enriched in the Cervix Compared to Whole Blood

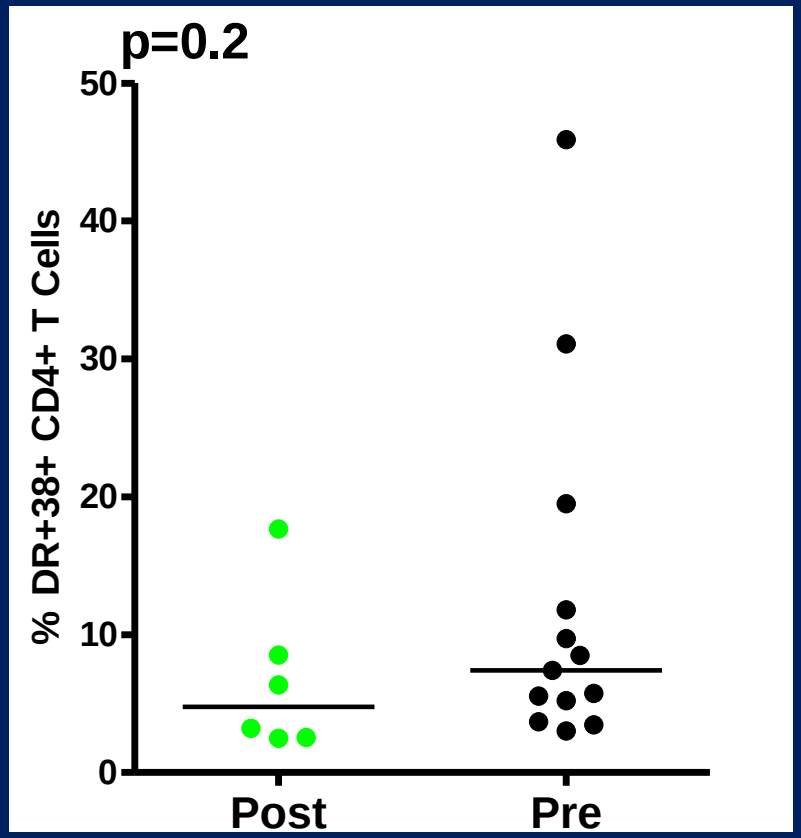


Percent Activated CD4+ T cells was Not Significantly Different in Post- vs. Premenopausal Women

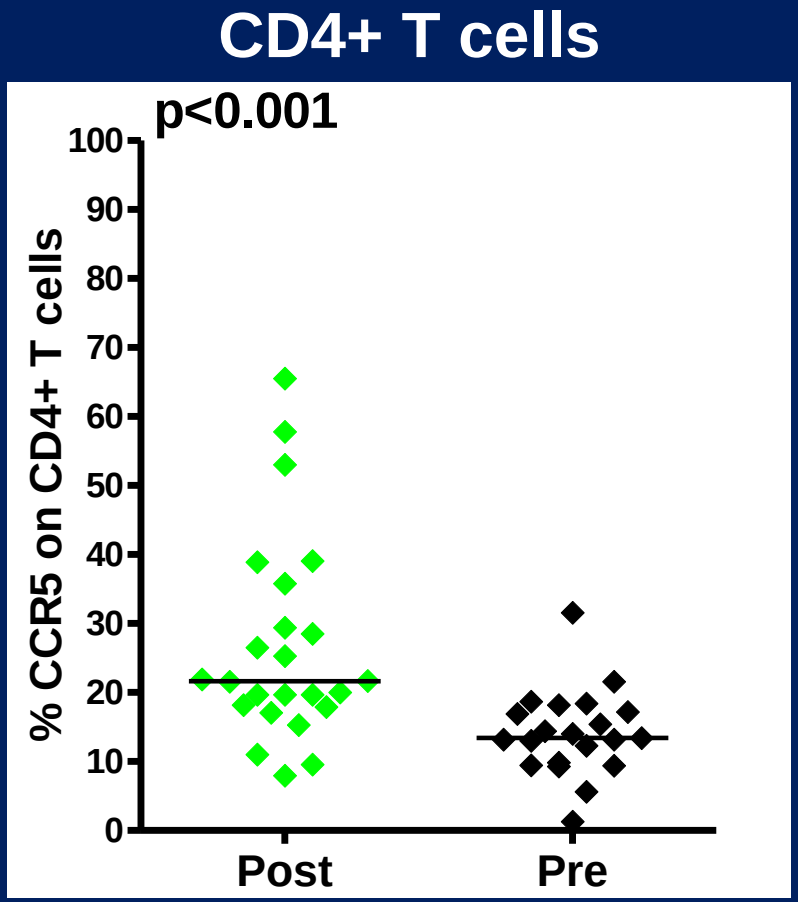
Whole Blood

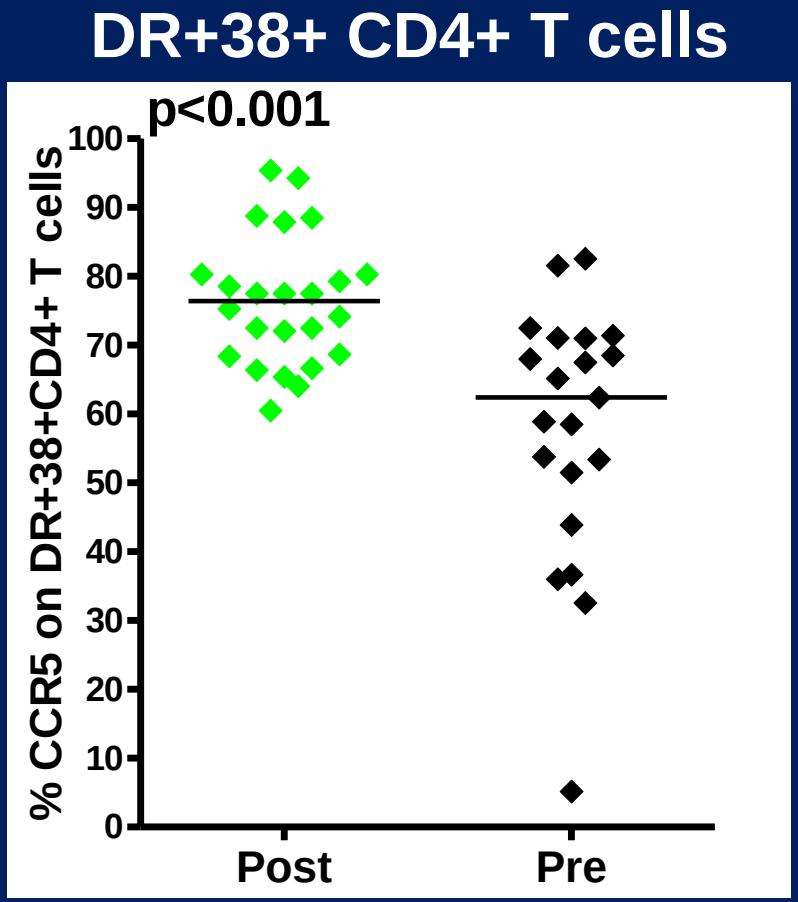


Cervix



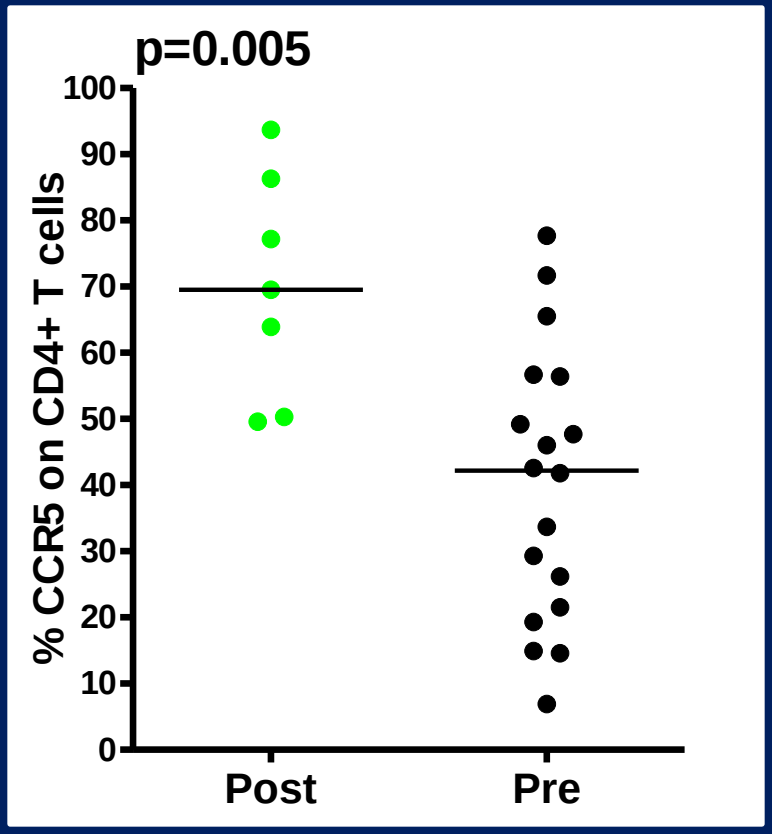
CCR5 Expression was Higher on Blood CD4+ and Activated CD4+ T Cells in Post- vs. Premenopausal Women



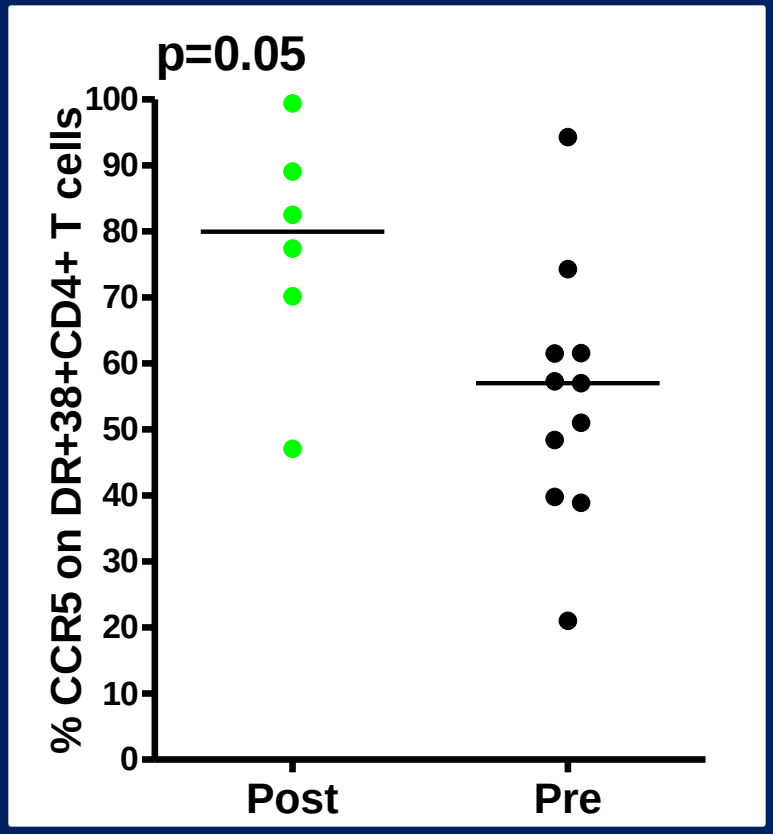


CCR5 Expression was Higher on Cervical CD4+ and Activated CD4+ T Cells in Post- vs. Premenopausal Women

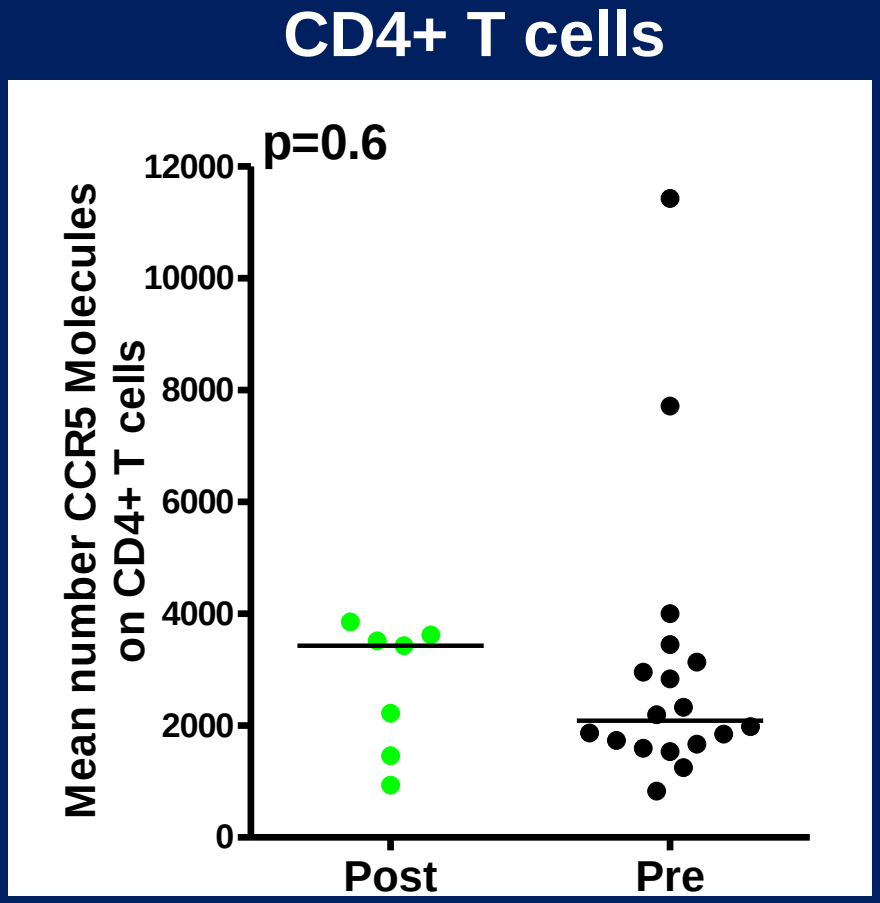
CD4+ T cells

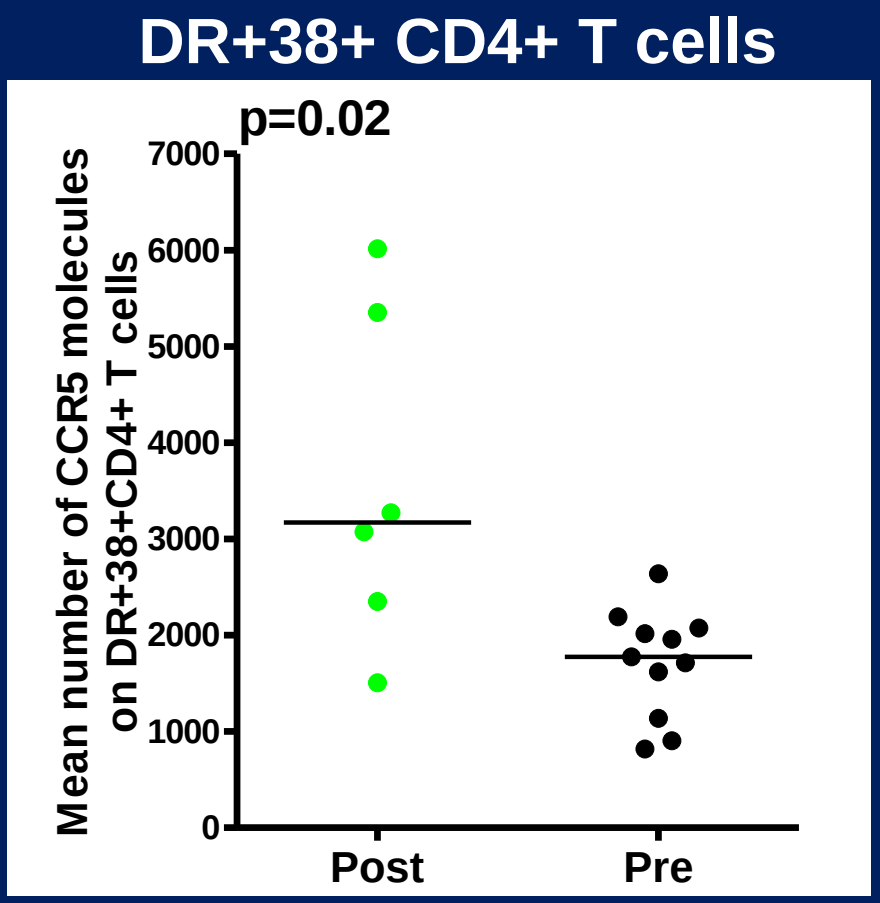


DR+38+ CD4+ T cells

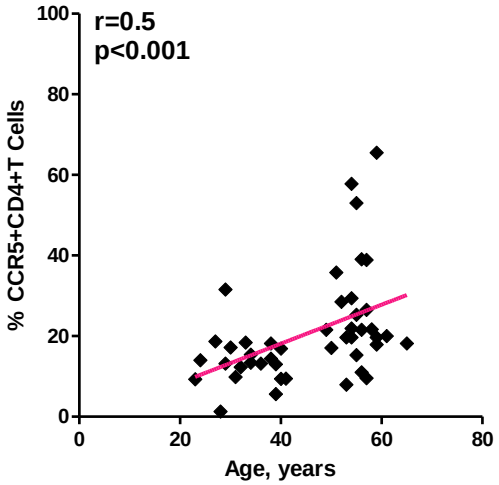
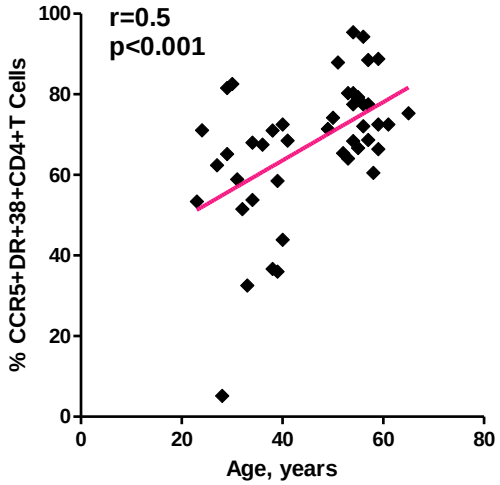
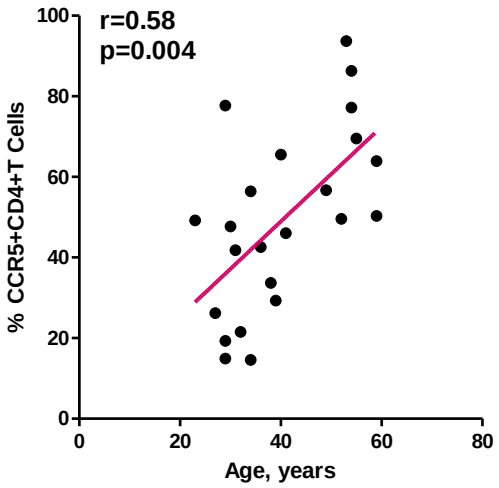
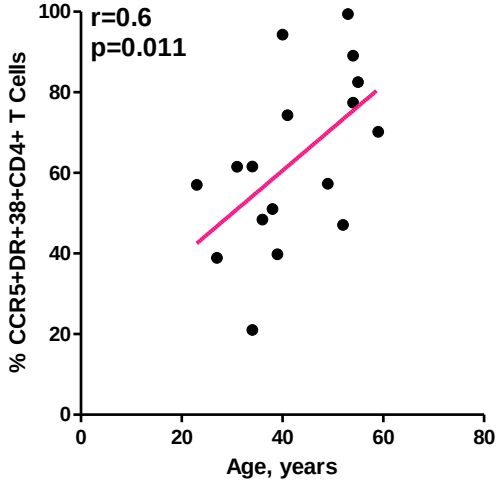


Number of CCR5 Molecules on Cervical CD4+ T cells in Post- vs. Premenopausal Women





CCR5 Expression on CD4+ and Activated CD4+ T cells Correlated with Age

	CD4+ T cells	DR+38+CD4+ T cells
Peripheral Blood		
Cervix		

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.

ACKNOWLEDGEMENTS

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- Don't shoot drugs. Sharing works can spread AIDS.

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