# Differences in associations of CD4/CD8 ratio, sex, and age on risk of mortality in HIV-infected adults on ART

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# Background

In elderly, HIV-uninfected populations, low CD4/CD8 ratio:

- associated with mortality, neurocognitive decline, & frailty
- characterized by expansion of CD8 T cell clonal populations and loss of CD28 expression on CD8 T cells (senescence)
- associated with male sex

In HIV-infected adults:

- Low CD4/CD8 ratio correlates with measures T cell activation and senescence
- Low CD4/CD8 ratio associated with HANA outcomes, particularly CVD
- The effects of sex and age on CD4/CD8 ratio and its associated clinical outcomes have not been described

Wikby et al. *Exp Gerontol*. 2002;37(2-3):445-53.
Strindhall et al. *Age*. 2013;35:985-91.
Peres et al. *Biogerontology.* 2003;21:289-96.
Serrano-Villar et al. *PLoS Pathogens.* 2014;10e1004078.
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# Hypothesis

*We hypothesized aging HIV-infected women would have higher CD4/CD8 ratio compared to men and this difference would be associated with decreased risk of mortality.*

# Methodology

- Vanderbilt Comprehensive Care Clinic
- Adult (≥ 18 years) who enrolled in care between January 1, 1998, and December 31, 2012
- Followed until death; December 31, 2012; or last clinic visit if gap in care > 1 year
- Inclusion criteria:
  - Two provider visits within first year
  - HIV-1 RNA <400 copies/mL for 1 year, documented by at least 2 laboratory values <12 months apart ("baseline" defined by this time point)
  - CD4 and CD8 cell counts available and HIV-1 RNA <400 copies/mL within 6 months of baseline

# Results: Table 1

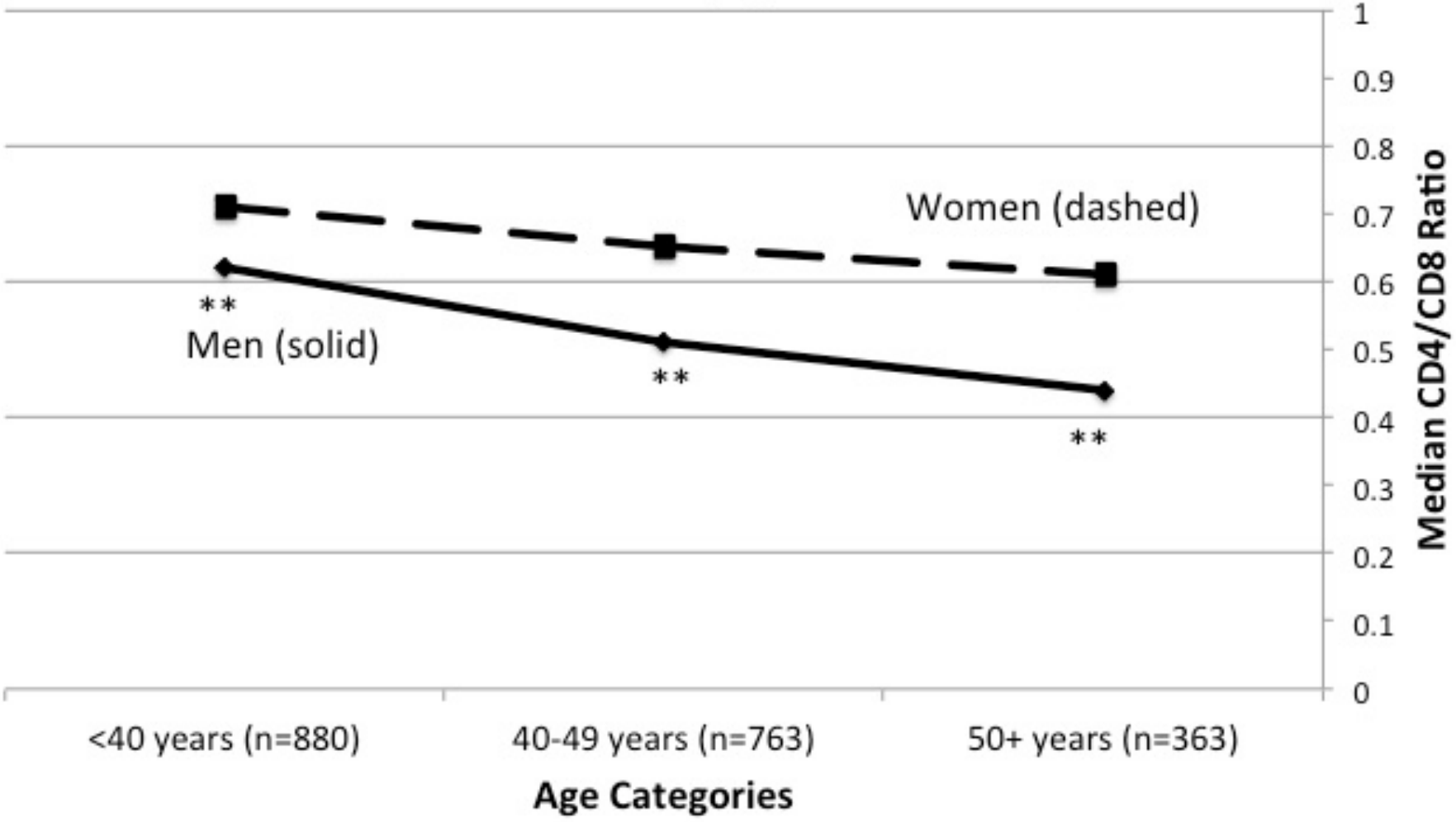
| Baseline Characteristics | Men | Women | *P* value |
|---|---|---|---|
| N (%) | 1554 (77) | 452 (23) | |
| Age in years, median (IQR) | 42 (25-48) | 40 (32-47) | 0.004[a] |
| Non-white race (%) | 589 (38) | 278 (62) | <0.001[b] |
| History of HCV infection (%) | 215 (14) | 73 (16) | 0.22[b] |
| History of HBV infection (%) | 136 (9) | 14 (3) | <0.001[b] |
| Anemia[c] at baseline (%) | 345 (24) | 93 (22) | 0.57[b] |
| Duration of ART in years, median (IQR) | 1.4 (1.1-3.2) | 1.3 (1.1-2.4) | <0.001[a] |
| **CD4/CD8 ratio, median (IQR)** | **0.54 (0.32-0.82)** | **0.67 (0.46-96)** | **<0.001[a]** |
| **CD4 cell count (cells/mm$^3$) , median (IQR)** | **450 (294-634)** | **528 (384-766)** | **<0.001[a]** |
| **CD8 cell count (cells/mm$^3$) , median (IQR)** | **833 (626-1139)** | **790 (568-1083)** | **0.004[a]** |

[a] Wilcoxon ranksum test for comparison of continuous variables

[b] Chi$^2$ test for comparison of categorical variables

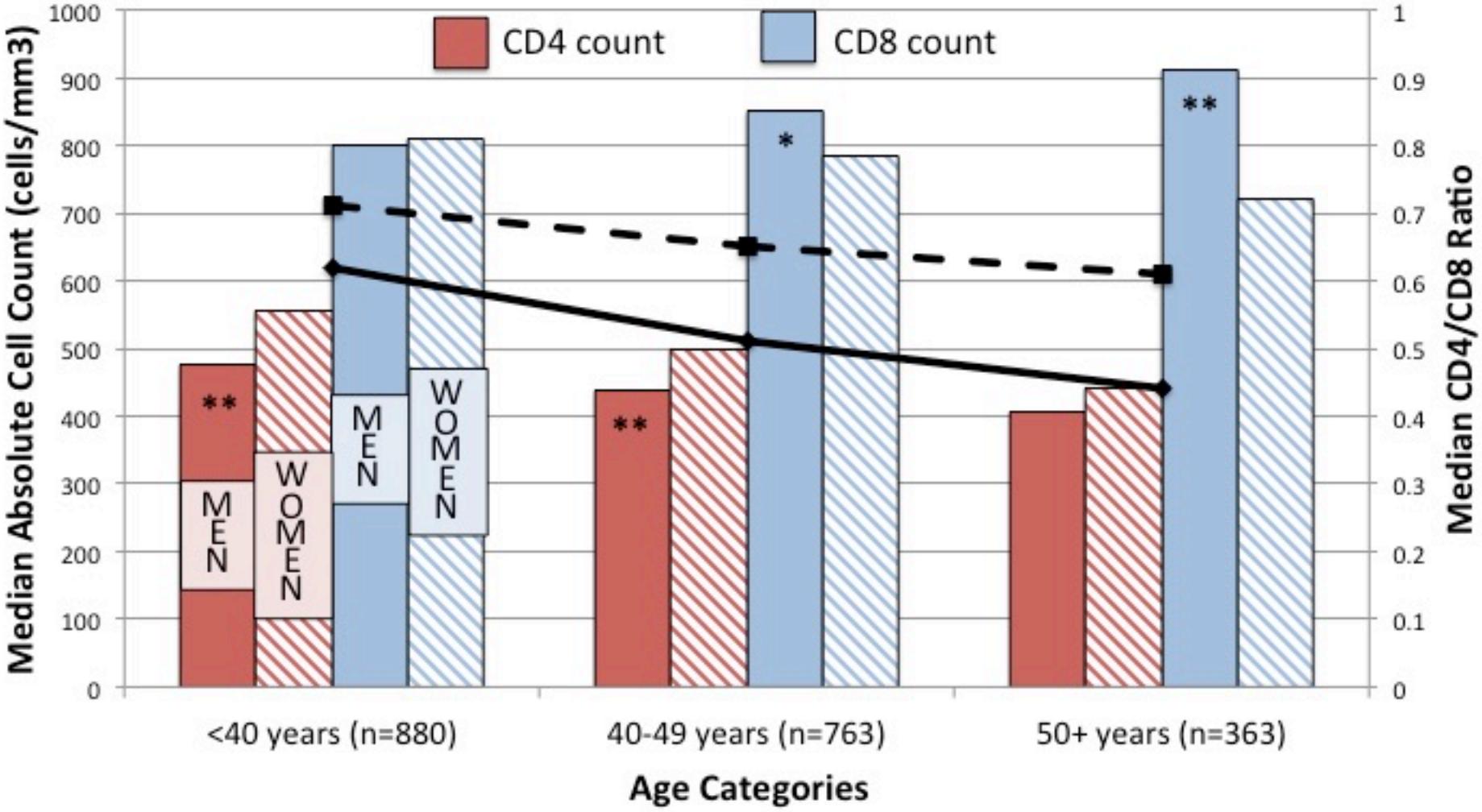
[c] Anemia defined as hemoglobin <11.8 (g/dL) for women and <14 (g/dL) for men.

# Sex differences in median CD4/CD8 ratio, CD4 count, and CD8 count by age




** Comparison of men vs. women = *P* <0.01

# Sex differences in median CD4/CD8 count ratio, CD4 count, and CD8 count by age




* Comparison of men vs. women = $P$ <0.10

** Comparison of men vs. women = $P$ <0.01

# Cox Proportional Hazards Models for Mortality

- No sex disparity in mortality was observed (aHR 1.08 [95% CI: 0.68-1.72])
- CD4/CD8 ratio no longer associated with mortality in adjusted models (aHR 0.97 [0.91-1.03])
- Interaction term for age and CD4/CD8 ratio suggestive of effect modification ($p = 0.06$)

| Age Groups | HR [95% CI] per 0.1 increase in CD4/CD8 ratio | *P* value | aHR* [95% CI] per 0.1 increase in CD4/CD8 ratio | *P* value |
|---|---|---|---|---|
| <40 years (27 deaths) | 0.86 [0.76-0.98] | 0.02 | 0.86 [0.74-1.02] | 0.08 |
| 40-49 years (64 deaths) | 0.95 [0.89-1.02] | 0.15 | 1.01 [0.94-1.09] | 0.73 |
| ≥ 50 years (38 deaths) | 0.94 [0.85-1.04] | 0.20 | 0.94 [0.83-1.07] | 0.34 |

* Adjusted models included sex and CD4 cell count

# Limitations

1. Single clinic cohort and limited number of outcomes

2. Used a single time point for CD4/CD8 ratio rather than time-updated

3. CMV serologic data not routinely collected in our clinic

4. Did not include cause of death data

# Conclusions

- For both men and women, CD4/CD8 ratio decreased with increasing age.
- Across all ages, women had consistently higher CD4/CD8 ratio values compared to men.
- Women did not have improved survival compared to men after accounting for this difference.
- Low CD4/CD8 ratio was not associated with mortality in older patients but may be predictive of mortality in the youngest HIV-infected adults, even after adjusting for CD4 cell count.

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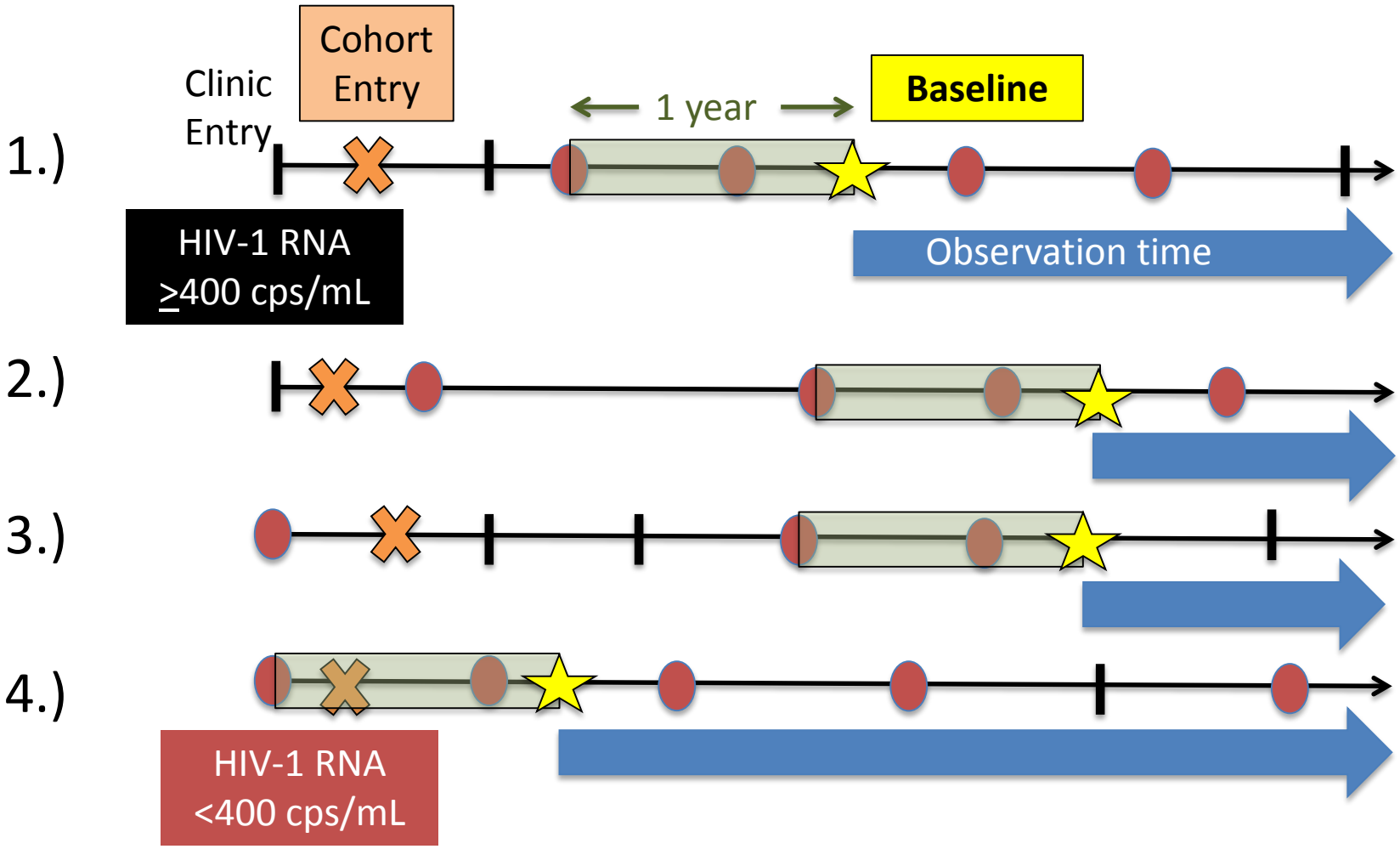
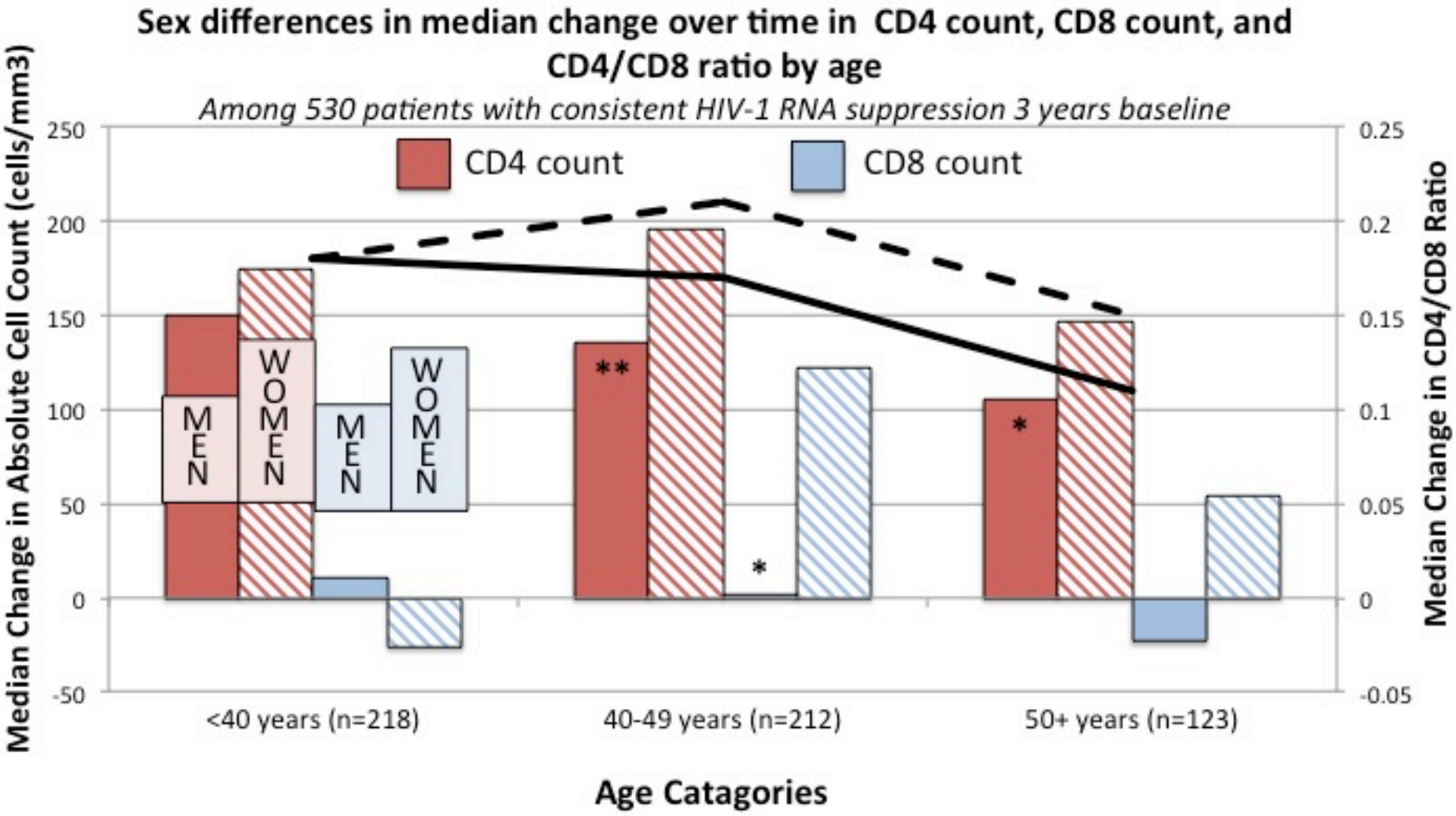
# “Baseline” definition






* Comparison of men vs. women = $P < 0.05$

** Comparison of men vs. women = $P < 0.01$