



# Does Sex Influence HIV Viral Load?



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**INTRODUCTION:** Recent UNAIDS statistics report that women constitute 48% of adults living with HIV/AIDS worldwide. In the US, 30% of incident HIV infections occur in women and 25% of adults living with AIDS in this country are women. HIV is now the 5th leading cause of death among women ages 25-44 in the US and the 3rd leading cause of death among African American women of the same age group.

Current recommendations for initiating antiretroviral therapy in HIV infection are based on the measurement of CD4 count and viral load, the predictive value of which has been studied in predominantly male cohorts. Studies examining the prognostic significance of viral loads in women seem to point towards lower HIV RNA levels in women than men, even at similar stages of infection. As women progress to AIDS and death at rates similar to men, despite possibly starting from lower viral load set-points, initiation of antiretroviral therapy in women at lower plasma HIV RNA thresholds may need consideration. We performed a systematic epidemiologic review of the evidence regarding sex effects on HIV viral loads.

**METHODS:** A search for studies examining the relationship between gender and HIV viral load was conducted using MEDLINE 1990-2002, AIDSLINE, Dissertation Abstracts Online, abstract examination from major HIV/AIDS conferences 1990-2002, and searching bibliographies of relevant review and articles. Inclusion criteria restricted the papers to those comparing viral loads among men and women. Studies were either cross-sectional in design or longitudinal, defined as multiple viral load comparisons between groups of men and women over time. All studies reviewed were required to report viral load differences between men and women with some attempt to control for stage of HIV infection.

**DATA (TABLES):**

**Nine** cross-sectional and **four** longitudinal studies met inclusion criteria and the following information was abstracted from each article: study design and year, sample size, CD4 ranges or median values, storage and assay conditions for viral RNA measurements, covariates analyzed, and estimates of the difference (with confidence intervals, provided or calculated from p-values when necessary) in log<sub>10</sub> viral load measurements between the groups and women being compared.

Possible confounders to the relationship between sex and viral load include age, race, CD4 count, time since seroconversion, use of antiretroviral therapy, active symptoms and active IV drug use. Covariates controlled for within each study are shown

CHARACTERISTICS OF STUDIES				
Study/Year published/Name of cohort	Sample size Men(%);Women(%)	CD4 range or median counts (cells/μl)	Mean log <sub>10</sub> RNA difference in women vs. men (95% CI)	p-value
Bush 1996	40 20 (50%); 20 (50%)	212 in men 210 in women	-0.32 (-1.00, 0.36)	0.36
Katzenstein 1996 ACTG 175	391 320 (82%); 71 (18%)	343 in men 346 in women	-0.35 (-0.54, -0.16)	<0.001
Farzadegan 1998 ALIVE	527 baseline sample 421 (80%); 106 (20%) 285 follow-up sample 196 (69%); 89 (31%)	518 (men and women) baseline; 390 (men) & 417 (women) in f/u	-0.29 (-0.51, -0.07) in baseline -0.31 (-0.62, 0.00) in follow-up	<0.01 <0.05
Moore 1999 Johns Hopkins	1173 1197(68%); 576(32%)	<100 to >750 Six strata	No difference seen in any CD4 strata	
Junghans 1999 Swiss cohort	1337 690 (52%); 647 (48%)	307/327 M/F IDU's 313/360 M/F Hetero	-0.23 (-0.40,-0.06) in IDU -0.04 (-0.10,0.02) in heterosexuals	0.009 0.21
Moroni 1999 ICONA	2011 1299 (65%); 712 (35%)	415 in men 469 in women	-0.13 (-0.21, -0.05)	<0.001
Rezza 2000. ICONA	415 245 (59%); 170 (41%)	487 in men 511 in women	-0.23 (-0.40, -0.05)	0.01
Anastos 2000 WIHS/MACS	2859 1603(56%);1256(44%)	<200 to >500 Three strata	+0.05 (-0.12,0.52); CD4 <200 -0.17 (-0.31,-0.02); CD4 200-350 -0.30 (-0.43, -0.17); CD4 350-500 -0.27 (-0.37, -0.16); CD4 >= 500	<0.05 <0.005 <0.005
Kalish 2000 VATS Study	494 392 (79%); 102 (21%)	16 in men 12.5 in women	+0.13 (-0.11, 0.37)	0.28
Evans 1997 / Tri-Service HIV-1 Prog.	42 14 (33%); 28 (67%)	700, 500, 400 (3 time points)	-0.5 (-0.52, -1.02) and -0.7 for first 2 years	0.03
Lyles 1999 ISS	149 98 (66%); 51 (34%)	485 in men and women	-0.33 (-0.68, 0.02)	0.065
Sterling 1999 ALIVE	71 51 (72%); 20 (28%)	723 in men 803 in women	-0.78 (-1.21, -0.35) at seroconversion	<0.001
Sterling 2001 ALIVE	202 156 (77%); 46 (23%)	659 in men 672 in women	-0.5 (-0.79, -0.21) at seroconversion	<0.001

Cross sectional

Longitudinal

**COVARIATES ADJUSTED FOR**

Study/year of publication	Age	CD4 count	Antiretroviral therapy	Time since seroconversion	Mode of Transmission	Active symptoms	Active IVDU	Race
Bush 1996	✓	✓						
Katzenstein 1996		✓						
Farzadegan 1998		✓	+/-		✓	✓	✓	✓
Moore 1999			✓		✓			✓
Junghans 1999		✓	+/-		✓			
Moroni 1999	✓	✓	✓		✓			✓
Rezza 2000	✓	✓	✓	✓	✓			✓
Anastos 2000		✓			✓		✓	✓
Kalish 2000	✓	✓			✓			✓

Cross sectional

Study/year of publication	Age	CD4 count	Antiretroviral therapy	Time since seroconversion	Mode of transmission	Active symptoms	Active IVDU	Race
Evans 1997	✓	✓		+/-				✓
Lyles 1999		✓		✓				
Sterling 1999	✓	✓	✓	✓	✓		✓	✓
Sterling 2001	✓	✓	✓	✓	✓			✓

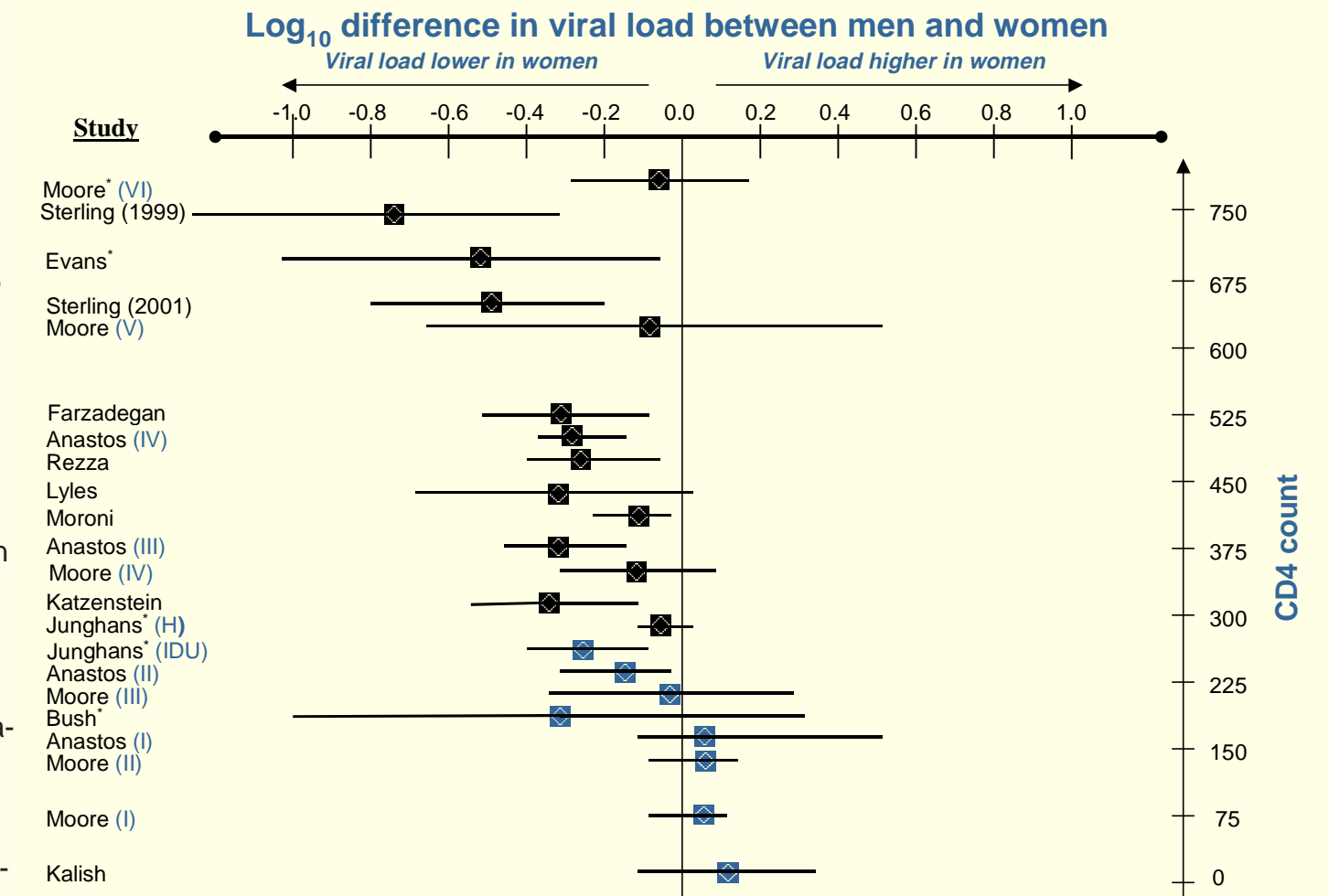
Longitudinal

**RESULTS:**

Seven of the nine cross sectional studies demonstrated that women had 0.13-0.35 log<sub>10</sub> lower HIV RNA levels than men, with women having approximately half the HIV RNA concentrations of men, even upon controlling for CD4 count. In the four longitudinal studies, women had 0.33-0.78 log<sub>10</sub> (2 to 6 fold) lower HIV RNA levels than men at similar stages of disease, despite controlling for time since seroconversion. Adjustment for other possible confounders of the relationship between sex and viral load, including age, race and use of antiretroviral therapy, did not change the outcome of lower HIV viral load values in women compared to men

**CONCLUSIONS:**

Women consistently have lower viral RNA loads than men at similar stages of HIV infection, an effect most marked early in the course of infection following HIV seroconversion. Sex differences in immune modulation presumably contribute to this phenomenon. Since estrogen and progesterone levels fluctuate in ovulating females, effects on immune function probably vary over the ovulatory cycle. In terms of HIV replication, viral loads in women do in fact vary over the ovulatory cycle, with levels falling a median of 0.16 log<sub>10</sub> from the early follicular to the midluteal phase. Possible hormonal mechanisms include the estrogen-mediated downregulation of TNF-α, an inflammatory mediator directly affecting HIV-1 expression. Furthermore, human lymphocytes express a glucocorticoid receptor with a distinct progesterone-binding domain, with progesterone exerting a dose-dependent inhibitory effect on CCR5 expression in activated T cells. CCR5 density is significantly lower on CD4 cells in women than in men and studies in male to female transsexuals show a decrease in CCR5 expression with female hormone administration. A strong correlation between HIV viral load and CD4 lymphocyte CCR5 density was recently reported. Hence, lower CCR5 density on CD4+ T cells in women could explain lower viral loads. Why women proceed to the clinical endpoints of AIDS and death as quickly as men despite lower levels of viremia, however, remains unexplained. This finding of lower viremia in women should serve as an impetus for further research on viral pathogenesis and its interplay with sex-related factors, inclusion of an adequate number of women in HIV-related studies, and a consideration of adjusting treatment guidelines for HAART initiation by gender.



**Figure.** Estimated differences in mean log<sub>10</sub> HIV-1 RNA level between women and men, with 95% confidence intervals. Studies are in ascending order of median CD4 count, with multiple strata indicated in parentheses for studies Moore (I-IV) and Anastos (I-IV). Two different groups of subjects are shown for Junghans: heterosexual transmission (H) and injection drug use (IDU). \* Assumes difference in mean log(RNA) would equal reported difference in median log(RNA), and t-test p-value would equal reported Mann-Whitney p-value.

**STUDIES IN REVIEW:**

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