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.

RESULTS:
Seven of the nine cross sectional studies demonstrated that women had 0.13-0.35 log10 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 log10 (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 log10 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 CCRS 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.