Considerations for Antiretroviral Therapy in Women

Several studies have suggested that plasma HIV RNA levels are significantly lower in adult women compared to men. Several analyses have been reported from the ALIVE cohort of intravenous drug users in Baltimore. In a cross-sectional study from this cohort, there was a consistent trend toward lower viral load (quantitative microculture as well as HIV RNA measured by branched chain DNA and RT-PCR) in women compared to men after adjustment for $CD4^+$ lymphocyte count, race and drug use within the prior 6 months; the difference in RNA levels was approximately 0.25 log *[1]*. When women and men were matched for $CD4^+$ T cell count there was no difference in the risk for progression to AIDS. However, when matched for RNA copy number, the risk of AIDS was 1.6-fold higher for women. In a further longitudinal case-control evaluation of seroconverters from this cohort, the sex-specific difference in viral load was present at seroconversion, but viral load tended to increase more rapidly in women and median viral loads in women and men became similar within 5-6 years of seroconversion *[2]*. The relationship between initial HIV RNA level at seroconversion and progression to AIDS was examined in a longitudinal study of 202 seroconverters (156 men and 46 women) from this cohort *[3]*. HIV RNA levels following seroconversion were significantly lower in women than men (by approximately 0.5 log), but these differences became attenuated over time. There was no significant sex-specific difference in rates of progression to AIDS. In another longitudinal study of 14 women and 28 men in the armed forces, median RNA levels were lower in women, but these differences were less than 0.5 log and diminished over time; no differences in HIV DNA load were observed *[4]*. In a virology substudy of ACTG 175, cross-sectional HIV RNA levels were 0.28 log lower in 71 women at baseline compared with men after adjustment for $CD4^+$ T cell count *[5]*.

Other large cohort studies have had less convincing results. In 647 women from the Swiss HIV Cohort Study, there was a slightly lower viral load among female injection drug users (0.13 log) but not among heterosexually infected women *[6]*. Additionally, there was no difference in disease progression between women and men matched for HIV RNA level and $CD4^+$ T cell count. In 712 women in the ICONA study, viral load was only 0.13 log lower in women after adjustment for $CD4^+$ T cell count; however, in contrast to the Swiss HIV Cohort Study, the sex-specific difference was larger in women with heterosexually acquired HIV infection compared with injection drug use-acquired HIV infection *[7]*. Data reported from Johns Hopkins showed little evidence of lower viral load after stratification by $CD4^+$ T cell count *[8]*, and in a comparison of 1262 women from the Women's Interagency HIV Study and men from the Multicenter AIDS Cohort Study, a small viral load difference of ~0.10-0.14 log was present only at higher CD4 count levels *[9]*. Finally, in an analysis of adults with advanced transfusion-acquired HIV infection, no significant differences in HIV RNA levels between women and men were observed *[10]* and no difference in viral load by sex was observed for age and $CD4^+$ T cell-matched antiretroviral naïve men and women either before or after antiretroviral therapy *[11]*.

Limited studies in HIV-infected adults have indicated that women may have higher $CD4^+$ T cell count than men. In a French study, this difference was observed only for CD4 percentage and was of borderline significance for CD4 absolute number once women and men were matched for age *[12]*. In a second European study, while absolute $CD4^+$ T cell count was higher in women than men, these differences were only statistically significant at AIDS onset and not at seroconversion or death *[13]*. Neither study evaluated the relationship of sex and $CD4^+$ T count to disease progression. However, other studies have shown similar rates of disease progression between men and women matched for $CD4^+$ T cell count and/or HIV RNA level *[6, 14, 15]*.

Taken together, these data suggest that gender-based differences in viral load occur predominantly during a window of time when the $CD4^+$ T cell count is relatively preserved and treatment is recommended only in the setting of high levels of plasma HIV RNA. Clinicians may wish to consider lower plasma HIV RNA thresholds for initiating therapy in women with $CD4^+$ T cell counts >350 cells/mm^3, although there are insufficient data to determine an appropriate threshold. In patients with $CD4^+$ T cell counts <350 cells/mm^3, very small sex-based differences in viral load are apparent; therefore, no changes in treatment guidelines for women are recommended for this group.

Further study is warranted regarding sex differences in viral and immunologic parameters. It is likely that any such differences would be hormonally related; estrogen-related effects have been described on immune function *[16]*. Consistent with this hypothesis are some preliminary studies of variation in viral load

according to menstrual cycle. One study has suggested that the ovulatory cycle influences circulating HIV-1 RNA levels *[17]*. Additionally, another study suggests that pharmacokinetic parameters may vary over the ovulatory cycle; considerable variations in indinavir pharmacokinetics were found during the menstrual cycle, with a trend to more drug exposure during the follicular phase *[18]*.

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