Feature

Age Differences by Sex in Antiretroviral-Naïve Participants: Pooled Analysis from Randomized Clinical Trials

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Age and sex effects on antiretroviral therapy (ART) response are not well elucidated. Our pooled analysis of 40 randomized clinical trials measured the association of age and sex on CD4+ T cell count changes and virologic suppression using multivariable regression modeling. The average increase in CD4+ T cell count from baseline to week 48 was 17.3 cells/mm^3 lower and clinically insignificant (95% confidence interval −30.8 to −3.8) among women ages ≥ 50 years (n = 573), compared to women ≤ 35 years (n = 3,939). Results were similar for men. Virologic suppression odds were 60% and 21% times greater among participants ≥50 years compared to ≤35 years, in women and men, respectively. In both sexes, larger increases in CD4+ T cell count changes were observed in younger, compared to older, participants; however, virologic suppression was higher in older, compared to younger, participants suggesting a non-sex-specific age effect response to ART.

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In 2015, an estimated 36.9 million people worldwide were living with HIV, approximately half of whom were women (UNAIDS, 2016). Around the world, women with HIV are living longer through improved health care and availability of combination antiretroviral therapy (ART). In the United States in 2014, 19% of incident HIV infections occurred in women (Centers for Disease Control and Prevention, 2017), as compared to sub-Saharan Africa, where 56% of HIV occurred in women (UNAIDS, 2016). As the pandemic of HIV enters its fourth decade, those infected with HIV worldwide are more likely to be female, with many becoming infected later in life or living beyond their reproductive years (Kaiser Family Foundation, 2016).

Estrogen is a known humoral immune system enhancer, and premenopausal women uninfected with HIV usually have higher titers of antibody responses, higher CD4+ T cell counts, and increases in proinflammatory markers such as interleukin-1 and -6, compared to postmenopausal uninfected women (Oertelt-Prigione, 2012; Patterson et al., 2009). Recently, estrogen was shown to block reemergence of HIV replication from latent HIV reservoirs (Karn et al., 2015). Therefore, the possibility of reduced ART efficacy in menopausal/postmenopausal women who have reduced estrogen has scientific interest.

Studies in the United States suggest that women infected with HIV may enter menopause earlier than women in the general population, occurring, on average, at 46.5 years in women living with HIV-1, compared to approximately 49 years and 51 years in the general population of African-American and Caucasian women, respectively (Kojic, Wang, & Cu-Uvin, 2007). However, few studies have explored the effects of menopause on HIV disease response to ART. Patterson and colleagues (2009) published findings evaluating the association between menopause and CD4+ T cell counts and HIV RNA levels at weeks 24, 48, and 96 in a subset of women, namely, 220 premenopausal women versus 47 postmenopausal treatment-naïve women. They found no significant differences in changes in CD4+ T cell counts or in HIV RNA suppression between postmenopausal and premenopausal women, but their sample size was small and their study was likely underpowered to detect a difference. Similarly, a study of 383 ART-naïve HIV-infected women conducted in Brazil compared ART response in 55 postmenopausal women to 328 premenopausal women. At 24 months after treatment initiation, the authors reported CD4+ T cell median changes among postmenopausal women that were significantly lower compared to premenopausal women, but the difference was attenuated when restricting the analysis to women with HIV RNA levels lower than 400 copies/mL (Calvet et al., 2014).

Given the paucity of information on the effects of menopause on HIV disease response to ART, we performed a participant-level pooled analysis of ART randomized clinical trials (RCTs) submitted to the U.S. Food and Drug Administration (FDA) to support New Drug Applications (NDA) and trials performed by the AIDS Clinical Trials Group (ACTG). Menopausal status is not routinely collected during clinical trials. Therefore, for these analyses, age (50 years of age or older) was used as a surrogate for menopause.

We explored three main research questions. We hypothesized that among treatment-naïve women living with HIV, those 50 years of age or older, compared to women 35 years of age or younger at the time of treatment initiation, would have the following responses to ART: (a) smaller increases from baseline in CD4+ T cell counts, (b) less virologic suppression (HIV RNA $<$ 400 copies/mL), and (c) a greater incidence of Grade 3 or higher selected laboratory abnormalities. If differences in ART outcomes were observed between groups comprising women 50 years of age or older, compared to women 35 years of age or younger, then additional analyses would be conducted among male participants ages 50 years or older and 35 years or younger to determine if age effects varied by sex.

Methods

Our research study was a collaborative effort between the FDA and the ACTG. The NDA trials selected for inclusion were compiled under an FDA Office of Women's Health grant-funded research project entitled "Women in HIV Trials: A