Published in final edited form as:

J Assoc Nurses AIDS Care. 2018 ; 29(3): 371–382. doi:10.1016/j.jana.2018.01.004.

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

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Disclosures: The authors have no real or perceived vested interests that relate to this article that could be construed as a conflict of interest.

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Abstract

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/mm³ lower and clinically insignificant (95% CI: -30.8, -3.8) among women ≥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.

Keywords

age; HIV; menopause; pooled-analysis; response to antiretroviral therapy; women

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 pro-inflammatory 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 re-emergence of HIV replication from latent HIV reservoirs (Karn et al., 2015). Therefore, the possibility of reduced ART efficacy in menopausal/post-menopausal 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 et al. (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 post-menopausal treatment-naïve women. They found no significant differences in changes in CD4+ T cell counts or in HIV RNA suppression between post-menopausal 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 post-menopausal women to 328 pre-menopausal 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 Comprehensive Review and Meta-Analysis," described previously (Soon et al., 2012). We selected RCTs for the treatment of HIV-1 infection in treatment-naïve adult participants of at least 48 weeks' duration. The FDA included all RCTs conducted in treatment-naïve participants and submitted to the FDA between the years 2000 and 2010. The included trials were used to support an initial approval or a major labeling change. Of note, some trials may have been conducted prior to 2000 but were submitted to the FDA between 2000 and 2010. All NDA trials had electronic, participant-level efficacy and safety data and were compiled using Clinical Data Interchange Standards Consortium standards with Study Data Tabulation Model format (Clinical Data Interchange Standards Consortium, 2013) including demographic, treatment discontinuation status, and HIV-1 RNA status.

The ACTG contributed nine RCTs, conducted between 1998 and 2010, of treatment-naïve participants with at least 48 weeks of follow-up data. An exception to the inclusion criteria was made for two ACTG trials, A5175 and A5208, which allowed for prior, limited ART use for the prevention of mother-to-child transmission in pregnant women. A complete list of included RCTs is available in Supplemental Table 1.

Our retrospective pooled analysis included outcomes that allowed for alignment of data across trials and networks so that participant-level pooled analyses were possible. All trials were performed in treatment-naïve populations; therefore, each participant was counted one time in the analysis.

Outcome Measures

HIV response to ART was evaluated by immune response, as measured by change in CD4+ T cell counts/mm³ from baseline (pre-treatment) to week 48 and virologic response, as measured by viral suppression defined as plasma HIV-1 RNA below 400 copies/mL (defined by the highest lower limit of quantification of the assays used in some studies) at week 48.

Within each designated age category (35 years, 36–49, 50 years), the proportions of participants experiencing a selected laboratory abnormality were compared at four time points: Week 4–8, Week 12–16, Week 24, and Week 48. The laboratory abnormalities included Grade 3 or higher laboratory measurements as per the U.S. Division of AIDS severity grading table, specifically hemoglobin (Hb) 7.4 gm/dL, aspartate and alanine amino transferases (AST and ALT; 5.1 times the upper limits of normal), and creatinine (> 1.9 times the upper limits of normal; (Division of AIDS, 2009).

Sex was determined by study personnel checking off either male or female for each participant. Within the ACTG trials, sex was characterized specifically as sex at birth. Menopausal status in women derived either from clinical information or laboratory tests (e.g., elevated follicle stimulating hormone) was not routinely documented across the included RCTs. Therefore, age was used as an indirect measure for menopause such that women entering the trial at ages 50 or older were categorized as being post-menopause. This approach aligned with the median age of menopause among women living with HIV of 47 to 50 years as reported in prior systematic reviews during the development of our study (Andany, Kennedy, Aden, & Loutfy, 2016; Kang & Fantry, 2016; Kojic et al., 2007).

Statistical Evaluation

Due to the generally rapid increase in CD4+ T cell count following initiation of ART following a non-uniform trajectory, differences in CD4+ T cell counts between the 35 and younger and 50 and older age groups were compared using Wilcoxon rank sum tests to account for the non-parametric distribution in CD4+ T cell count. For the binary outcomes of virologic response and incidences of selected Grade 3 and above laboratory abnormalities, the difference of proportions between the 35 and younger and 50 and older age groups were compared using the Pearson's chi-square test. If results between the age groups of 35 and younger and 50 and older women were statistically significantly different, the same analyses were repeated in the cohort of men enrolled in the RCTs within the same age groups. Secondary analyses assessed for differences between age groups including the intermediate age category defined as 36 to 49 years, inclusive.

To control for variables that might contribute to heterogeneity across trials, participant-level data were modeled using generalized linear and logistic models for the immunological and virologic endpoints, respectively. Model output included estimated mean coefficients, adjusted odds ratios (aOR), and 95% confidence intervals (CI). Along with age group,

multivariable models included the following predictive variables: assigned ART (nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors [NRTI/NNRTI], nucleoside reverse transcriptase inhibitors and protease inhibitors [NRTI/PI], or other ART regimen), region (Africa, Asia, Central or South America, Europe, North America), and race/ethnicity (Asian, Black, Hispanic or Latino, Caucasian, other, and unknown) as fixed effects and trial number as the random effects variable. The full models included a test for age group by sex interaction. Data on adherence and hormonal or contraception use were not consistently collected and, therefore, these variables were not included in models. The regression of change from baseline in immunologic response included categorized HIV RNA at baseline (< 400 copies/mL, 400–20,000 copies/mL, 20,001–100,000 copies/mL, > 100,000 copies/mL, or missing). Baseline CD4+ T cell count (< 200 cells/mm³, 200–349, 350–499, 500 cells/mm³, or missing) was included in the adjusted logistic regression of virologic response. Statistical significance was set at $p = 0.05$. All statistical analyses were performed using R version 3.4.0 Copyright© (2017) using the MASS and STATS packages.

Ethical Approval

All participants provided informed consent to participate in the primary ART RCTs, and de-identified data from the primary ART RCTs were used in this pooled retrospective analysis. Our project was approved by the ACTG Antiretroviral Therapy Strategies Subcommittee and the ACTG Scientific Agenda Steering Committee.

Results

Analysis was performed using data from 25,759 participants enrolled in 31 FDA and 9 ACTG-independent RCTs that were conducted in the Americas, Africa, Asia, or Europe, and were either conducted between the years 1998 and 2010 or submitted to the FDA between 2000 and 2010 (Supplemental Table 1). Most participants (69%) originated from trials submitted for the FDA regulatory review; 44% were enrolled at sites in North America and another 24% in sites in Africa (Table 1). Approximately 27% ($n = 6929$) of participants were female; overall, 10% ($n = 573$ females, $n = 1,977$ males) were 50 years of age or older at the time of enrollment, and 50% and 29% were Caucasian and Black, respectively. Forty percent of the participants had baseline CD4+ T cell counts lower than 200 cells/mm³ and 77% had baseline HIV RNA levels greater than 20,000 copies/mL (Table 1).

CD4+ T Cell Count Outcome

At week 48 post-treatment initiation, we observed median changes from baseline CD4+ T cell count that were statistically significantly larger among women ages 35 years or younger (164 cells/mm³) compared to women 50 years or older (152 cells/mm³), p -value = 0.022 (Table 2). Similarly, among men the median change from baseline in CD4+ T cell count was 165 cells/mm³ and 134 cells/mm³ in the 35 and younger and 50 and older age groups ($p < 0.0001$ for difference in medians), respectively. While the increases in both women and men from baseline in CD4+ T cell counts were larger among the younger participants compared to those 50 years of age or older, the difference between age groups was not considered clinically relevant.

After adjusting for baseline viral load, ART, region, study, and race/ethnicity, the estimated change in CD4+ T cell count from baseline at week 48 was 17.34 cells/mm³ lower (95% CI: -30.92, -3.76) among women 50 years of age or older compared to women 35 years or younger (Table 3). Similarly, among men 50 years of age or older, the change from baseline at week 48 in CD4+ T cell count was 24.19 cells/mm³ lower (95% CI: -31.68, -16.70) compared to men 35 years of age or younger. Smaller changes from baseline were observed in the intermediate age group compared to those 35 years of age or younger in both women and men.

HIV-1 RNA Outcome

Overall, more women 50 years of age or older (74%) had HIV RNA levels lower than 400 copies/mL at week 48 compared to women 35 years of age or younger (68%), $p = 0.006$. Similarly, more men 50 years or older had HIV RNA levels lower than 400 copies/mL (71%) at week 48 compared to men 35 years of age or younger (67%), $p = 0.002$ (Table 2). The proportion of participants achieving an HIV RNA level lower than 400 copies/mL at week 48 was greater in the intermediate age group of women 36 to 49 years of age (71%) compared to women 35 year of age or younger (67%; $p = 0.007$). A similar pattern was seen among men when comparing the HIV RNA suppression in the intermediate age group (70%) versus the younger age. No differences were noted between the intermediate and older age groups in either sex group. In multivariable models, the adjusted odds of achieving viral suppression at week 48 remained significant when comparing participants ages 50 years or older to those 35 years or younger: 1.60 (95% CI: 1.30, 1.98) in women and 1.21 (95% CI: 1.08, 1.35) in men, suggesting a 60% and 21% increase in the proportion achieving virologic suppression, respectively (Table 4). There was no evidence of an interaction between age and sex on virologic response.

Laboratory Abnormalities Outcome

No differences were observed between women 35 years or younger and 50 years or older with respect to the incidence of Grade 3 or higher ALT, AST, serum creatinine, or hemoglobin laboratory abnormalities through week 48 (Table 5). Because no statistically significant differences were found between the different age groups in women at the four time points (Weeks 4–8, Weeks 12–16 and Weeks 24 and 48), no additional comparisons were performed among men (data not shown). Additionally, the mean change from baseline through week 48 for ALT, AST, serum creatinine, and hemoglobin also did not reveal any clinically significant differences between the different age groups in women.

Discussion

The ability to investigate the association of menopause on ART response in women has been limited because clinical information or laboratory tests (e.g., follicle stimulating hormone) have not routinely been documented across the included RCTs. Therefore, age (≥ 50 years) was used as a surrogate to classify presumed menopausal status. Even if age were used, individual RCTs were underpowered to address ART efficacy responses across the various age ranges. To address this question, the FDA and ACTG collaborated to conduct a pooled analysis of 40 RCTs in more than 25,000 HIV treatment-naïve participants, of which 573

were women 50 years of age and older. This participant-level pooled-analysis of HIV-infected women and men included a large representation of ART-naïve participants 50 years of age and older from around the world and is one of the largest known to date.

Among women and men analyzed separately, the difference between the 35 and younger and 50 and older age groups in median change from baseline at week 48 in CD4+ T cell counts was small and not considered clinically significant. These findings were consistent with other reports in the literature (Balestre et al., 2012; Mutevedzi, Lessells, Rodger, & Newell, 2011; Rosin et al., 2015; Silverberg et al., 2007). In addition, because the smaller increases in CD4+ T cell counts at week 48 with increasing age occurred in both sexes, this change appeared to be driven by age and not sex. Finally, when controlling for prognostic factors including randomly assigned ART, region, and race/ethnicity, the differences in the trajectory of CD4+ T cell counts among age groups remained small and clinically insignificant in both women and men separately.

A statistically significant difference in the proportion of participants achieving HIV RNA lower than 400 copies/mL was observed for older (≥ 50 years) women (74%) and older men (71%) compared to younger (< 35 years) women (68%) and younger men (67%), respectively in contrast to our initial hypotheses. After adjusting for ART, region, race/ethnicity, trial, and baseline CD4+ T cell count, models suggested a significant increase of 60% and 21%, for women and men, respectively, in the odds of achieving viral suppression among participants 50 years or older compared to 35 years or younger. As with the CD4+ T cell count change, the difference in HIV RNA suppression seen in our analysis was not modified by sex but rather by age. These findings of smaller CD4+ T cell count increases and a higher percentage with suppressed HIV RNA in people 50 years of age or older compared to those 35 years of age or younger at week 48 were consistent with other studies. A large retrospective cohort study in HIV-1-infected adult members of a California Kaiser health plan found that younger patients had larger CD4+ T cell count increases within 1 year of ART initiation when compared to people ages 50 years or older ($p = 0.046$) and that improved HIV RNA suppression in older participants may have been associated with improved treatment adherence (Silverberg et al., 2007). Similar results were observed in a cohort of Ugandan participants suggesting a smaller CD4+ T cell count change in older individuals (comparing participants < 50 to > 60 years) with an average increase in CD4+ T cell count of 45 cells/mm³; 95% CI: 17,72, $p = 0.001$ (Semeere et al., 2014). The reduction of CD4+ T cell response in older people may be due to a decline of thymus reserve, which occurs with the process of aging. Another study reported that for every increase of 10 years of age, a small increase was found in HIV RNA suppression at week 144; adjusted relative risk = 1.05, 95% CI: 1.01, 1.09, $p = 0.007$ (Bosch, Bennett, Collier, Zackin, & Benson, 2007). Our findings differ from those presented by Patterson et al. (2009) and Calvet et al. (2014); however, these studies were smaller in comparison to ours and likely underpowered to detect differences among age and sex subgroups. Finally, we had hypothesized that older participants would have more severe side effects to the antiretroviral medications, limiting their ability to continue treatment and thus result in more virologic failures. Fortunately, we found that older participants did not experience more medication-associated toxicities and had higher viral suppression rates compared to younger participants. Our findings on the

incidence of laboratory abnormalities differed from others (Silverberg et al., 2007; Tumbarello et al., 2004), possibly related to the use of different abnormality cutoffs.

Although our pooled analyses of participant-level data across 40 RCTs represented one of the largest pooled analyses exploring HIV-1 ART response by sex and age to our knowledge, our analyses had some limitations. First, the analyses were limited because age was used as an indirect measure of menopausal status and there was an unknown level of possible misclassification of menopausal status within each group. However, our selection of age 50 or older to classify menopausal status was consistent with previous studies suggesting that the mean age of menopause ranged from 47–50 years (Boonyanurak et al., 2012; Calvet et al., 2015). Another limitation of the pooled analysis was that the comparison groups per age category were not randomly assigned, and thus were subject to confounding by measured or unmeasured factors. To address this limitation, several adjusted analyses were conducted to control for baseline factors thought to be prognostic for the outcomes, but additional confounders may remain even after these adjustments. Additionally, our analyses only included antiretrovirals approved before 2010. Immunologic or virologic response by age to newer antiretrovirals such as integrase inhibitors or potent once daily complete ART regimens may be different. Lastly, data on ART adherence were unavailable or minimal, thereby limiting the ability to assess if improved adherence in the older population was associated with improved HIV RNA suppression.

Conclusion

Our findings suggest that age could be more important than sex with regard to HIV RNA suppression in response to ART because similar changes were seen in both men and women ages 50 and older compared to younger participants. In contrast, older men and women did not experience the same CD4+ T cell increases compared to younger participants, despite having higher viral suppression rates at week 48. Additionally, for the selected laboratory abnormalities assessed, no differences were observed across the assessed age groups. However, other differences in laboratory abnormalities could exist and should be investigated in more detail in future studies.

Future research is warranted to continue these evaluations and compare immunologic and virologic responses in participants receiving currently-recommended ART regimens with a focus on once daily, fixed-dose combination products by age and sex with attention to gathering other potentially important factors such as ART adherence, menopausal status, and hormonal therapy use in women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant funding: Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases under Award Numbers AI068636 (PI: Kuritzkes, Daniel), UM1AI068634 (PI: Hughes, Michael), UM1AI106701 (PI: Coombs, Robert), UM1U01AI69471 (PI: Taiwo, Babafemi), 5UM1AI069463 (PI: Sanne, Ian), UM1AI069424 (PI: Currier, Judith), and UM1AI069503-10 (PI: Gordin, Fred). The content is solely

the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

This project was supported in part by an appointment to the ORISE Research Participation Program at the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA), administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA/CDER and by the FDA Office of Women's Health and FDA CDER Critical Path Program. Disclaimer: This article should not be construed to represent the U.S. Food and Drug Administration's views or policies.

We would like to thank the participants who enrolled in these studies and the executive-level leadership of the FDA, AIDS Clinical Trials Group and study teams who graciously allowed this analysis to be performed.

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Key Considerations

- Immune responses change with age, and estrogen is thought to prevent reactivation of HIV from viral reservoirs. Thus, as the population with HIV ages, understanding how men and women patients respond to ART is important for understanding how to optimize therapy and minimize side effects.
- From a clinical perspective, older men and women should be offered the same aggressive HIV ART regimens as younger patients, as soon as HIV infection has been identified, with equal likelihood of virologic response and no increased risk of side effects. This includes treatment for older women, regardless of menopausal status.
- Whether the decreased rise in CD4+ T cell count seen among older patients treated for HIV infection has prognostic implications for long-term health status or survival requires further study. Additional research will be required to more fully understand why older patients tended to have better viral suppression than younger patients, including their patterns of adherence.

Table 1

Baseline Descriptive Characteristics of Study Participants, by Sex and Age Group

Women														Men				All	
Variable		35	36-49	50	35	36-49	50	Total		35	36-49	50	Total		35	36-49	50	Total	
Group	FDA	2568	65%	1473	61%	369	64%	6437	73%	5632	70%	1386	70%	17865	69%				
	ACTG	1371	35%	944	39%	204	36%	2385	27%	2399	30%	591	30%	7894	31%				
ART	NRTI/NNRTI	1841	47%	1156	48%	282	49%	4431	50%	4161	52%	1033	52%	12904	50%				
	NRTI/PI	1787	45%	1069	44%	225	39%	3484	40%	3007	37%	739	37%	10311	40%				
	Other	311	8%	192	8%	66	12%	907	10%	823	11%	205	11%	2544	10%				
Region	Asia	414	11%	159	7%	22	4%	369	4%	247	3%	37	2%	1248	5%				
	Central, South America	521	13%	268	11%	70	12%	1192	14%	727	9%	145	7%	2923	11%				
	Europe	514	13%	274	11%	88	15%	1452	16%	1459	18%	443	22%	4230	16%				
	North America	842	21%	876	36%	246	43%	4091	46%	4169	52%	1031	52%	11255	44%				
	Africa	1648	42%	840	35%	147	26%	1718	19%	1429	18%	321	16%	6103	24%				
Race/ Ethnicity	Asian	450	11%	165	7%	22	4%	489	6%	325	4%	48	2%	1499	6%				
	Black	2000	51%	1267	52%	236	41%	1841	21%	1754	22%	407	21%	7505	29%				
	Hispanic, Latino	291	7%	181	7%	54	9%	1191	14%	703	9%	136	7%	2556	10%				
	Caucasian	1003	25%	669	28%	239	42%	4806	54%	4931	61%	1333	67%	12981	50%				
	Other, unknown	195	5%	135	6%	22	4%	495	6%	318	4%	53	3%	1218	5%				
CD4+ T cell count	< 200 cells/mm ³	1667	42%	1202	50%	256	45%	2957	34%	3319	41%	820	41%	10221	40%				
	200-349 cells/mm ³	1337	34%	746	31%	186	32%	3046	35%	2595	32%	647	33%	8557	33%				
	350-499 cells/mm ³	535	14%	274	11%	68	12%	1683	19%	1191	15%	294	15%	4045	16%				
	500+ cells/mm ³	360	9%	177	7%	56	10%	1065	12%	851	11%	201	10%	2710	11%				
	Missing	40	1%	18	1%	7	1%	71	1%	75	1%	15	1%	226	1%				
HIV RNA	< 400 copies/ml (suppressed)	28	1%	42	2%	27	5%	50	1%	221	3%	139	7%	507	2%				
	400-20,000 copies/ml	1013	26%	592	24%	121	21%	1821	21%	1354	17%	276	14%	5177	20%				
	20,001-100,000 copies/ml	1592	40%	1001	41%	253	44%	4237	48%	3832	48%	898	45%	11813	46%				
	100,000+ copies/ml	1306	33%	779	32%	172	30%	2709	31%	2621	33%	664	34%	8251	32%				

Variable	Women			Men			All		
	35	36-49	50	35	36-49	50	11	50	Total
Missing	0	0%	3	< 1%	0	0%	11	0%	<1%

Note. FDA = U.S. Food and Drug Administration; ACTG = AIDS Clinical Trials Group; ART = antiretroviral therapy; NRTI/NNRTI = nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors; NRTI/PI = nucleoside reverse transcriptase inhibitors and protease inhibitors; Other = another ART regimen, e.g., integrase inhibitors and combination regimens. Percentages are column percentages by variable within each category.

Table 2

Observed Change from Baseline CD4+ T Cell and Viral Response at Week 48, by Sex and Age Group

Variable	Overall	35 years	36–49 years	50 years	Difference (95% CI)	35 – 50	35 – (36–49) (36–49) – 50
CD4 cells/mm ³							
Women							
<i>n</i>	6929	3939	2417	573	-	-	-
Median	160	164	154	152	-	-	-
<i>p</i> -value* (vs. 50 years)	0.022	0.022	0.392	-	-	-	-
Mean (SE)	174.6 (1.8)	178.8 (2.5)	170.5 (3.1)	163.9 (6.4)	-	14.9 (1.4, 28.4)	8.3 (0.5, 16.1)
						6.6 (-7.4, 20.6)	
Men							
<i>n</i>	18830	8822	8031	1977	-	-	-
Median	155	165	151	134.5	-	-	-
<i>p</i> -value* (vs. 50 years)	<0.0001	<0.0001	<0.0001	-	-	-	-
Mean (SE)	170.5 (1.1)	178.8 (1.6)	166.3 (1.7)	150.7 (3.4)	-	28.1 (20.6, 35.6)	15.5 (7.9, 23.1)
						12.6 (7.9, 17.2)	
HIV RNA < 400 copies/ml[#]							
Difference (95% CI), <i>p</i> -value [#]							
						35 – 50	35 – (36–49) (36–49) – 50
Women							
<i>n</i>	6929	3939	2417	573	-	-	-
%	69.8	68.2	71.4	73.8	-	-5.7 (-9.4, -1.7), 0.006	-3.2 (-5.5, -0.9), 0.007
						-2.4 (-6.4, 1.6), 0.241	
Men							
<i>n</i>	18830	8822	8031	1977	-	-	-
%	69.0	67.3	70.3	70.9	-	-3.5 (-5.7, -1.3), 0.002	-3.0 (-4.4, -1.6), <0.0001
						-0.5 (-2.8, 1.7), 0.631	

Note.

* Wilcoxon Rank Sum test to compare median CD4+ T cell count; SE = standard error of the mean;

[#] Pearson's chi-square test of proportions.

Table 3
Change in CD4+ T Cell Count from Baseline to Week 48, Unadjusted and Adjusted Coefficients (95% CI) in Women and Men

Variable	Level	Women		Men	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Age group	35		Referent		Referent
	36-49	-8.32 (-16.10, -0.55)*	-9.34 (-17.15, -1.54)*	-12.58 (-17.22, -7.93)*	-11.86 (-16.48, -7.24)*
	50	-14.93 (-28.41, -1.45)*	-17.34 (-30.92, -3.76)*	-28.09 (-35.58, -20.59)*	-24.19 (-31.68, -16.70)*
ART	NRTI/NNRTI		Referent		Referent
	NRTI/PI	12.12 (4.56, 19.67)*	10.06 (2.51, 17.61)*	15.73 (11.03, 20.42)*	10.11 (5.43, 14.79)*
	Other	5.81 (-7.80, 19.42)	4.93 (-8.79, 18.65)	8.73 (1.31, 16.15)*	5.99 (-1.40, 13.39)
Region	North America		Referent		Referent
	Africa	0.52 (-8.42, 9.47)	-8.50 (-18.28, 1.28)	10.85 (4.82, 16.89)*	5.42 (-0.74, 11.59)
	Asia	-4.97 (-19.24, 9.29)	-5.40 (-39.53, 28.72)	25.35 (12.85, 37.85)*	16.57 (-5.0, 38.14)
	Central, South America	13.81 (1.55, 26.08)*	2.65 (-10.44, 15.73)	16.96 (9.65, 24.28)*	10.34 (2.69, 18.0)*
	Europe	-17.64 (-29.83, -5.45)*	-26.39 (-39.37, -13.40)*	11.73 (5.67, 17.78)	10.46 (4.15, 16.77)*
Race/Ethnicity	Caucasian		Referent		Referent
	Asian	-15.99 (-29.94, -2.05)*	-24.57 (-57.46, 8.32)	9.68 (-1.18, 20.53)	-6.11 (-24.87, 12.66)
	Black	-13.34 (-21.89, -4.79)*	-22.44 (-32.23, -12.64)*	-15.23 (-20.79, -9.67)*	-14.37 (-20.05, -8.70)*
	Hispanic, Latino	-13.63 (-28.39, 1.13)	-23.68 (-38.75, -8.60)*	-9.03 (-16.29, -1.77)*	-13.57 (-20.96, -6.17)*
	Other or unknown	-14.58 (-32.00, 2.85)	-26.08 (-43.83, -8.33)*	-11.91 (-22.52, -1.30)*	-18.66 (-29.47, -7.85)*
BL HIV RNA	< 400 copies/ml (suppressed)		Referent		Referent
	400-20,000 copies/ml	51.02 (20.00, 82.04)*	38.78 (7.10, 70.47)*	87.15 (71.66, 102.65)*	82.05 (66.13, 97.62)*
	20,001-100,000 copies/ml	81.49 (50.80, 112.18)*	69.11 (37.64, 100.57)*	123.12 (108.14, 138.10)*	119.13 (103.71, 134.56)*
	100,000+ copies/ml	98.03 (67.21, 128.85)*	88.44 (56.77, 120.11)*	141.36 (126.22, 156.51)*	134.65 (119.12, 150.18)*

Note.

* P -value < 0.05

ART = Antiretroviral therapy; NRTI/NNRTI = nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors; NRTI/PI = nucleoside reverse transcriptase inhibitors and protease inhibitors; Other = another ART regimen, e.g., integrase inhibitors, BL = baseline; adjusted generalized linear models including age group, drug class, region, race, and baseline HIV RNA as fixed effects and trial number as a random effects variable.

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Table 4

Logistic Regression of Viral Response (HIV RNA < 400 copies/mL) at Week 48, Unadjusted and Adjusted Odds Ratios in Women and Men

Variable	Level	Women		Men	
		Unadjusted OR	Adjusted OR	Unadjusted OR	Adjusted OR
Age group	35		Referent	Referent	Referent
	36–49	1.13 (0.92, 1.39)	1.25 (1.01, 1.56)*	1.03 (0.92, 1.14)	1.04 (0.93, 1.16)
	50	1.32 (1.08, 1.61)*	1.60 (1.30, 1.98)*	1.18 (1.06, 1.31)*	1.21 (1.08, 1.35)*
ART	NRTI/NNRTI	Referent	Referent	Referent	Referent
	NRTI/PI	0.84 (0.76, 0.94)*	0.79 (0.71, 0.89)*	0.89 (0.83, 0.95)*	0.95 (0.89, 1.02)
	Other	0.94 (0.78, 1.14)	0.90 (0.73, 1.10)	0.96 (0.86, 1.01)	1.08 (0.96, 1.20)
Region	North America	Referent	Referent	Referent	Referent
	Africa	0.30 (0.25, 0.36)*	0.52 (0.41, 0.65)*	0.49 (0.34, 0.69)*	0.82 (0.56, 1.16)
	Asia	0.33 (0.26, 0.41)*	0.34 (0.20, 0.58)*	0.38 (0.31, 0.47)*	0.36 (0.25, 0.51)*
	Central, South America	0.66 (0.55, 0.79)*	0.35 (0.28, 0.43)*	0.57 (0.50, 0.64)*	0.34 (0.30, 0.39)*
	Europe	0.99 (0.84, 1.17)	0.59 (0.49, 0.72)*	0.99 (0.91, 1.07)	0.70 (0.63, 0.76)*
Race	Caucasian	Referent	Referent	Referent	Referent
	Asian	0.44 (0.35, 0.55)*	0.65 (0.39, 1.05)	0.56 (0.47, 0.67)*	0.91 (0.68, 1.21)
	Black	0.87 (0.77, 0.98)*	1.24 (1.07, 1.43)*	1.22 (1.13, 1.32)*	1.45 (1.33, 1.58)*
	Hispanic, Latino	1.30 (1.06, 1.59)*	1.39 (1.12, 1.73)*	1.29 (1.17, 1.42)*	1.43 (1.28, 1.59)*
	Other or unknown	0.96 (0.75, 1.22)	1.16 (0.88, 1.51)	0.95 (0.82, 1.11)	1.19 (1.01, 1.40)*
Baseline CD4+ T Cell Count	< 200 cells/mm ³	Referent	Referent	Referent	Referent
	200–349 cells/mm ³	1.11 (0.98, 1.26)	0.94 (0.83, 1.08)*	0.96 (0.89, 1.03)	0.88 (0.81, 0.95)*
	350–499 cells/mm ³	1.93 (1.65, 2.26)*	1.44 (1.21, 1.70)*	1.34 (1.23, 1.47)*	1.18 (1.08, 1.30)*
	500+ cells/mm ³	2.46 (2.05, 2.95)*	1.86 (1.53, 2.26)*	2.13 (1.93, 2.36)*	1.87 (1.68, 2.08)*

Note.

* P -value < 0.05.

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Models adjusted for ART class, region, race, and baseline CD4+ T Cell count category; ART = Antiretroviral therapy; NRTI/NNRTI = nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors; NRTI/PI = nucleoside reverse transcriptase inhibitors and protease inhibitors; Other = another ART regimen, e.g., integrase inhibitors.

Table 5

Proportion with Grade 3 or Higher Laboratory Abnormalities by Week and Age Cohort in Women

Lab Parameter	Age Group	Week 4–8			Diff (35 - 50), 95% CI	Week 12–16			Diff (35 - 50), 95% CI	Week 24			Diff (35 - 50), 95% CI	Week 48			Diff (35 - 50), 95% CI
		< 35	36–49	50		< 35	36–49	50		< 35	36–49	50		< 35	36–49	50	
ALT (IU/L)		2.97	2.81	2.62	0.35 (-1.23, 1.66)	3.27	3.23	3.32	-0.04 (-1.78, 1.41)	5	4.55	4.54	0.46 (-1.53, 2.19)	5.99	5.50	5.58	0.41 (-1.77, 2.31)
AST (IU/L)		3.55	4.01	4.19	-0.63 (-2.53, 0.99)	4.16	4.88	5.76	1.60 (-3.75, 0.30)	4.49	5.06	5.30	-0.81 (-2.63, 1.23)	5.41	6.25	6.46	-1.05 (-3.33, 0.97)
Serum Creatinine		1.04	1.23	2.09	-1.05 (-2.45, 0.06)	0.96	1.17	1.28	-1.13 (-2.52, -0.02)	0.99	1.37	2.09	-1.10 (-2.50, 0.00)	1.09	1.37	2.27	-1.18 (-2.62, -0.02)
Hemoglobin		2.13	1.99	2.27	0.14 (-1.62, 1.06)	2.18	2.44	3.14	0.96 (-2.63, 0.43)	2.08	2.48	3.14	1.06 (-2.73, 0.33)	2.64	2.77	3.32	-0.68 (-2.39, 0.77)

Note: Grade 3 or higher laboratory measurements as per the U.S. Division of AIDS severity grading table (Version 1.0): AST and ALT 5.1 times the upper limits of normal, serum creatinine > 1.9 times the upper limits of normal, and hemoglobin (Hb) 7.4 gm/dL.