Treatment Responses in Antiretroviral Treatment–Naïve Premenopausal and Postmenopausal HIV-1–Infected Women: An Analysis from AIDS Clinical Trials Group Studies

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Menopause may affect antiretroviral treatment (ART) response. Immunologic and virologic responses to ART were compared in 220 premenopausal and 47 postmenopausal women enrolled in 2 studies involving ART-naïve persons. Changes in CD4 counts or human immunodeficiency virus type 1 RNA levels were similar at 24, 48, and 96 weeks after treatment initiation. ART-naïve women should respond to ART regardless of menopausal status.

One-half of the individuals living with human immunodeficiency virus type 1 (HIV-1) infection and/or AIDS worldwide are women [1]. In 2006, 15% of newly diagnosed cases of HIV-1 infection in the United States were in individuals aged ≥50 years [2]. The number of mature women who will become HIV-1–infected or who will live with HIV-1 is expected to increase as overall life expectancy increases. HIV-1–infected women will have already undergone or will undergo the menopause transition during the course of the disease. The differences between how HIV-1–infected and HIV-1–uninfected women experience menopause have only recently been investigated [3]. Despite these efforts, there is a paucity of information regarding initial treatment responses to antiretroviral therapy (ART) in postmenopausal women.

Younger HIV-1–infected women have higher CD4 counts and lower HIV-1 RNA levels, on average, compared with age-matched HIV-1–infected men during the early stages of disease and prior to receiving ART [4–7]. These differences may be explained by estrogen’s effect on immune function and HIV-1 replication [8]. Menopause is the natural aging process that results in decreased ovarian synthesis of estrogen. Postmenopausal women may therefore have different baseline CD4 counts and HIV-1 RNA levels, as well as different ART treatment responses, compared with premenopausal women. The goal of this study is to compare long-term immunologic and virologic responses to initial ART in premenopausal and postmenopausal women participating in 2 treatment trials.

METHODS

Women who participated in 2 recently completed multicenter studies of treatment-naïve individuals coordinated by the AIDS Clinical Trials Group (ACTG 5095 and ACTG 5142) were enrolled [9, 10]. Women were included if gynecological data within the first 24 weeks of ART were obtained. Menopause was defined as a cessation of menses for ≥6 months plus documented follicle stimulating hormone ≥35 mIU/mL at any age. Women aged ≤30 years without bilateral oophorectomy at ART initiation were classified as premenopausal. Women aged ≥55 years were categorized as postmenopausal. Women with bilateral oophorectomy were classified as postmenopausal, regardless of age. Menopause status of women aged 31–54 years was determined by self-report and standard questionnaire. CD4 counts and HIV-1 RNA levels were obtained at predetermined intervals according to the protocol of the parent study. All CD4 counts and HIV-1 RNA levels were obtained at predetermined intervals according to the protocol of the parent study. All CD4 counts were determined at local Clinical Laboratory Improvement Amendment–certified laboratories, and HIV-1 RNA levels (ultrasensitive Amplicor HIV-1 RNA Assay; Roche Diagnostic Systems) were determined at 1 central laboratory.

Immunologic and virologic responses after 24, 48, and 96 weeks of ART, irrespective of type or changes in ART, were analyzed. All women received 1 of 4 randomized treatment categories according to the original study protocols: nucleoside reverse-transcriptase inhibitor only, nucleoside reverse-transcriptase inhibitor plus nonnucleoside reverse-transcriptase inhibitor, protease inhibitor plus nucleoside reverse-transcriptase inhibitor, or protease inhibitor plus nonnucleoside reverse-transcriptase inhibitor.

Quantitative variables were compared between premenopausal and postmenopausal women with use of the Kruskal-Wallis test, and categorical variables were compared using Fisher’s Exact test. Logistic regression was used to compare the
Table 1. Baseline demographic characteristics for premenopausal and postmenopausal antiretroviral-naive women at the start of antiretroviral therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 267)</th>
<th>Menopause status</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Premenopause (n = 220)</td>
<td>Postmenopause (n = 47)</td>
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<td></td>
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<tr>
<td>Age, median years (IQR)</td>
<td>36 (31–44)</td>
<td>35 (30–40)</td>
<td>54 (48–58)</td>
<td>&lt; .001</td>
<td></td>
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<tr>
<td>Race/ethnicity</td>
<td></td>
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<td></td>
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<tr>
<td>White, non-Hispanic</td>
<td>54 (20)</td>
<td>42 (19)</td>
<td>12 (26)</td>
<td>.591</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>164 (61)</td>
<td>139 (63)</td>
<td>25 (53)</td>
<td></td>
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<tr>
<td>Hispanic</td>
<td>46 (17)</td>
<td>36 (16)</td>
<td>10 (21)</td>
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<tr>
<td>Native American/Alaskan</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Injection drug use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; .99</td>
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<tr>
<td>No</td>
<td>246 (92)</td>
<td>202 (92)</td>
<td>44 (94)</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>21 (8)</td>
<td>18 (8)</td>
<td>3 (6)</td>
<td></td>
<td></td>
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<tr>
<td>CD4 count, median cells/µL (IQR)</td>
<td>185 (63–299)</td>
<td>181 (63–283)</td>
<td>244 (53–338)</td>
<td>.215</td>
<td></td>
</tr>
<tr>
<td>CD4 percentage, median % (IQR)</td>
<td>14 (8–21)</td>
<td>14 (8–21)</td>
<td>17 (8–22)</td>
<td>.247</td>
<td></td>
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<tr>
<td>HIV-1 RNA level, median copies/mL (IQR)</td>
<td>52,542 (19,282–210,299)</td>
<td>45,938 (16,936–167,827)</td>
<td>96,021 (41,860–536,626)</td>
<td>.006</td>
<td></td>
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<tr>
<td>Drug class</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NRTI</td>
<td>44 (16)</td>
<td>33 (15)</td>
<td>11 (23)</td>
<td>.081</td>
<td></td>
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<tr>
<td>NRTI and NNRTI</td>
<td>134 (50)</td>
<td>115 (52)</td>
<td>19 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI and NRTI</td>
<td>39 (15)</td>
<td>28 (13)</td>
<td>11 (23)</td>
<td></td>
<td></td>
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<tr>
<td>PI and NNRTI</td>
<td>50 (19)</td>
<td>44 (20)</td>
<td>6 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy at baseline</td>
<td>28 (10)</td>
<td>2 (1)</td>
<td>26 (55)</td>
<td>&lt; .001</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of women, unless otherwise indicated. HIV-1, human immunodeficiency virus type 1; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

* P values were obtained using a nonparametric analysis of variance Kruskal-Wallis test for age, CD4 counts, and HIV-1 RNA level and a Fisher’s exact test for race/ethnicity, injection drug use, drug class, and history of hysterectomy.

odds of virologic suppression adjusting for pretreatment log_{10} HIV-1 RNA levels.

RESULTS

Characteristics of study population. Among 367 women who entered into the 2 protocols studying treatment-naive persons, 319 (87%) had gynecological data obtained within 24 weeks of ART initiation. Most of the women who did not have data were enrolled prior to the parent protocol amendment that introduced this data collection. Sixty-three women aged <31 years and 23 women aged ≥55 years at the time of ART initiation were characterized as premenopausal and postmenopausal, respectively. Of the 233 women aged 31–54 years, 157 were categorized as premenopausal and 24 as postmenopausal. The remaining 52 women were excluded because of reported perimenopausal symptoms (n = 13), unknown menopausal status (n = 12), or changed menopausal status during follow-up (n = 27). In summary, 267 women were included in the final analysis: 220 premenopausal and 47 postmenopausal women.

Age was statistically significantly lower for premenopausal versus postmenopausal women (median age 35 vs. 54 years; P < .001). Premenopausal women were less likely than postmenopausal women to have undergone a hysterectomy (2% vs. 55%; P < .001) (table 1). Race/ethnicity, injection drug use, or initial treatment regimens did not differ between the 2 groups. Median pretreatment CD4 counts were 181 and 244 cells/µL (P = .22) in premenopausal and postmenopausal groups, respectively. Premenopausal women had significantly lower median pretreatment HIV-1 RNA levels (45,938 vs. 96,021 copies/mL, corresponding to a difference of 0.32 log_{10} copies/mL; P = .006).

Primary end points. Of the 267 women, 259 (97%), 251 (94%), and 220 (82%) were followed to 24, 48, and 96 weeks after treatment initiation, respectively, with similar follow-up between premenopausal and postmenopausal women. Nineteen percent (n = 41) of the premenopausal and 13% (n = 6) of the postmenopausal women were without 96-week follow-up (P = .40). Fifteen women completed protocol follow-up before week 96 (12 premenopausal vs. 3 postmenopausal women), 10 were no longer able to get to the clinic for follow-up (8 premenopausal vs. 2 postmenopausal women), 9 were not able to comply with protocol requirements (9 premenopausal vs. 0 postmenopausal women), 7 were no longer able to be contacted.
(7 premenopausal vs. 0 postmenopausal women), 3 had severe debilitation and were unable to continue (2 premenopausal vs. 1 postmenopausal women), and 3 premenopausal women were unavailable for miscellaneous reasons (1 deceased, 1 withdrew consent, and 1 for unspecified reason).

The median change in CD4 count did not differ between premenopausal and postmenopausal women at 24 weeks (118 vs. 116 cells/μL; P = .99), 48 weeks (185 vs. 195 cells/μL; P = .42), or 96 weeks (260 vs. 273 cells/μL; P = .51); nor were there significant differences in median change in CD4 percentage at 24 weeks (7.0% vs. 7.0%; P = .77), 48 weeks (9.0% vs. 9.0%; P = .74), or 96 weeks (11.0% vs. 12.0%; P = .79).

Although premenopausal women had lower median pre-treatment HIV-1 RNA levels, there were no differences between groups in the proportion of women who achieved an HIV-1 RNA level ≤50 copies/mL at 24 weeks (74% vs. 68%; P = .46), 48 weeks (77% vs. 81%; P = .69), or 96 weeks (75% vs. 77%; P > .99). There were no differences in the odds of achieving an HIV-1 RNA level ≤50 copies/mL for premenopausal, compared with postmenopausal women after adjusting for pre-treatment HIV-1 RNA level at 24 weeks (odds ratio, 1.17; 95% confidence interval, 0.57–2.41), 48 weeks (odds ratio, 0.78; 95% confidence interval, 0.33–1.82), or 96 weeks (odds ratio, 0.82; 95% confidence interval, 0.36–1.89).

**DISCUSSION**

The increase in the incidence of HIV-1 infection in individuals aged >50 years [2, 11] is likely attributable to greater acceptability of testing, refinement of surveillance testing, incorporation of testing into daily medical care, and increases in prevalences of AIDS-defining illnesses in previously undiagnosed individuals [12]. The prevalence is also increasing because of more widespread use of ART. Postmenopausal women may be especially vulnerable to HIV-1 acquisition because of the physiological changes in the vaginal mucosa associated with diminished estrogen. Postmenopausal women may not perceive themselves to be at risk and therefore may not practice safe sex [13]. Compounded, these factors will likely result in an increase in new HIV/AIDS diagnoses in postmenopausal women, which in turn, will increase the number of ART-naive postmenopausal women requiring treatment.

With the growing population of HIV-1–infected women, understanding differences in immunologic and virologic responses to ART across the naturally occurring physiological changes is important. This analysis demonstrates the similarity in virologic and immunologic responses to ART in treatment-naive premenopausal and postmenopausal women initiating ART in a clinical trial setting. Among women who were followed up for 96 weeks after initiating ART, there were no differences in the median change in CD4 count or CD4 percentage. Nor were there differences in the proportion of women who achieved HIV-1 RNA levels ≤50 copies/mL at 24, 48, or 96 weeks. Differentiating between age and adherence effects is difficult and can only be performed with larger numbers of participants. Nonetheless, this study supports the results of a smaller clinical cohort study [14] that women respond equally well to ART in the short and long term regardless of menopause status.

There were some notable differences in pretreatment characteristics between the 2 groups that are worth noting. Postmenopausal women had higher median HIV-1 RNA levels at baseline. This difference was small (0.32 log10 copies/mL) but was statistically significant and is also similar to that observed between men and predominantly premenopausal women [12]. A study analyzing differences between age-matched men and women is planned within the AIDS Clinical Trials Group. Nonetheless, the percentages of postmenopausal women achieving HIV-1 RNA levels ≤50 copies/mL at prespecified time points did not differ from that for premenopausal women. This observation is consistent with other clinical trial outcomes suggesting that baseline HIV-1 RNA level is not a strong predictor of long-term virologic responses [15, 16]. Because time since seroconversion is unknown, we cannot rule out the possibility that our findings might be affected by other factors, such as healthy survivor effects or frailty selection bias.

This analysis used clinical trial data in which care was standardized and, therefore, avoids some of the problems seen in cohort studies. The similarity observed in CD4 count and viral load after initiating ART suggests that all women should be treated similarly regardless of age. Although the number of postmenopausal women was small in this analysis, the confidence intervals for the odds ratio comparing groups in the proportion of women achieving HIV-1 RNA levels ≤50 copies/mL allow us to rule out substantial differences in long-term suppression rates. This report did not, however, include measurements of antiretroviral-related toxicity or other adverse events, which have been reported to be increased among older individuals [17–19]. Despite this theoretical concern, 77% of the postmenopausal women (and 75% of premenopausal women) with HIV-1 RNA measurements were virologically suppressed at 96 weeks. Future analysis should address differences in toxicities that may impair adherence and sustainable responses.

We present data on the largest number of ART-naive women with well-characterized menopause status who received standardized care with ART through 96 weeks of follow-up. This study demonstrates that postmenopausal women benefit from ART and achieve responses similar to those in premenopausal women and that responses are maintained through 2 years of follow-up. Therefore, clinicians should anticipate that treatment-naive HIV-1–infected women should achieve immuno-
logic and virologic responses to ART regardless of menopause status.

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References