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Treatment Responses in Antiretroviral Treatment (ART) Naïve Pre- and Post-menopausal HIV-infected Women: An Analysis from ACTG Studies

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Abstract

Menopause may affect antiretroviral treatment (ART) response. Immunologic and virologic responses to ART were compared in 220 pre- and 47 post-menopausal women enrolled in two ART-naive studies. Changes in CD4 counts or HIV-1 RNA were similar at 24, 48, or 96 weeks. Treatment-naïve women should respond to ART regardless of menopausal status.

Keywords

Women; Menopause; HIV; Treatment Naïve; Antiretroviral Therapy

Introduction

Half of the individuals living with HIV/AIDS worldwide are women [1]. In 2006, 15% of newly diagnosed cases of HIV in the United States were in individuals above the age of 50 [2]. The number of mature women who will become HIV-infected or who will live with HIV is expected to increase as overall life expectancy increases. HIV-infected women will have already undergone or will undergo the menopause transition during the course of their disease. The differences between how HIV-infected and HIV-uninfected women experience menopause are only recently under investigation [3]. Despite these efforts, there is a paucity of information regarding initial treatment responses to antiretroviral therapy (ART) in post-menopausal women.

Younger HIV-infected women have higher CD4 counts and lower HIV-1 RNA, on average, when compared to age-matched HIV-infected men in early disease and prior to receiving ART [4-7]. These differences may be explained by estrogen's effect on immune function and HIV

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replication [8]. Menopause is the natural aging process resulting in decreased ovarian synthesis of estrogen. Post-menopausal woman may therefore have different baseline CD4 counts and HIV-1 RNA as well as different ART treatment responses as compared to pre-menopausal women. The goal of this study is to compare long-term immunologic and virologic responses to initial ART in pre- and post-menopausal women participating in two treatment trials.

Methods

Women who enrolled into two recently completed multi-center treatment-naïve studies coordinated by the AIDS Clinical Trials Group (ACTG 5095 and ACTG 5142)[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 ≥ 6 months plus documented follicle stimulating hormone > 35 miu/mL at any age. Women ≤ 30 years and without bilateral oophorectomy at ART initiation were classified as pre-menopausal. Women ≥ 55 years were categorized as post-menopausal. Women with bilateral oophorectomy were classified as postmenopausal, regardless of age. Menopause status of women > 31 to < 54 years was determined by self-report and standard questionnaire. CD4 counts and HIV-1 RNA were collected at pre-determined intervals according to the parent protocol. All CD4 counts were processed at local CLIA certified labs and HIV-1 RNA (ultrasensitive Amplicor HIV-1 RNA Assay, Roche Diagnostic Systems) were processed at one 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 one of four randomized treatment categories according to the original protocols: NRTI only, NRTI plus NNRTI, PI plus NRTI, or PI plus NNRTI.

Quantitative variables were compared between pre- and post-menopausal women using the Kruskal-Wallis Test, and categorical variables were compared using Fisher's Exact Test. Logistic regression was used to compare the odds of virologic suppression adjusting for pre-treatment $\log_{10}$ HIV-1 RNA.

Results

Characteristics of Study Population

Among 367 women who entered into the two treatment-naïve protocols, 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 < 31 years and 23 women ≥ 55 years at the time of ART initiation were characterized as pre- and post-menopausal, respectively. Of the 233 women ≥31 and <55 years, 157 were categorized as pre-menopausal and 24 as post-menopausal. The remaining 52 women were excluded for reporting peri-menopausal 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 pre-menopausal and 47 post-menopausal women.

Age was significantly lower for pre- versus post-menopausal women (median 35 vs. 54 years; $p < 0.001$) Pre-menopausal women were less likely than post-menopausal women to have undergone a hysterectomy (2% vs. 55%; $p<0.001$) (Table 1). Race/ethnicity, injection drug use or initial treatment regimens did not differ between the two groups. Median pre-treatment CD4 count was 181 and 244 cells/ul ($p=0.22$) in pre- and post-menopausal women, respectively. Pre-menopausal women had significantly lower median pre-treatment HIV-1 RNA level (45,938 vs. 96,021 copies/ml corresponding to a difference of 0.32 $\log_{10}$ copies/ml; $p= 0.006$).

Primary Endpoints

Of the 267 women, 259 (97%), 251 (94%) and 220 (82%) were followed to 24, 48 and 96 weeks, respectively, with similar follow up between pre- and post-menopausal women. Nineteen percent (n= 41) of the pre- and 13% (n=6) of the post-menopausal women were without 96 weeks follow-up (p=0.40). Fifteen completed protocol follow-up before week 96 (12 pre vs 3 postmenopausal, respectively), 10 were no longer able to get to the clinic for follow up (8 vs 2), 9 were not able to comply with protocol requirements (9 vs 0), 7 were no longer able to be contacted (7 vs 0), 3 had severe debilitation and were unable to continue (2 vs 1), and 3 pre-menopausal women for miscellaneous reasons (1 deceased, 1 withdrew consent and 1 for unspecified reason).

The median change in CD4 count did not differ between pre- and post-menopausal women at 24 weeks (118 vs. 116; p=0.99), 48 weeks (185 vs. 195; p= 0.42) or 96 weeks (260 vs. 273 cells/ul; p= 0.51); nor were there significant differences in median change in CD4 % at 24 (7.0 vs 7.0; p=0.77), 48 (9.0 vs 9.0; p=0.74) or 96 weeks (11.0 vs 12.0%; p=0.79).

Although pre-menopausal women had lower median pre-treatment HIV-1 RNA, there were no differences between groups in the proportion of women with measurements who achieved an HIV-1 RNA ≤50 copies/ml at 24 (74% vs. 68%; p=0.46), 48 (77% vs. 81%; p=0.69) or 96 weeks (75% vs. 77%; p>0.99). There were no differences in the odds of achieving an HIV-1 RNA ≤50 copies/mL for pre-menopausal compared with post-menopausal women after adjusting for pre-treatment HIV-1 RNA at 24 (OR 1.17; 95% CI: 0.57, 2.41), 48 (OR 0.78; 95% CI: 0.33, 1.82) or 96 weeks (OR 0.82; 95% CI: 0.36, 1.89).

Discussion

The increase in HIV incidence in individuals above the age of 50 [2,11] is likely due to greater acceptability of testing; refinement of surveillance testing; incorporation of testing into daily medical care; and increases in AIDS-defining illnesses in previously undiagnosed individuals [12]. The prevalence is also increasing due to more widespread use of ART. Post-menopausal women may be especially vulnerable to HIV acquisition due to the physiological changes in the vaginal mucosa associated with diminished estrogen. Post-menopausal 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-naïve postmenopausal women requiring treatment.

With the growing population of HIV-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 naïve pre- and post-menopausal women initiating ART in a clinical trial setting. Among women followed for 96 weeks after initiating ART, there were no differences in the median change in CD4 count or CD4% between these pre- and postmenopausal women. Nor were there differences in the proportion of women who achieved HIV-1 RNA ≤ 50 copies/ml at 24, 48 or 96 weeks. Differentiating age and adherence effects is difficult and can only be performed with larger numbers of participants. Nonetheless, this study supports 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 between the two groups in pre-treatment levels worth noting. Post-menopausal women had higher median HIV-1 RNA at baseline. This difference was small (0.32 $\log_{10}$ copies/ml) but was significant and is also similar to that seen between men and predominantly pre-menopausal women [12]. An analysis between age-matched men

and women is a planned within the ACTG. Nonetheless, the percentages of post-menopausal women achieving HIV-1 RNA ≤ 50 copies/mL at pre-specified time points did not differ from those of pre-menopausal women. This observation is consistent with other clinical trial outcomes suggesting that baseline HIV-1 RNA 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 by 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 in CD4 counts and viral load after initiating ART suggest that all women should be treated similarly regardless of age. While the number of post-menopausal women was small in this analysis, the confidence intervals for the odds ratio comparing groups in the proportion of women achieving HIV-1 RNA ≤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 post-menopausal 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 naïve women with well-characterized menopause status who received standardized care with ART through 96 weeks of follow up. This study demonstrates that post-menopausal women benefit from ART and achieve responses similar to those in pre-menopausal women which are maintained through 2 years of follow-up. Therefore, clinicians should anticipate treatment naïve HIV-infected women should achieve immunologic and virologic responses to ART regardless of menopause status.

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Table 1

Baseline demographics for pre-menopausal and post-menopausal ARV naïve women at start of ART (*N* = 267)

			Menopausal Status		
		Total (*N* = 267)	**Pre-menopausal (*N* = 220) (82%)**	**Post-menopausal (*N* = 47) (18%)**	**P value[1]**
Age, years	Median (Interquartile Range)[2]	36 (31 – 44)	35 (30 – 40)	54 (48 – 58)	**< 0.001**
Race/Ethnicity	White, non-Hispanic	54 (20%)	42 (19%)	12 (26%)	0.591
	Black, non-Hispanic	164 (61%)	139 (63%)	25 (53%)	
	Hispanic	46 (17%)	36 (16%)	10 (21%)	
	Native American/Alaskan	2 (1%)	2 (1%)	0 (0%)	
	More than one race	1 (0%)	1 (0%)	0 (0%)	
Injection Drug Use	Never	246 (92%)	202 (92%)	44 (94%)	1.000
	Ever	21 (8%)	18 (8%)	3 (6%)	
CD4 Count, cells/ul	Median (Interquartile Range)[1]	185 (63 – 299)	181 (63 – 283)	244 (53 – 338)	0.215
CD4 Percentage, (%)	Median (Interquartile Range)[1]	14 (8-21)	14 (8-21)	17 (8-22)	0.247
HIV-1 RNA, copies/ml	Median (Interquartile Range)[1]	52,542 (19,282 – 210,299)	45,938 (16,936 - 167,827)	96,021 (41,860 - 536,626)	**0.006**
Drug Class	NRTI	44 (16%)	33 (15%)	11 (23%)	0.081
	NRTI+NNRTI	134 (50%)	115 (52%)	19 (40%)	
	PI+NRTI	39 (15%)	28 (13%)	11 (23%)	
	PI+NNRTI	50 19%)	44 (20%)	6 (13%)	
Hysterectomy at baseline		28 (10%)	2 (1%)	26 (55%)	**< 0.001**

[1]P-values were obtained using a non-parametric ANOVA Kruskal-Wallis test for age, CD4, HIV-1 RNA, and initial step regimen duration. P-values were obtained using a Fisher's exact test forty, injection drug use, drug class, and history of hysterectomy.

[2]Interquartile range was defined as 25%-75% quartiles.