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HIV and menopause: A systematic review of the effects of HIV infection on age at menopause and the effects of menopause on response to antiretroviral therapy

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HIV and menopause: A systematic review of the effects of HIV infection on age at menopause and the effects of menopause on response to antiretroviral therapy

By

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M.D., University of Yamanashi, 2007

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An abstract of
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ABSTRACT

HIV and menopause: A systematic review of the effects of HIV infection on age at menopause and the effects of menopause on response to antiretroviral therapy

By Kentaro Imai

More than half of persons living with HIV infection in the United States will be aged 50 years or older by 2020, and half of those persons will be women, including menopausal women. Despite this trend among older persons living with HIV, huge gaps exist in our understanding of the impact of HIV on menopausal women. Understanding details about the age of menopause in women living with HIV can contribute to the development of preventive and therapeutic interventions that minimize any long-term, synergistic effects of estrogen deficiency and HIV for HIV-infected older women. Understanding the effect of menopause on immunologic and virological responses to antiretroviral therapy (ART) can contribute to ART optimization across menopause, especially when considered with other co-morbid medical conditions that accompany the aging process. We conducted a systematic review of the effects of HIV infection on age at menopause and effects of menopause on response to ART. We used the electronic Ovid Medline database from 1946 to August 2012. We included English-language studies which focused on HIV-infected persons, had full text available, included post-menopausal women, and reported outcome data for either age at menopause, or response to ART across menopause. Six original research articles were selected for the review of age at menopause; five for the review of response to ART across menopause. Our review revealed that the current data on the effects of HIV infection on age at menopause and the effects of menopause on response to ART are inconclusive, and more rigorous studies are needed. Future studies should recruit a large number of both HIV-infected and HIV-uninfected women across menopause, use a combination of questionnaires and measurements of serum FSH levels for menopause diagnoses, and consider confounders related to age of menopause. Additionally, disentangling the effects of menopause requires well-designed studies that sample a sufficient number of matched HIV-infected pre-menopausal women followed longitudinally across the years of menopause.

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INTRODUCTION

Globally, persons with human immunodeficiency virus (HIV) are living longer, healthier lives, largely due to the widespread use of effective highly active antiretroviral therapy (HAART) [1, 2]. It is projected that by 2015-2020, half of the people living with HIV infection in the United States will be 50 years of age or older [3, 4] and likely living with and managing other comorbid, chronic medical conditions that often accompany the aging process. These conditions include hypertension, diabetes, and for women, who make up half of all persons living with HIV worldwide, menopause [5]. For HIV-infected women on effective ART, this longer survival translates into many women likely living beyond the median age of onset of menopause (49.0 years; interquartile range 45.0 - 51.0 years) [6] and well into their postmenopausal years. Despite these trends toward a more elderly cohort of persons living with HIV, huge gaps exist in our understanding about the effect of HIV on the normal aging process for HIV-infected women as they approach and live through menopause. Prioritizing efforts to learn more about the potential impact of HIV on the lives of menopausal women are warranted in an effort to optimize care and treatment for aging women living with HIV.

In the United States, in 2010, an estimated 25% of adults and adolescents living with HIV infection were women; an estimated 26% of women living with HIV infection were aged 35 - 44 years; and an estimated 36% of female living with HIV infection were women aged 45 - 54 years, and near or already into their menopausal years [7] (Figure 1). Among women who were newly diagnosed with HIV infection in 2011, African Americans and Hispanics/Latinos are disproportionately represented [7, 8] (Figure 2);

understanding the effects of HIV infection on women and menopause will also contribute to the national efforts to understand and close HIV-related racial/ethnic disparity gaps.

To date, there have been varying and inconsistent reports regarding several areas related to HIV-infected women and menopause. HIV-infected women were reported to lose ovarian function earlier in life than HIV-uninfected women, leading to an earlier onset of menopause among HIV-infected women [9]. Over the short term, a menopausal transition is associated with an altered mood state and sexual dysfunction, both of which can impact quality of life among women with and without HIV infection [10, 11]. Over the long term, menopause accelerates the acquisition of chronic diseases of aging among women, including cardiovascular diseases, hypertension, diabetes and reduced mineral bone density [12, 13]. All of these risks suggest a possible increased number of years and burden of disease for HIV-infected women if they enter menopause at an earlier age and are living longer lives with effective treatments [14]. Data are inconsistent regarding these areas of menopause and HIV. Additionally, little is known about the difference in response to ART across menopause for women living with HIV. Our objectives were to conduct a systematic review of literature to summarize data regarding: 1) the age of menopause among women living with HIV infection, and 2) the immunological and virological response to ART in HIV-infected, menopausal women. This paper also identifies research gaps and informs future initiatives for perimenopausal HIV-infected women to ensure optimal medical management of comorbid conditions among older women.

METHODS

We conducted this search using the electronic Ovid Medline database from 1946 to August 2012 to identify relevant articles. The search was limited to articles published in English language that described studies of menopausal transition among humans and animals with HIV infection. We focused on two topics: 1) age at menopause, and 2) immunological and virological response to ART across menopause. Search strategies used the keywords "HIV" and "menopause." Additional search terms were added to yield the highest number of possible articles. Additional search terms for the two topics were: 1) for age at menopause, "age," "aging," "age at menopause," "age of menopause," "early," or "early menopause"; and 2) for response to ART across menopause, "antiretroviral (ARV)," "HAART," "ART," "ARV," "treatment," "response," "response to ART," "CD4," or "viral load." Final original research articles included: 1) original research articles that studied age at menopause in HIV-infected women, and 2) original research articles that examined the difference in response to ART across menopause in HIV-infected women.

To provide additional data regarding immunological and virological ART responses among adults, including men and pre- and post-menopausal women, we reviewed supplemental articles that focused on HIV-infected persons ages ≤40 and ≥ 55 years, as comparison groups. This was particularly important, because of the range of ages that have been documented for menopause among women living with HIV-infection. For example, according to a few studies [15-17], the median age at menopause in HIV-infected women seems to fall between age of 39 and 53 years. Most women have either entered or completed their menopausal transition by the age of 50, and almost all by the

age of 55 [6, 18]. So, HIV-infected women aged ≤40 years or aged ≥55 years could be characterized as pre-menopausal or post-menopausal, respectively. Without menopause specific information in some studies, it is difficult to characterize HIV-infected women aged 41-54 years as either pre- or post-menopausal. Additionally, some studies have shown that immunological and virological response to ART do not differ by gender after adjusting other factors, including age, race/ethnicity, and antiretroviral regimen [19-23]. Hence, we reviewed additional research articles that studied differences in ART response among HIV-infected persons (both men and women) who include the two age groups, ages ≤ 40 years and ≥ 55 years, for supplemental data to estimate the difference in ART response across menopause among HIV-infected women. From these additional articles, original research articles that discussed ART response among HIV-infected persons were selected as supplemental articles and included in the final review.

RESULTS

Final articles included in review

The final selection process is summarized in Figure 3. For age at menopause, 63 articles were identified. Of those, four original research articles [15, 17, 24, 25] and 11 review articles were identified [9, 14, 16, 26-33]; 48 of 63 were excluded, because age at menopause in HIV-infected women was not discussed. In the 11 review articles, two more original research articles [16, 34] that did not duplicate the four original research articles [15, 17, 24, 25] were identified, for a total of 6 original research articles [15-17, 24, 25, 34] for the review of age at menopause in HIV-infected women (Figure 3).

For ART response among HIV-infected persons, 54 articles were identified. Of those, a single original research article [35] and five review articles [4, 27, 33, 36, 37] that reported response to ART in HIV-infected women were identified; 48 of 54 were excluded, because immunological response to ART in HIV-infected patients was not discussed. In the five review articles, 16 original research articles regarding response to ART in HIV-infected patients [23, 38-52] were also reviewed as possible supplementary articles. Of these, four original research articles [38-41] that showed useful data of the two age groups, ages ≤ 40 years and ≥ 55 years, of HIV-infected men and women were selected as supplemental articles for the final review. Overall, five original research articles [35, 38-41] were selected for the final review of response to ART among HIV-infected persons across menopause (Figure 3).

Age at menopause

Age at menopause of HIV-infected women was reported in six studies [15-17, 24, 25, 34] and summarized in Table 1. Four studies were conducted in the United States [15, 16, 25, 34], one in Brazil [24], and one in France [17]. In four of the six studies, the authors assessed median age at menopause in describing age at menopause [15-17, 24]; the remaining two studies used mean age at menopause [25, 34] .

Three of the six authors concluded that age at menopause appeared to be similar among HIV-infected and HIV-uninfected women [16, 17, 34]. Cejtin et al., in the Women Interagency HIV Study that recruited 1,335 HIV-infected women, found no statistically significant difference in the mean age at menopause between HIV-infected and HIV-uninfected women within the same cohort: 47.7 years in HIV-infected women and 48.0 years in uninfected women (p-value was not reported) [34]. The participants in this study were similar to those in the Fantry et al study [16] in terms of race/ethnicity, level of education, socioeconomic status, and drug use, all of which may influence age at menopause [53]. The median age at menopause was 50 years (95%CI: 49-53) in the Fantry et al study [16] and 49 years (IQR: 40-50) in the de Pommerol et al. study [17], which does not seem to differ from what has been reported in the HIV-uninfected women [54-57].

Twelve percent of post-menopausal HIV-infected women reached menopause before age of 40 [17], which corresponds to premature menopause. The prevalence of premature menopause among these HIV-infected women seemed to be higher than among the general population: 6.3% of the 1,994 post-menopausal women of the

American Study of Women's Health Across the Nation cohort [58] and 1.8% of the 15,253 women in the study [59]. Other studies found a comparable mean age at menopause between HIV-infected and HIV-uninfected women within the same cohort, but found a disproportionate number of HIV-infected women reaching menopause early [60, 61].

A single study examining how HIV infection influences age at menopause showed a significant reduction in the median age at menopause: the median age at menopause in HIV-infected women was 46.0 years (IQR: 39.0-49.0), compared with 47.0 years (IQR: 44.5-48.0) in HIV-uninfected women within the same cohort (p=0.03) [15]. Additionally, the results of multivariate analyses using logistic regression with adjustment for age demonstrated that HIV-infected women were 73% more likely to experience onset of menopause, compared to HIV-uninfected women (OR: 1.73, 95%CI: 1.08-2.80, p=0.024) [15]. Ferreira et al. described that the median age at menopause in HIV-infected women was 47.5 years [24]. Clark et al. reported that the mean age at menopause in that group was 47 years [25]. In contrast, menopause of HIV-uninfected women in large, multiethnic, population-based samples seemed to occur around the age of 50-52 years, whether in the United States [54, 55] or European countries [56, 57]. According to these three studies [15, 24, 25], menopause could start earlier in HIV-infected women and at around the ages of 46.0-47.5 years.

Earlier age at menopause is associated with increased mortality [62, 63] and increased morbidity, including decreased bone mineral density [64] and cardiovascular disease [65] among all women and may be heightened in women living with HIV infection. It is important to consider whether natural menopause occurs earlier in HIV-

infected women. However, data are conflicting; the Santoro et al. study showed that data on HIV-infected populations were usually confounded with other risk factors for early menopause, as well as risk factors for irregular menses [14]. Factors associated with early onset of menopause include drug use [17], current smoking [66], African-American ethnicity [17], lower educational level [15, 55], and lower CD4 cell count [15, 17]. These findings underscore the importance of using comparable groups, since, for example, women in both HIV-infected and HIV-uninfected groups of the Schoenbaum et al. study were highly enriched in risk factors for early menopause: over 50% of the cohort of HIV-infected women used drugs [15]. In another study, drug use was independently associated with an earlier age at menopause (HR: 2.46, 95%CI: 1.03-5.85, p=0.042) [17]. So, this difference in age at menopause between HIV-infected and HIV-uninfected women could be partly explained by the existence of several confounding factors of an early onset of menopause.

A variety of additional factors were associated with earlier menopause, including current smoking (RR: 1.41, 95%CI: 1.32-1.50) [66], African-American ethnicity (HR: 8.16, 95%CI: 2.23-29.89, p=0.001) [17], and lower education level [15, 55], all of which are common among persons with HIV [17, 54, 57, 67-69]. However, the data are also inconsistent regarding smoking; a few studies showed that age at menopause among HIV-infected women was not associated with current smoking [15], ethnicity [15], or lower educational level (HR:1.04, p=0.90) [17, 60].

Lower body mass index (BMI) was reported as a risk factor of earlier menopause [57, 60], but another study showed no association between lower BMI and age at menopause of HIV-infected women [17]. Although women with more advanced HIV

infection and potentially lower BMI and/or wasting may be more likely to have amenorrhea, the association between BMI and the onset of menopause is inconsistent [54, 70] or absent [55].

As an additional risk factor associated with early menopause, lower CD4 cell count was reported to increase the likelihood of onset of menopause. CD4 cell counts of >500 cells/mm^3 (OR: 0.19, 95%CI: 0.076-0.48, p=0.001) and CD4 cell counts of 200-500 cells/mm^3 (OR: 0.35, 95%CI: 0.15-0.81, p=0.015) were independently associated with a decreased risk of onset of menopause, compared to CD4 cell counts of <200 cells/mm^3 [15]. De Pommerol et al reported that CD4 cell counts of <200 cells/mm^3 at enrolment were associate with an earlier onset of menopause, compared to CD4 cell counts of >350 cells/mm^3 (HR: 2.25, 95%CI: 0.94-5.39, p=0.069) [17]. The median age of menopause was 42.5 years in HIV-infected women with CD4 cell counts of <200 cells/mm^3, consistent with an AIDS diagnosis[2, 15], while the median age of menopause was 46.0 years in those with CD4 cell counts of 200-500 cells/mm^3 and 46.5 years in those with CD4 cell counts of >500 cells/mm^3 (p=0.009) [15]. Given that women with advanced-stage HIV infection were predominant in these study samples, age at menopause of HIV-infected women in the study would be skewed to an earlier age. However, a few studies showed no substantial association between lower CD4 cell counts and onset of menopause [16, 60]. On the other hand, neither use of ART nor high HIV viral loads was associated with onset of menopause [15, 60, 71].

Amenorrhea, which is defined by missing menstrual periods for at least three months in a row, seemed to be more common among HIV-infected women because of associated wasting [72] or anovulation [73]. Amenorrhea from central nervous system

causes may be misinterpreted as menopause if it continues for at least 12 months. Cejtin et al. reported that HIV infection was significantly associated with prolonged amenorrhea from causes other than menopause (OR: 3.16, 95% CI: 1.26-7.95, p=0.02) when adjusted for age [74]. All six studies [15-17, 24, 25, 34] defined menopause as when a woman has not had a period for 12 consecutive months [75]. Cejtin et al. reported that only 74.6% of HIV-infected women who were 45 years old or older and had prolonged amenorrhea were truly menopausal [74], while nearly 90% of HIV-uninfected women who were in that age group and had prolonged amenorrhea were truly menopausal [76]. HIV-infected women were about three times more likely to have prolonged amenorrhea without ovarian failure, compared to HIV-uninfected women [74].

With the exception of the Cejtin et al. study[34], the other five studies [15-17, 24, 25] used only questionnaires to detect age at menopause and did not confirm menopause biologically. Thus, age at menopause of HIV-infected women in the five studies [15-17, 24, 25] could be younger than the age when they actually experienced their menopause, due to misdiagnoses of menopause in HIV-infected women. For diagnosing menopause, in addition to self-reported menopausal status, consistently elevated serum follicle stimulating hormone (FSH) level is the most useful when the preset probability is midrange [18]. An elevated FSH level is helpful for distinguishing menopause from other causes of amenorrhea [74, 77]. This aspect must be considered in future studies, such that use of biochemical markers, such as FSH, be encouraged to evaluate age at menopause in HIV-infected women.

For HIV-infected women on ART, use of ART was significantly related to higher FSH ($p<0.05$) [15]. Both use of ART (HR=0.48, 95%CI=0.32-0.71, p=0.003) and higher

CD4 cell counts (p= 0.007) were linked to a lower incidence of amenorrhea [71]. HIV-infected women who have HIV-related hypothalamic amenorrhea, especially those on ART, may have a return of menses, once CD4 cell counts increase. In all of the six studies [15-17, 24, 25, 34], menopause was evaluated at a single time point. This could have led to a slight overestimation of the prevalence of menopause, which was followed by misinterpretation of age at menopause in HIV-infected women.

Response to ART, baseline CD4 cell counts, and baseline HIV viral loads across menopause

Menopause is the natural aging process that results in decreased ovarian synthesis of estrogen. Estrogen and progesterone regulate HIV replication in peripheral blood mononuclear cells [78]. In animals, estrogen deficiency has been reported to reduce the percentage of T cells in bone marrow [79]. Among HIV-uninfected women, post-menopausal women have fewer CD4 cell counts than pre-menopausal women [80]. Furthermore, older age is associated with decreased thymic volume [81], which reflects the report that the maximum CD4 cell recovery by ART was inversely related to age (p=0.02) [43]. Estrogen deficiency associated with menopause and reduced thymic volume with aging could have additive effects on CD4 cell recovery and HIV replication. So, post-menopausal women may have a different response to ART, as well as different baseline CD4 cell counts and HIV viral loads, compared with pre-menopausal women.

Immunological and virological response to ART across menopause

To evaluate response to ART, we reviewed studies that examined a change in CD4 cell counts from the baseline that was assessed as an immunological response to

ART, and a change in HIV viral loads from the baseline that was assessed as a virological response to ART. The relationship between aging and response to ART in HIV-infected persons (both men and women) was examined in several studies [20, 38, 39, 43, 48-50]. We identified only one study that examined response to ART in HIV-infected women with well-characterized menopause status [35]. The Patterson et al. study is summarized in Table 2. This study included 267 HIV-infected women (220 pre-menopausal and 47 post-menopausal) and demonstrated that the median change in CD4 cell counts and CD4 percentage did not differ between pre-menopausal and post-menopausal women two years after the initiation of ART (260 versus 273 cells/mm^3, p=0.51; 11.0% versus 12.0%, p=0.79, respectively) [35]. There was no difference in the proportion and the odds of achieving HIV viral loads <50 copies/ml at two years of HAART initiation between pre-menopausal and post-menopausal women (75% versus 77%, p>0.99; OR: 0.82, 95%CI: 0.36-1.89, respectively) [35]. These data suggest that HIV-infected women responded equally well to ART, before and after menopause, at least within two years after the initiation of ART, regardless of menopause status.

The four supplementary original research articles [38-41] are summarized in Table 3. The two groups of HIV-infected persons (both men and women), assumed to be pre-menopausal and assumed to be post-menopausal, in the two studies [40, 41] were all naïve to ART at study enrollment, whereas not all patients in the two studies [38, 39]were naïve to ART at study enrollment. The two studies [38, 39] were comparable in both the number of patients who were naïve to ART at baseline and the duration of previous ART in experienced patients at baseline.

For immunological response to ART, Manfredi et al. found that all persons (both men and women) aged ≥55 years who started ART had a significantly smaller increase in mean CD4 cell counts from the baseline, compared to those aged ≤35 (77 versus 114 cells/mm^3, p=0.0001) [38]. However, Knobel et al. and Althoff et al. concluded that there was no significant difference in immunological response between HIV-infected persons (both men and women) assumed to be pre-menopausal and assumed to be post-menopausal [39, 41]. The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) study showed that HIV-infected patients aged 55-59 years had a similar immunological response to ART, compared with those aged 30-39 years (HR: 0.97, 95%CI: 0.92-1.03, p=0.31) [40]. However, HIV-infected women aged ≥60 years in the COHERE study were 7% less likely to experience immunological response, compared with those aged 30-39 years (HR: 0.93, 95%CI: 0.87-0.98, p<0.001) [40]. For virological response to ART, Manfredi et al. and Knobel et al. reported that HIV-infected patients aged ≤35 years or aged ≤40 years had no significant difference in either the decrease in mean HIV viral loads or the number of patients achieving <50 copies/ml of HIV viral loads, compared with those aged ≥55 or aged ≥60, respectively [38, 39]. However, the COHERE study showed that the probability of virological response was 24% higher in patients aged of 55-59 years than those aged 30-39 years (HR: 1.24, 95%CI: 1.17-1.32, p<0.001) [40]. Althoff et al. showed that the hazard of achieving <500 copies/ml of HIV viral loads within two years of ART initiation in HIV-infected patients aged ≥60 years was 26% less than that in patients aged 18-29 years [41]. This difference was statistically significant [41].

Taken together, the outcomes in the four studies [38-41] were conflicting. Possible reasons why the outcomes of the four studies [38-41] were different from each other may be because different age categories were used for comparison, the number of study samples varied, or data for women only were not available. In terms of types of study design, smaller sample size of women, and/or shorter duration of study, the outcomes of the Manfredi et al. and Knobel et al. studies [38, 39] seem to be less reliable in evaluating the difference in long-term immunological and virological response to ART across the assumed age at menopause, compared with the other studies [40, 41]. Moreover, the results of the four studies [38-41], which sampled both men and women with HIV infection, could not be fully assessed with the study population in the Patterson et al study [35], which consisted of only HIV-infected women.

Some studies reported that immunological and/or virological response to ART differed by gender after adjusting for other factors [21, 82, 83]. The number of men was significantly greater than that of women in all four studies [38-41]. The greater numbers of men could have affected the study outcomes. Additionally, some studies showed that younger age had better immunological and/or virological response to ART [43, 49, 51]. The results of the four studies [38-41] mostly describe the effect of aging through the menopausal transition.

The COHERE study showed that immunological response to ART was similar in the patients aged 55-59 years, but poorer in those aged ≥60 years, compared with the patients who were younger than the assumed age at menopause [40]. This difference in response to ART between the different age groups of patients who were older than the assumed age at menopause could not be explained only by the effect of menopause. This

finding may imply that age-related immune impairment has a substantial negative effect on CD4 recovery regardless of the presence of menopause, or gives an additional negative effect to poor CD4 recovery caused by menopause-related estrogen deficiency. Taking all outcomes of the five studies together [35, 38-41], HIV-infected women seem to have similar response to ART in terms of CD4 recovery and HIV viral load suppression without regard to menopause status. Age-related immune impairment, instead of menopause-related estrogen deficiency, may be associated with response to ART.

Baseline CD4 cell counts and HIV viral loads across menopause

Regarding a difference in baseline CD4 cell counts and HIV viral loads in HIV-infected women across menopause, two studies discussed baseline CD4 cell counts [35, 84] and a single study discussed baseline HIV viral loads [35]. In the two selected studies [35, 84], menopause status of the comparative groups was clearly characterized, and baseline CD4 cell counts and HIV viral loads were measured before initiation of ART. For baseline CD4 cell counts, the two studies showed that the baseline CD4 cell counts were similar in the pre-menopausal and post-menopausal HIV-infected women: (181 versus 244 cells/mm^3 (median), p=0.22)[35], (399 versus 333 cells/mm^3 (median), p=0.09) [84, 85]. Van Benthem et al. reported that there was no significant change in the rate of CD4 cell counts decline after menopause, compared to that before menopause (p=0.54) [84]. For baseline HIV viral loads, Patterson et al showed that the baseline HIV viral loads in pre-menopausal women was significantly lower than that in post-menopausal women (45,938 (95%CI: 16,936-167,827) versus 96,021 (95%CI: 41,860-536,626) copies/ml (median); p=0.006) [35]. Due to the small numbers of the study, it is

difficult to conclude whether menopause itself affects baseline CD4 cell counts and HIV viral loads. Additionally, unknown duration of time since seroconversion occurred in the Patterson et al. study may have led to a misinterpretation of the effect of menopause on baseline CD4 cell counts and HIV viral loads. Further studies should include a large number of post-menopausal HIV-infected women whose menopause is diagnosed by both self-reported menstrual status and biochemical markers and whose HIV histories, in terms of ART status, are similar to their pre-menopausal counterparts.

CONCLUSION/RECOMMENDATIONS FOR NEXT STEPS

Previous studies have reported that HIV-infected women are vulnerable to worse menopausal symptoms, increased risk of cardiovascular diseases, diabetes, osteoporosis, and cognitive impairment [9, 14, 69, 85, 86]. However, our review demonstrates that the available data on the effects of HIV infection on age at menopause and the effects of menopause on response to ART are inconclusive and that future studies are vital for further efforts to maximize care for this expanding group of women living with HIV who approach and live through menopause. There have not been enough conclusive data to confirm whether age of menopause in HIV-infected women is greater or lower than that in HIV-uninfected women. Thus, further studies should recruit a large number of both HIV-infected and HIV-uninfected women across menopause and consider factors related to age of menopause, including ethnicity, smoking, drug use, level of education, BMI, use of ART, CD4 cell counts, and HIV viral loads. Furthermore, a combination of questionnaires and measurement of serum FSH levels could minimize the possibility of misinterpreting prolonged amenorrhea as menopause in women, especially in HIV-infected women. Detangling these menopausal issues, especially for disproportionately affected women of color, can have a huge impact on reducing the HIV-related disparities noted among women living with HIV disease. Additional data may also be helpful for clinicians managing the co-morbid medical conditions that also disproportionately affect older women of color who may be living with HIV, such as diabetes and hypertension.

Determining the effect of menopause on response to ART and baseline HIV status is important for alerting clinicians and researchers to consider whether ART for middle aged women with HIV infection should be modified across menopause. However,

studies that described well-defined menopause status have been limited, and comparative age groups and time since seroconversion have differed by studies. Menopause is intimately entangled with aging. Even if post-menopause was clinically and biologically diagnosed, it would be hard to determine the criterion of a post-menopausal group in terms of how long it takes after completion of menopause to fall into a post-menopausal group (e.g., group of aged 55-57 or group of aged 60-62) or what age range of a post-menopausal group is appropriately representative of a post-menopausal group that is compared to a pre-menopausal counterpart (e.g., group of aged 55-57 or group of aged 55-60). To further clarify the effects of menopause and to disentangle the effects of menopause from effects of aging, well-designed studies that sample a sufficient number of background-matched HIV-infected pre-menopausal women at enrolment and follow them up for several years across menopause are required. This review is limited by the fact that there have been too few studies to adequately address the questions that are raised as women go through menopause while living with HIV, and available data are inconclusive and not rigorously obtained.

Today, over thirty years since HIV was first identified, we are experiencing an expanded cohort of women who are taking ARTs and living longer and healthier lives. Our scientific studies of older, menopausal women, as well animal studies that address menopausal questions, will need to expand in conjunction with the shifting epidemiology among older persons living with HIV. This will be especially important as we prepare to care for this growing cohort of post-menopausal women living with HIV.

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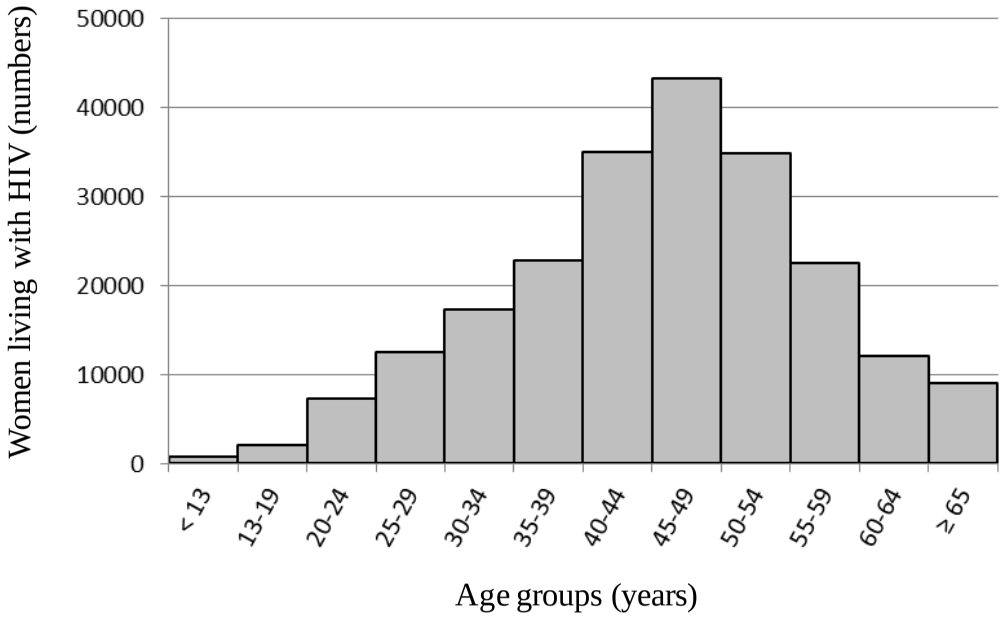
Figure 1. Estimated numbers of women living with HIV infection in 46 states of the United States in 2010



Cite source: Diagnoses of HIV Infection in the United States and Dependent Areas, 2011, HIV Surveillance Report Vol.23, Centers for Disease Control and Prevention [7]

Figure 2. Estimated rates of women living with HIV infection who are around the median age of menopause among all women, by race/ethnicity in 46 states of the United States in 2010

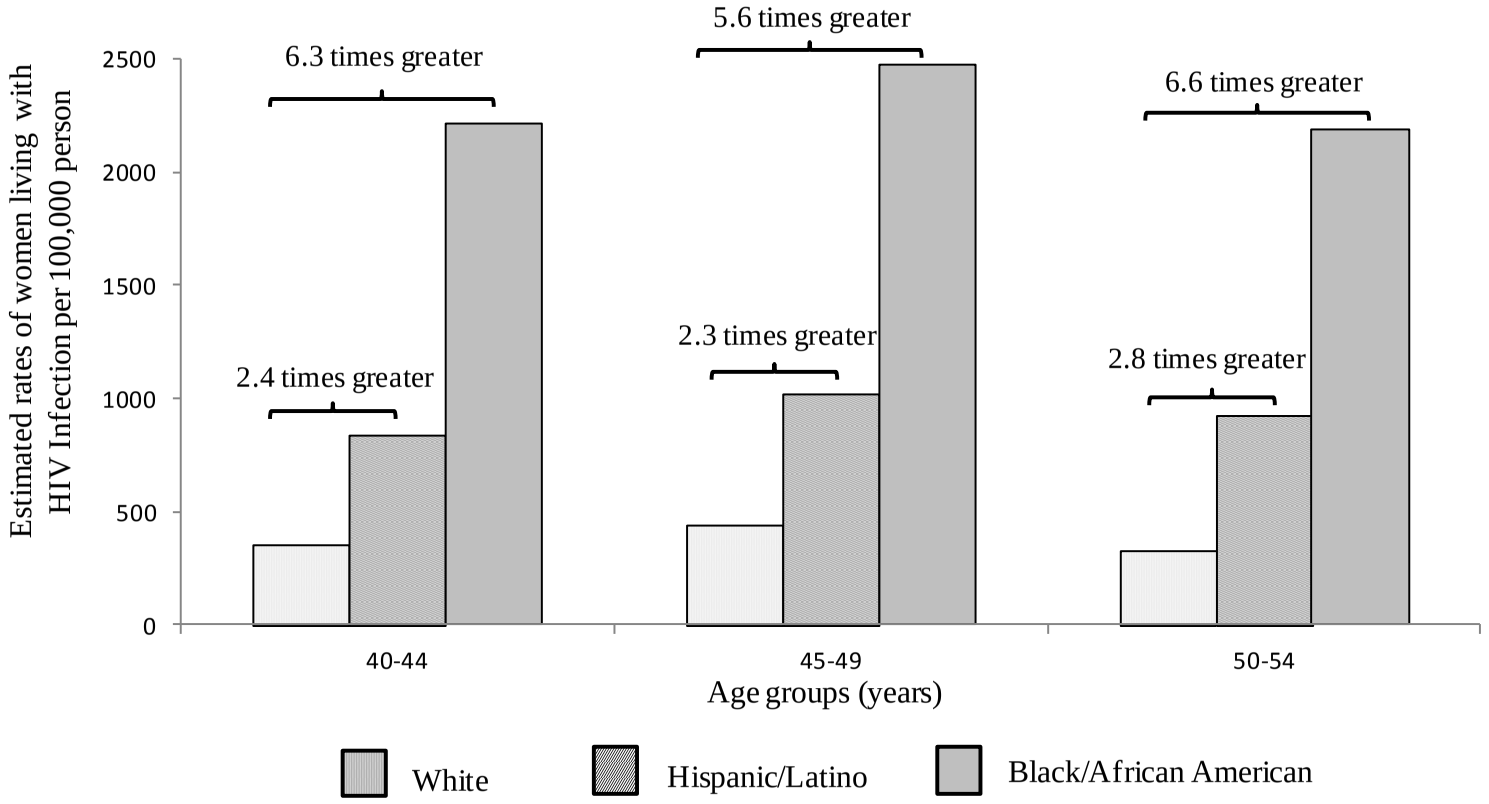


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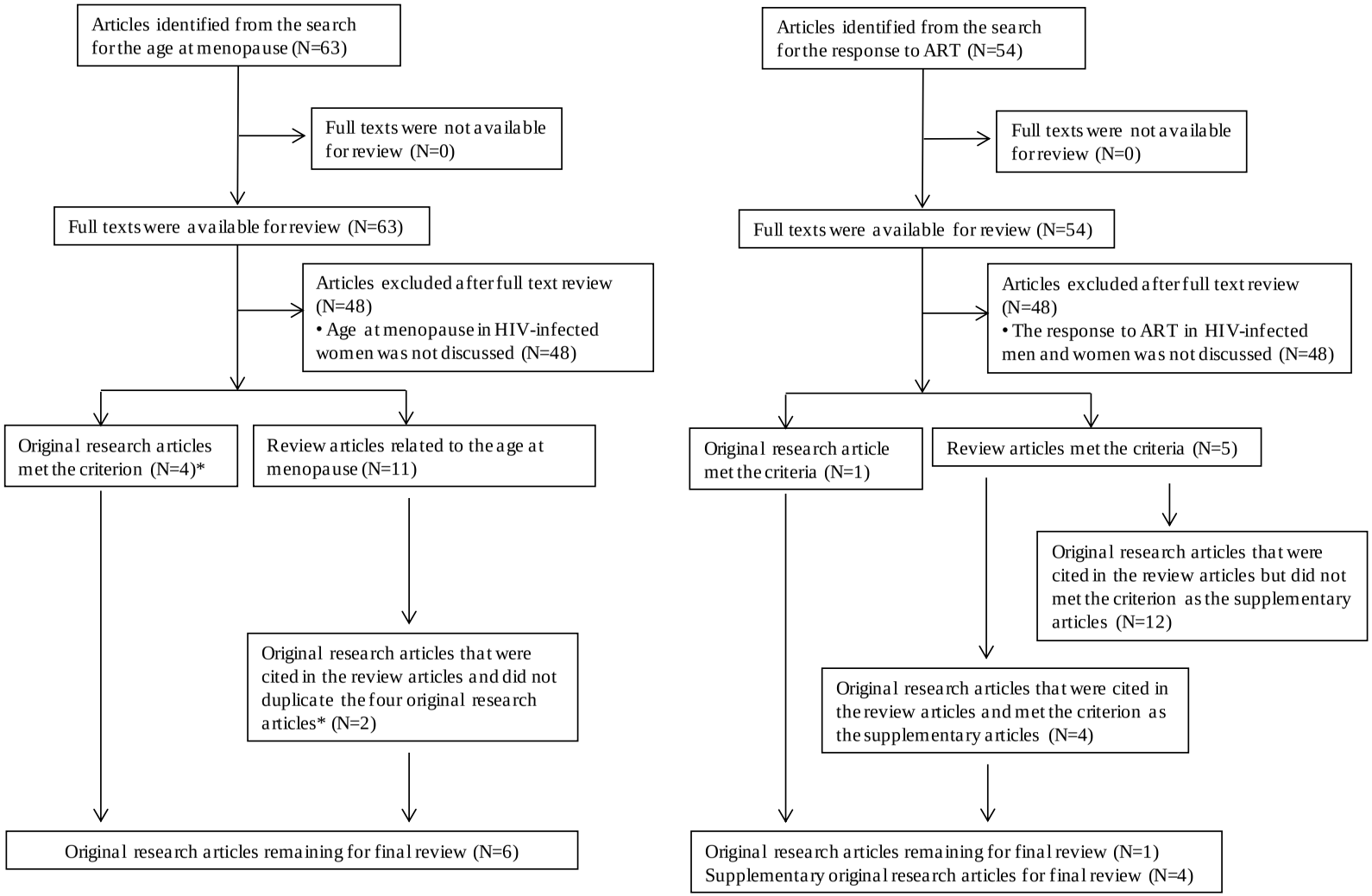
Figure 3. Process of article selection for the final review



N: the number of articles

Table 1. Studies evaluating age at menopause in HIV-infected women

Authors (year)	Country	N of women for analysis	HIV status	N	N of women with menopause	Median age at onset of menopause	p
Clark et al. (2000) [25]	U.S.	52	Infected Uninfected	52 0	26 (50.0%) NA	47(IQR 32-57) (mean) NA	NA
Cejtin et al. (2004) [34]	U.S.	1335	Infected Uninfected	1063 272	NR NR	47.7 (mean) 48.0	NS
Fantry et al. (2005) [16]	U.S.	120	Infected Uninfected	120 0	NR NA	50.0 (IQR 49.3-53.0) (median) NA	NA
Schoenbaum et al. (2005) [15]	U.S.	571	Infected Uninfected	302 269	62 (20.5%) 40 (14.9%)	46.0 (IQR 39.0-49.0) 47.0 (IQR 44.5-48.0)	0.03
Ferreira et al. (2007) [24]	Brazil	251	Infected Uninfected	96 155	NR NR	47.5 (median) NR	NR
de Pommerol et al. (2011) [17]	France	404	Infected Uninfected	404 0	69 (17.1%) NA	49 (IQR 40-50) (median) NA	NA

IQR: interquartile range, NS: not significant, NR: not reported, NA: not applicable

Table 2. A study evaluating response to ART in HIV-infected women

Authors (year)	Study design (follow-up)	Menopause status	N of patients	N of women	CD4 cell counts in women after ART			HIV viral loads in women after ART		
					Change	Results	p	Change	Results	p
Patterson et al. (2009) [35]	Cohort (2 years)	Pre Post	267 (total)	220 47	Increase in median CD4 from baseline	260 (11.0%) 273 (12.0%)	0.51	Women achieving <50 copies/ml viral load	75% 77%	>0.99
								Odds ratio of achieving <50 copies/ml viral load for pre-menopausal women	0.82 (0.36-1.89)	NS

Pre: pre-menopausal, Post: post-menopausal, NS: not significant

Table 3. Studies evaluating response to ART in HIV-infected persons (both men and women)

Authors (year)	Study design (follow-up)	Age groups	N of patients	N of women	CD4 cell counts in patients after ART			HIV viral loads in patients after ART		
					Change	Results	p	Change	Results	p
Manfredi et al. (2000) [38]	Case control (1 year)	≤35 ≥55	84 21	29 (34.5%) 8 (38.1%)	Patients with CD4 increase ≤20 cells/mm^3 or ≤10% from baseline	4 (4.8%) 5 (23.8%)	0.02	Decrease in mean viral load (copies/ml)	31,225 (98.7%) 49,325 (98.4%)	NS
					Increase in mean CD4 from baseline (% of increase)	114 (49.4%) 77 (36.3%)	0.0001	Patients achieving <50 copies/ml viral load	62 (73.8%) 15 (71.4%)	NS
Knobel et al. (2001) [39]	Cohort (2 years)	≤40 ≥60	671 28	219 (32.6%) 9 (32.1%)	Increase in mean CD4 from baseline	196 (SD 100) 228 (SD 145)	NS	Patients achieving <50 copies/ml of viral load	342 (50.9%) 19 (66.7%)	NS
COHERE Study (2008) [40]	Cohort (5 years)	30-39 55-59 ≥60 All ages	22,410 1,656 1,613 49,921	6239 (27.8%) 303 (18.3%) 320 (19.8%)	Hazard ratio of immunological response	REF 0.97 (0.92-1.03) 0.93 (0.87-0.98)	 0.31 <0.001	Hazard ratio of virological response	REF 1.24 (1.17-1.32) 1.18 (1.12-1.26)	 <0.001 <0.001
Althoff et al. (2010) [41]	Cohort (2 years)	18-29 30-39 ≥60 All ages	1,342 3,930 598 12,196	320 (24.8%) 767 (19.5%) 50 (8.4%)	Hazard ratio of CD4 increase of at least 100 cells/mm^3 within two years of ART initiation	REF 0.71 (0.89-1.05) 1.05 (0.92-1.20)	 NR	Hazard ratio of achieving <500 copies/ml viral load within two years of ART initiation	REF 0.92 (0.85-1.00) 0.74 (0.65-0.85)	 NR

NS: not significant, NR: not reported, SD: standard deviation, REF: reference