REVIEW ARTICLE

Collection of menopause data in studies of women living with HIV: A systematic literature review

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Abstract

Objectives: An increasing number of women living with HIV are transitioning through midlife and menopause. Women living with HIV may experience earlier menopause and a higher symptom burden than women without HIV, but more evidence is needed. Data collection on menopause in women living with HIV is scarce and often not standardized. We sought to assess how menopause data are collected in cohorts and studies of women living with HIV.

Methods: This was a literature review conducted within the PubMed database. We included original studies and cohorts assessing menopause and/or menopausal symptoms in women living with HIV. Study characteristics and menopause data collection, including the definition of menopause, symptom assessment tools, and measurement of biomedical parameters, were noted and summarized systematically in data tables.

Results: We included 40 articles describing 37 separate studies published between 2000 and 2023; 27 of these were conducted in high-income countries, the majority in the USA ($n = 16$). Ten studies were from low- and middle-income countries; four of these were conducted in Brazil. In 20 studies, menopause was defined according to the World Health Organization's definition of over 12 months of amenorrhea. Twelve studies used the Menopause Rating Scale to characterize menopausal symptoms, five studies used other specified symptom assessment tools, and 12 studies used a study-specific tool.

Conclusions: Menopause data collection in women living with HIV is heterogeneous. We propose that standardized tools should be used to enable comparisons between studies and countries, thereby improving the quality of research and clinical treatment. Further research into the validity of menopausal symptom scoring tools is warranted.

Anna Hatchfeld and Ellen Moseholm shared last authorship.

INTRODUCTION

Women and girls make up 54% of the 38.4 million people living with HIV globally [1]. As life expectancies improve among women living with HIV receiving antiretroviral therapy (ART), an increasing number of women living with HIV are reaching middle age and transitioning through menopause [2]. Studies have suggested that women living with HIV may experience menopause earlier than those without HIV, with some studies reporting onset 2–3 years earlier [3, 4].

The menopause transition is a complex physiological process resulting from decreased ovarian secretion of the hormones oestrogen and progesterone and a decline in circulating testosterone levels [5, 6]. Menopause manifests in a range of symptoms, including vasomotor symptoms, urogenital complaints, and mood changes [5]. Evidence suggests that women living with HIV experience a high prevalence of menopausal symptoms [7, 8] and that these symptoms are potentially more severe than in the general population [9–11], although further research is needed [12, 13]. Oestrogen depletion is a well-recognized driver of cardiovascular disease and loss of bone mineral density in the general population [14, 15]. Studies have shown an increased risk of cardiovascular comorbidity and reduced bone mineral density in women living with than without HIV [16–18]. Menopausal hormone therapy (MHT) can help alleviate menopausal symptoms [19], although few studies have investigated the management of menopause in women living with HIV specifically, and low rates of MHT use have been reported in this group [13]. Women living with HIV and their healthcare providers face the additional challenge of discerning symptoms of HIV and ART side effects from symptoms of menopause, which may lead to suboptimal treatment. Additionally, it has been shown that severe menopausal symptoms may even be associated with reduced adherence to ART, which could worsen HIV-related outcomes [12].

The nomenclature of menopause and its stages varies in the scientific literature [20]. Natural menopause is defined by the World Health Organization (WHO) as the cessation of menstruation for over 12 consecutive months without any other physiological or pathological cause and in the absence of clinical intervention [21]. To further characterize menopausal status, the Stages of Reproductive Aging Workshop (STRAW) criteria have been widely applied. These were revised in 2011, resulting in the updated STRAW +10 criteria for staging the menopausal transition [22]. The STRAW +10 criteria elaborate on the WHO definition of menopause, requiring a 12-month period of amenorrhea to define that the final menstrual period has occurred, while also including hormonal markers and symptoms as supportive criteria [22]. The WHO and STRAW +10 classifications are prevalent in the literature on menopause, although variation still exists [20].

In addition to the challenges of defining menopause consistently, multiple tools for menopause symptom assessment exist. Some of the most common tools include the Greene Climacteric Scale (GCS), the Menopause Rating Scale (MRS), and the Menopause-Specific Quality of Life (MENQOL) questionnaire [23–26]. These all evaluate selected symptom domains (e.g., vasomotor, psychological, and somatic) and include a severity rating for each symptom. They have been translated into multiple languages and are used internationally [23]. However, all relevant symptoms may not be covered by all tools, and they may not fully take cultural variations in symptom prevalence and severity into account [23, 27]. As of the date of writing, no menopause rating tools have been developed specifically for use in women living with HIV.

This project was initiated within Women Against Viruses in Europe (WAVE), a collaboration between healthcare professionals and community representatives promoting the welfare of women living with HIV in Europe. WAVE is part of the European AIDS Clinical Society (EACS) and focuses on addressing gaps in the care of women living with HIV. Although an increasing number of articles on menopause in women living with HIV are being published, data on menopausal symptoms and menopause assessment in HIV cohorts are scarce and often not standardized [2], making it more difficult to get robust evidence. The aim of this study was to review how menopause data are collected in cohorts and studies of women living with HIV in order to enhance understanding and facilitate research and research collaborations on a national and international scale.

MATERIALS AND METHODS

This study was designed as a systematic literature review in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) reporting guidelines [28]. The nature of the study meant that ethics

approval and patient consent were not relevant. Registration was not relevant for this literature review as we assessed methods used for data collection and not outcomes.

Search strategy

The database search was carried out in PubMed (MEDLINE database) starting on 11 November 2022 and updated on 9 August 2023. Additional studies were retrieved from reference lists of the included studies.

The PICOS method (Population, Intervention, Comparison, Outcomes, and Study) was used to structure the search strategy and develop the PICO question "Which tools are used to measure menopause symptoms in women living with HIV?" [29]. The search terms were identified by two reviewers (EEG and EM) through an initial broad search of the literature and included "Premature menopause", "perimenopause", "premenopause", "postmenopause", "Menopause", "Menopause, Premature", and "HIV". Both text search terms and medical subject heading topics were used. See Table S1. for details of the search terms.

Results from the literature search were uploaded to the Rayyan.ai® online screening tool, and studies were assessed for relevance based on their title and abstract [30]. Two independent reviewers (EEG and EM) screened the study titles and abstracts for eligibility. Conflicts were resolved through discussion and mutual agreement between the two reviewers. After the initial screening, EEG assessed the full-text articles and extracted data into a structured data table, which EM and AH then assessed for accuracy. Relevant data for inclusion in the table were agreed upon by all reviewers before the final screening.

Eligibility

We included original observational studies with prospective, retrospective, and cross-sectional cohorts assessing age at menopause and/or menopausal symptoms in women living with HIV. Only peer-reviewed studies reporting original data were included, with no exclusion based on country of origin. No publication date limits were imposed on the search. Only studies available in English were eligible.

Studies were excluded if menopause was not defined or if the primary outcome was not associated with menopause. Furthermore, studies without original data, such as reviews, meta-analyses, commentaries, guidelines, and care recommendations were excluded. Clinical trials of pharmaceutical drugs or products, case reports, and non-human studies were also excluded. Inclusion and exclusion criteria are listed in Table 1.

In cases where several papers used data from the same cohort, the overall cohort description was used for data extraction and the individual articles were excluded. If no cohort description was available, the most descriptive article was used. If several cohort descriptions were available, the most recent and/or most detailed paper was included. For studies collecting new data on menopause in an existing cohort, the study focusing on menopause was included. If menopause data were recorded for an entire cohort, the number of cohort members was reported. In individual studies or subsets of a cohort, we reported the number of individuals who had menopause data recorded.

Data extraction

Data from the included studies were extracted into Microsoft Excel [31]. The following descriptive data

TABLE 1 Inclusion and exclusion criteria.

Criteria	Included	Excluded
Population	Women living with HIV	Women not living with HIV
Controls	Included studies with and without HIV-negative control group	
Outcomes	Assessing menopause and/or menopause symptoms in women living with HIV	No definition of menopause, or primary outcome not associated with menopause
Study design	Peer-reviewed original study or cohort	Clinical trials of pharmaceutical drugs or products, case reports and non-human studies Not original data e.g. reviews, meta-analyses, guidelines, and recommendations for care
Geographical provenience	No restriction	None
Publication date	No restriction	None
Language of the publication	English	Other languages

were extracted where applicable and presented in a descriptive overview: first author, year of publication, country, title of cohort or site of recruitment, study population including comparison with women without HIV, age of the study population, definition of menopause, methods of recording menopausal symptoms, methods of recording mental health symptoms, whether data were collected routinely in the cohort or specifically for the study, and whether data on hormone measurements and MHT were collected, as well as the level of detail with which MHT was reported. As this review aimed to evaluate the tools used for data collection, rather than the validity of these methods, we also included studies that did not report information for all the listed data points. For ease of comparison, the tables were grouped into high-income countries (HICs) and low- or middle-income countries (LMICs) by gross national income per capita [32]. High-income was defined as gross national income per capita of ≥$13 206 [33].

Risk-of-bias assessment

No risk-of-bias assessment was conducted, as this review aimed to assess how menopause data are collected in HIV cohorts and not the validity of the included studies.

RESULTS

Search results

As shown in Figure 1, the systematic literature search identified 550 articles. After excluding four duplicates, 546 articles were screened. A total of 509 articles were excluded. Four cohort profile description articles did not appear in the initial search and were found through the reference lists of other articles [34–37]. Three of these more detailed cohort descriptions were preferred for inclusion, and the articles through which they were found were subsequently excluded, as described in the methods section [4, 38, 39]. One was included along with the article through which it was retrieved because it reported details on MHT not mentioned in the cohort description [40]. One cohort description article was retrieved from the website for the cohort [41]. Thus, a total of 40 articles describing 37 separate studies were included in the review. The results extracted from the included articles are displayed in Tables 2 and 3.

Study characteristics

The 37 included studies were published between 2000 and 2023. In total, 27 studies were conducted in HICs; of these, 16 were from the USA [7,9,35,45-47,49,50,52,53,55,56,58-61].
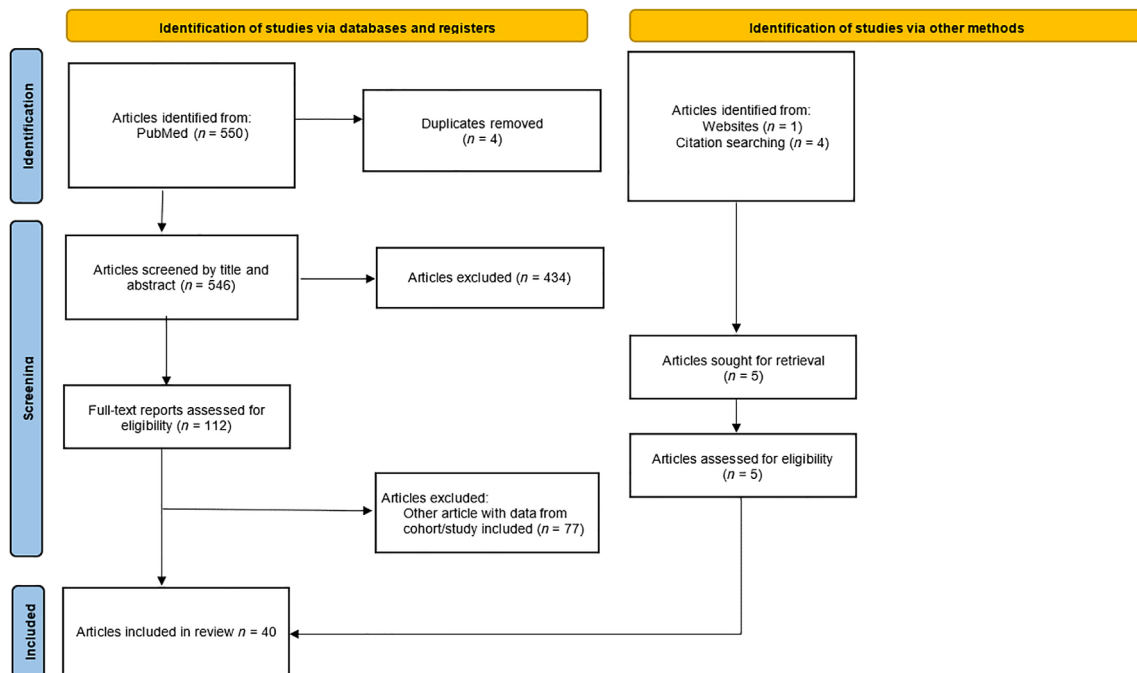
FIGURE 1 PRISMA flowchart: article screening and selection. Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) flowchart template retrieved from https://guides.lib.unc.edu/prisma.

TABLE 2 Menopause studies in high-income countries.

Author, study	Year[a]	Country	Cohort	Population[b]	Age (years)	Definition of menopause	Recording of menopause symptoms	Mental health symptoms	Data collection	Hormone measurements	MHT[c]	Comparison with HIV (−) women
Scofield et al. [42]	2023	Denmark	SHARE study, comparing participants from Project SEXUS	WLWH, n = 144; WWOH, n = 1440	≥18	WHO or age ≥65 years	MRS	PHQ-2, GAD-7	Collected for study	No	Not registered	Yes
Chirwa et al. [43]	2022	UK	Women attending an HIV menopause clinic	WLWH, n = 55	Mean age 49 (SD 6)	WHO	Study specific	Recorded symptoms of anxiety/depression	Collected for study	No	Reported current use of MHT, including type	No
Hachfeld et al. [13] Scherrer et al. [44]	2022 2021	Switzerland	Swiss HIV Cohort Study (SHCS)	WLWH. By 2019, total n = 5697; 2726 still under follow-up	≥18	Not reported in cohort description, WHO in Hachfeld et al.	Did not report menopause symptoms	Depression diagnosis and/or psychiatric care	Collected in cohort	Blood samples in biobank	Reported use of MHT within 6 months before inclusion	No
Suarez-García et al. [8]	2021	Spain	Cohort of Spanish HIV/AIDS Research Network (CoRIS)	WLWH, n = 251	45–60	WHO	MRS	4-item PHQ	Collected for study	No	Registered if ever used or currently using MHT	No
Toribio et al. [45]	2021	USA	Recruited from Boston area, USA.	WLWH, n = 23; WWOH, n = 19	40–75	WHO	Study specific (primarily hot flashes)	Not reported	Collected for study	AMH	Reported current or former use of MHT	Yes
Garbose et al. [7]	2020	USA	Recruited from Johns Hopkins HIV clinic	WLWH, n = 23	40–50	WHO	GCS	Anxiety and depression based on GCS	Collected for study	No	Not registered	No
Zanni et al. [46]	2020	USA/global	REPRIEVE trial (Randomized Trial to Prevent Vascular Events in HIV)	WLWH, n = 1449	40–75	3-group reproductive aging spectrum based on time since last menstrual period and AMH levels	Did not report menopause symptoms	Not reported	Collected in cohort/trial, but AMH analyzed for study	AMH	Reported current or former use of MHT	No
Schnall et al. [47]	2020	USA	PWH recruited from community-based organizations and an outpatient clinic in New York City, USA	MWH, n = 25; WLWH, n = 75	>18	STRAW +10 and FSH >25 mIU/mL; estradiol <20 pg/mL	Did not report menopause symptoms	PROMIS-29	Collected for study	FSH and estradiol	Excluded women using MHT 3 months before inclusion	No
King et al. [36]	2020	Canada	Children and women: Antiretrovirals and Markers of Aging (CARMA) cohort	WLWH, n = 129; WWOH, n = 129	19–68	WHO and FSH >25 IU/L	Study specific	Studyspecific questionnaire	Collected in cohort	FSH	Reported current use of MHT	Yes
Howells et al. [48]	2019	UK	Postmenopausal WLWH attending an HIV gynaecology clinic in a tertiary referral hospital, London, UK	WLWH, n = 73	Mean age at presentation 47 years (SD 10.32)	By age as premature (<40 years), early (40–45 years), and natural (>45 years)	Study specific (registered presenting symptoms)	Study specific (registered "low mood")	Collected for study	No	Reported current use of MHT, including type	No

(Continues)

TABLE 2 (Continued)

Author, study	Year[a]	Country	Cohort	Population[b]	Age (years)	Definition of menopause	Recording of menopause symptoms	Mental health symptoms	Data collection	Hormone measurements	MHT[c]	Comparison with HIV (−) women
Tariq et al. [2]	2019	UK	Positive tRansItions through the MEnopause (PRIME) Study	WLWH. 3 focused group discussions n = 24; Questionnaire n = 869; Semi-structured interviews n = 20 who completed questionnaire	45–60	STRAW +10	MRS, the National Survey of Sexual Attitudes and Lifestyle Sexual Function measure, and HFRDIS	EuroQoL 5D and PHQ	Collected in cohort	FSH measured in a subset of participants	Reported use of MHT in previous 6 months; excluded if currently using	No
Schnall et al. [49]	2019	USA	WLWH recruited from community-based organizations and an outpatient clinic in New York City, USA	WLWH, n = 73	>18	STRAW +10 and FSH >25 mIU/mL; estradiol <20 pg/mL	Study specific	Reported on depressive symptoms	Collected for study	FSH and estradiol	Excluded women using MHT in past 3 months	No
Schnall et al. [50]	2018	USA	Anonymous, cross-sectional online survey, recruited through banner ads on five large social networking websites	MWH, n = 957; WLWH, n = 385	>18	STRAW +10	Study specific (survey based on STRAW 10+)	Reported anxiety and depression in HIV symptom questionnaire	Collected for study	No	Reported current use of MHT	No
Adimora et al. [35] Bullington et al. [40]	2018	USA	Women's Interagency HIV Study (WIHS)	WLWH, n = 3677; WWOH, n = 1305 (26 of these acquired HIV during follow-up)	25–60	STRAW +10	Did not report menopause symptoms	CESD and use of antidepressants or antipsychotics	Collected in cohort	AMH	Reported current use of MHT including type	Yes
Duff et al. [12]	2018	Canada	Sexual health and HIV/AIDS: Women's Longitudinal Needs Assessment	WLWH, n = 109	≥ 30	Diagnosed by a health care provider as perimenopausal or menopausal or self-reported perimenopause or menopause	MRS	Psychological symptoms included in MRS. Also recorded mental health diagnosis	Collected in cohort	No	Reported current use of MHT	No
Loutfy et al. [34]	2017	Canada	The Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS)	WLWH, n = 2360	≥16	Not reported	MRS + "modified MRS"	CESD	Collected in cohort	No	Reported if ever used MHT	No
Sherr et al. [51]	2016	UK	Consecutive clinic attenders in a large London outpatient HIV clinic	WLWH, n = 140	Compares >45 with <45 years	Not reported	MENQOL	PHQ-9, Depression Test Questionnaire and GAD-7	Collected for study	No	Reported current use of MHT	No
Looby et al. [52]	2016	USA	Recruited from HIV clinics, community health centres and newspaper advertisements. Controls recruited from the same communities, Boston, USA	WLWH, n = 49; WWOH, n = 25	18–60	WHO and undetectable AMH (<0.023 ng/mL)	Did not report menopause symptoms	Not reported	Collected for study	AMH, estradiol, and FSH	Not registered	Yes

TABLE 2 (Continued)

Author, study	Year[a]	Country	Cohort	Population[b]	Age (years)	Definition of menopause	Recording of menopause symptoms	Mental health symptoms	Data collection	Hormone measurements	MHT[c]	Comparison with HIV (−) women
Looby et al. [9]	2014	USA	Subjects enrolled at Massachusetts General Hospital, 2010–2012	WLWH, n = 33; WWOH, n = 33	45–52	Excluded women with amenorrhea >12 months. Perimenopausal = 1 menstrual cycle >60 days in the prior 6 months or irregular menses in 2 or more cycles within the past 6 months	MRS and HFRDIS	Psychological symptoms included in MRS	Collected for study	FSH and estradiol	Excluded women using MHT 6 months before inclusion	Yes
Tuchman et al. [53]	2013	USA	Recruited women from two methadone maintenance treatment clinics in New York City, USA	Women in methadone treatment, n = 55. 73% WWOH	41–56	WHO	MRS	Psychological symptoms included in MRS	Collected for study	No	Excluded women currently using MHT	Yes
M de Pommerol et al. [54]	2011	France	ANRS CO3 Aquitaine cohort	WLWH, n = 404	19–79	WHO	Did not report menopause symptoms	Not reported	Collected new data in cohort for study	No	Not registered	No
Tuchman et al. [55]	2007	USA	Recruited from participants in the Bronx HIV Epidemiologic Research on Outcomes (HERO) study, and in methadone maintenance treatment and the office-based methadone study	Women in methadone maintenance treatment, n = 135; 26% WLWH	40–55	WHO	Study specific	CESD, irritability, and depression	Collected for study	No	Excluded women currently using MHT	Yes
Miller et al. [56] Schoenbaum et al. [57]	2005	USA	Natural History of Menopause in HIV-Infected Women'' (Ms Study)	620 women overall, aim: 50% WLWH, 50% WWOH	35–59	WHO	Study specific	CESD and negative life events	Collected in cohort	FSH, estradiol, luteinizing hormone, prolactin, and inhibin B	Excluded women currently using MHT	Yes
Santoro et al. [58]	2005	USA	Participants from The HIV Epidemiology Research Study (HERS), The HIV Epidemiologic Research on Outcomes (HERO), + historical controls	WLWH, n = 47; WWOH, n = 50	18–56	WHO and age >40 years	Study specific	Not reported	Collected in cohorts grouped for study	FSH, prolactin, human chorionic gonadotropin, and estradiol	Excluded controls using MHT, not listed for cohort subjects	Yes
Fantry et al. [59]	2005	USA	Recruited from an infectious diseases clinic in Baltimore, USA	WLWH, n = 120	40–57	WHO	Study specific	Not reported	Collected for study	No	Reported if ever used MHT	No
Clark et al. [60]	2001	USA	Adult AIDS clinical trials group protocols	WLWH, n = 52	20–42	FSH >40 mIU/mL	Did not report menopause symptoms	Not reported	Collected in cohort	Progesterone (n = 33) and FSH (n = 24)	Excluded women currently using MHT	No

(Continues)

TABLE 2 (Continued)

Author, study	Year[a]	Country	Cohort	Population[b]	Age (years)	Definition of menopause	Recording of menopause symptoms	Mental health symptoms	Data collection	Hormone measurements	MHT[c]	Comparison with HIV (−) women
Clark et al. [61]	2000	USA	Adult AIDS Clinical Trial Group (ACTG) sites (survey of female pts aged >40 years)	WLWH, n = 101	40–69	FSH >35 mU/ML, investigator's diagnosis, or ≥6 months amenorrhea and age ≥55 years	GCS	Psychological symptoms included in GCS	Collected for study	FSH	Reported current use of MHT	No

Abbreviations: AMH, Anti-müllerian hormone; CESD, Centers for Epidemiologic Studies – Depression; FSH, follicle-stimulating hormone; GAD-7, General Anxiety Disorder-7; GCS, Greene Climacteric scale; HFRDIS, Hot Flash-Related Daily Interference Scale; MENQOL, Menopause Specific Quality of Life questionnaire; MHT, menopausal hormone therapy; MRS, Menopause Rating Scale; MWH, men with HIV; PHQ, Patient Health Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; PWH, people with HIV; SD, standard deviation; STRAW, Stages of Reproductive Aging Workshop; WHO, World Health Organization definition of menopause; amenorrhea ≥12 months; WLWH, women living with HIV; WWOH, women without HIV.

[a]Year of publication.

[b]If menopause data were recorded for an entire cohort, the number of cohort members is reported. In individual studies or subsets of a cohort, the number of individuals who had menopause data recorded is reported.

[c]Unless specified, the type of MHT was not reported in the study.

The additional studies of HICs included three studies from Canada [12,34,36], four from the UK [2,43,48,51], one from France [54], one from Spain [8], one from Switzerland [13,44], and one from Denmark [42]. Ten studies were from LMICs, including four studies from Brazil [3,63,67,69], one from Cambodia [64], one from Thailand [68], one from Nigeria [66], one from South Africa [37], one from Zimbabwe [62], and one from Peru [65]. Notably, all of the older HIC studies from between 2000 and 2007 (n = 6) were conducted in the USA [55-61], and nearly half of the LMIC studies (n = 4) were from Brazil [3,63,67,69], including the oldest LMIC study from 2007 [69]. Ten of the HIC studies [2,8,12,34-36,44,46,56,60] and three of the LMIC studies [3,37,63] included cohorts collecting menopause data in women living with HIV. The number of participants included in the single original studies ranged from 23 to 607 women living with HIV, whereas in the included cohort studies, the range was from 52 to 5697 cohort participants. Ten of the HIC studies [9,35,36,42,45,52,53,55,56,58] and four of the LMIC studies [62,66,67,69] had an HIV-negative control group.

Definition of menopause

The most common definition of menopause was amenorrhea for ≥12 months, in accordance with WHO (n = 20/37) [21]. Fourteen of the HIC studies [7,8,13,36,42,43,45,52-56,58,59] and six of the LMIC studies [3,62,66-69] used this definition. Some studies used additional criteria, including age >40 years or hormone levels such as follicle-stimulating hormone (FSH) >25 IU/L [36,58]. Two studies used a three-group reproductive aging classification scheme based on time since the last menstrual period and levels of anti-müllerian hormone (AMH) as a marker of ovarian reserve [46,52]. Five HIC [2,35,47,49,50] and three LMIC [37,63,65] studies used the STRAW +10 criteria to define menopause, which elaborate on the WHO definition. The STRAW +10 were cited in studies from 2015 onwards, following their revision in 2011 [22]. Two studies supplemented the STRAW +10 criteria with measurements of FSH and estradiol [47,49]. One study from Cambodia defined menopause according to guidelines by the Study of Women's Health across the Nation [64].

Assessment of menopause symptoms

Menopause symptoms were assessed in the majority of studies (n = 29/37), although there was considerable variation in how symptoms were recorded. The most

TABLE 3 Menopause studies in low- and middle-income countries.

Author, study	Year[a]	Country	Cohort	Population[b]	Age (years)	Definition of menopause	Recording of menopause symptoms	Mental health symptoms	Data collection	Hormone measurements	MHT[c]	Comparison with HIV (−) women
Madanhire et al. [62]	2023	Zimbabwe	Recruited from Sally Mugabe and Parirenyatwa HIV clinics; acquaintances of patients as controls	WLWH, n = 185; WWOH, n = 193	40–60	WHO	MRS	Shona symptom questionnaire, WHOQOL	Collected for study	No	Reported current use, including type	Yes
Jalil et al. [63]	2021	Brazil	HIV-Infected Women's Cohort	WLWH, n = 328	≥30	STRAW +10	WHQ	Psychological symptoms included in WHQ	Collected new data in cohort for study	FSH and estradiol	Excluded women using MHT 12 months prior to inclusion	No
Thapa et al. [64]	2020	Cambodia	Recruited from outpatient department of a hospital in Phnom Penh, Cambodia	WLWH, n = 201	40–60	SWAN guidelines	MRS	Psychological symptoms included in MRS	Collected for study	No	Not registered	No
Cutimanco-Pacheco et al. [65]	2020	Peru	Multicentre study in three general hospitals of the Peruvian Ministry of Health (Lima and Callao)	WLWH, n = 313	40–59	STRAW +10	MRS	Peruvian version of PHQ-9	Collected for study	No	Reported current use, including type	No
Agaba et al. [66]	2017	Nigeria	Recruited from HIV outpatient clinic at the Jos University Teaching Hospital and controls from the general outpatient clinic, Jos, Nigeria	WLWH, n = 607; WWOH, n = 107	40–80	WHO	MRS	Psychological symptoms included in MRS + WHO Quality of Life Brief Version	Collected for study	No	Not registered	Yes
Jaff et al. [37]	2014	South Africa	Study of Women Entering and in Endocrine Transition (SWEET)	Women, n = 702. HIV status was recorded for 404 of these women; 21.3% had HIV	40–60	STRAW +10	MRS	Psychological symptoms included in MRS	Collected in cohort	FSH, estradiol, dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, and sex hormone-binding globulin	Reported use of MHT	No
Calvet et al. [3]	2015	Brazil	Instituto de Pesquisa Clinica Evandro Chagas (IPEC) HIV/AIDS Women's Cohort	WLWH, n = 667	≥30	WHO	Did not report menopause symptoms	Not reported	Collected in cohort	No	Reported if ever used MHT	No
Lui-Filho et al. [67]	2013	Brazil	Multicentre study recruiting women from three sites in Belo Horizonte and Campinas, Brazil.	WLWH, n = 273; WWOH, n = 264	40–60	WHO	Study specific	Psychological symptoms/depression in questionnaire	Collected for study	No	Reported use of MHT	Yes
Boonyanurak et al. [68]	2012	Thailand	Recruited from patients at anonymous clinic and HIV-NAT, Thai Red Cross AIDS Research Centre in Bangkok, Thailand	WLWH, n = 268	>40	WHO	MENQOL	Psychological symptoms included in MENQOL	Collected for study	No	Excluded women using MHT 8 weeks before inclusion	No

(Continues)

TABLE 3 (Continued)

Author, study	Year[a]	Country	Cohort	Population[b]	Age (years)	Definition of menopause	Recording of menopause symptoms	Mental health symptoms	Data collection	Hormone measurements	MHT[c]	Comparison with HIV (−) women
Ferreira et al. [69]	2007	Brazil	Recruited from health clinics at two sites in São José do Rio Preto, Brazil	WLWH, n = 96; WWOH, n = 155	≥40	WHO	Study specific	Psychological symptoms, primarily depression	Collected for study	No	Excluded women using MHT 6 months before inclusion	Yes

Abbreviations: FSH, follicle-stimulating hormone; MENQOL, Menopause Specific Quality of Life questionnaire; MHT, menopausal hormone therapy; MRS, Menopause Rating Scale; PHQ, Patient Health Questionnaire; STRAW, Stages of Reproductive Aging Workshop; SWAN, Study of Women's Health across the Nation; WHO, World Health Organization definition of menopause; amenorrhea ≥12 months; WHQ, Women's Health Questionnaire; WHOQOL, World Health Organization Quality of Life Scale; WLWH, women with HIV; WWOH, women without HIV.

[a]Year of publication.

[b]If menopause data were recorded for an entire cohort, the number of cohort members is reported. In individual studies or subsets of a cohort, the number of individuals who had menopause data recorded is reported.

[c]Unless specified, the type of MHT was not reported in the study.

prevalent tool was the MRS (*n* = 12/37) [24]. This tool was used in seven of the HIC studies [2,8,9,12,34,42,53] and five of the LMIC studies [37,62,64-66]. A total of five studies used other tools, including the MENQOL questionnaire [25,51,68], the Women's Health Questionnaire [63,70], and the GCS [7,26,61]. Ten of the HIC [36,43,45,48,50,55-59] and two of the LMIC [67,69] studies used a study-specific tool created by the study group to assess menopausal symptoms. The level of detail included in these tools varied. In several cases, the authors noted that a questionnaire on menopausal symptoms was administered to subjects but did not list the specific questions in the article [43,59,67]. In other cases, subjects were asked to list their top menstrual/menopausal symptoms of the day [49]. Some studies used multiple tools for symptom assessment [2,9]. Seven of the HIC [13,35,46,47,52,54,60] and one of the LMIC [3] studies did not report on menopause symptoms, focusing primarily on reproductive history, age at menopause, and menstrual irregularities.

The majority of studies (*n* = 29/37) reported psychological symptoms to some degree, chiefly anxiety and depression [2,7-9,12,13,34-37,42,43,47-51,53,55,56,60,62-69]. In about one-third of the studies (*n* = 10/37), these symptoms were included in the menopausal symptom rating scale, such as MRS or MENQOL. Other studies used a study-specific tool that included questions regarding anxiety and depression or a validated tool such as the Centers for Epidemiologic Studies – Depression score [71].

Hormone measurements and menopausal hormone therapy

Around one-half of the studies (*n* = 16/37) measured data on hormone levels, most commonly FSH, estradiol, progesterone, and AMH. These included 14 of the HIC studies [2,9,35,36,44-47,49,52,56,58,60,61], 11 of which were studies from the USA [9,35,45-47,49,52,56,58,60,61]. Two of the LMIC studies included data on hormonal parameters, including one study from Brazil [63] and one study from South Africa [37].

Most studies (*n* = 31/37) recorded data on whether or not a participant was using MHT, including 23 HIC studies [2,8,9,12,13,34-36,43,45-51,53,55,56,58-61] and eight LMIC studies [3,37,62,63,65,67-69], whereas only five studies included details on the type of MHT [35,43,48,62,65]. A total of 11 studies excluded women using MHT from their analyses [2,9,47,49,53,55,56,58,60,63,69]. Six studies did not include data on MHT [7,42,52,54,64,66].

DISCUSSION

This study aimed to review how menopause data are collected in cohorts and studies of women living with HIV globally. We assessed the collection of menopause data in a total of 37 studies of women living with HIV, published in 40 papers, and including 27 HIC studies and 10 LMIC studies.

Overall, we found considerable heterogeneity in the methods used to record data on menopausal symptoms, as well as how menopause is defined in the literature. The WHO definition of menopause was the most prevalent ($n = 20/37$), and MRS was the most common symptom-recording tool ($n = 12/37$). Around one-half of the studies ($n = 16/37$) recorded data on hormone levels. The majority of studies ($n = 31/37$) included data on MHT, though 11 of these excluded women using MHT from their analyses.

The challenge of clearly defining menopause stages in the scientific literature has previously been described [20]. Several staging tools and terminologies exist, and these are often used inconsistently. In particular, it has proven difficult to define the stage leading up to menopause, i.e. premenopause or perimenopause, with vague starting points and overlapping terminology reported in the literature [20]. Over one-half of the studies in this review defined menopause in accordance with the WHO definition ($n = 20/37$), which is widely recognized but less detailed in staging the menopausal transition than other common classification methods such as the STRAW +10 criteria, which elaborate on the WHO definition and also consider symptoms and biochemical measurements [22]. Both are broadly applied in studies of women living with HIV, although it has been noted that standard staging methods may be less accurate in women with chronic illnesses such as HIV because of a lack of reliability of bleeding patterns and hormonal markers [22, 46]. For this reason, some study authors have proposed supplementing menstrual bleeding patterns with hormonal markers [46, 52]. It is possible that hormonal markers may contribute to more accurate staging of the menopause in women living with HIV with irregular periods, although further research is warranted into the accuracy and optimization of menopausal staging tools in women living with HIV.

In the studies that recorded data on menopausal symptoms, 17 used validated tools to record symptoms, and 12 used a study-specific tool. The level of detail in these tools varied significantly, which was not always described in the article text. The MRS was the most widely used tool, containing 11 items (symptoms or complaints) and a subjective severity scoring for each. It has been deemed to provide high-quality measurements and

comparisons of quality of life in different regions and over time [24]. However, it may not take all cultural variations in symptom severity reporting into account [24]. Women living with HIV come from many and diverse backgrounds, which may be relevant to consider when recording menopausal symptoms. The most common menopause symptom rating tools have been translated into multiple languages and used in different countries; however, to our knowledge, no tools have been developed for use in women of specific cultural backgrounds [23]. Furthermore, information on which tools are most relevant during the different menopausal stages is limited, making it difficult to make recommendations. EACS guidelines recommend yearly assessment of menopausal symptoms in women living with HIV aged >40 years using a validated tool [72]. MRS and GCS are mentioned as examples, but no suggestions are made as to which tool should be preferred [72].

Validated tools and definitions make for more accurate comparisons between study populations. A validated instrument may also facilitate routine data collection in cohorts, enabling retrospective analyses of a greater number of participants. However, data collected with a standardized tool rather than a study-specific tool will be less tailored to any specific aims of the study. It is outside the scope of this review to assess the validity of the instruments and definitions used in menopause research. Nevertheless, we propose that future studies and cohorts of women living with and without HIV use a validated tool for menopausal data collection.

Most of the studies ($n = 31/37$) recorded data on MHT, but often not the specific type and formulation. MHT as a group includes a range of synthetic or bioidentical hormones, administered as transdermal, oral, or vaginal formulations of different content [19]. Specific knowledge of the type, dosage, and administration route of MHT would be valuable for future studies evaluating the effects and potential adverse effects of MHT in women living with HIV. Furthermore, nearly one-third of studies ($n = 11$) excluded women using MHT from their analyses. The uptake of MHT in women living with HIV has been reported to be low [48], and—as women with HIV may experience more severe and more frequent menopausal symptoms than other women [7–9]—optimization of MHT in women living with HIV is an important focus for future research.

Strengths of this review include the systematic approach and the global perspective, including data from 14 countries. We included all relevant cohorts and articles from our systematic literature search, although studies from the USA and Brazil were overrepresented. This could indicate a greater focus on menopause in women living with HIV in these countries. We did not find relevant studies from other countries, suggesting that

menopausal data in women living with HIV may not be systematically collected or researched in all countries. A limitation of this study is that we only used PubMed (MEDLINE database). Given the scope of the review, reporting data collection methods rather than outcomes, we determined that one database would be sufficient to elucidate the research question. However, it is possible that searching other databases may have retrieved additional studies. Our review was limited to studies of women living with HIV. It would be relevant for future studies to explore how menopause data are collected in non-HIV cohorts.

With an increasing number of women living with HIV transitioning through menopause, accurate symptom assessment and menopause staging are imperative. Through the ongoing projects within WAVE, we aim to optimize data collection and, in turn, facilitate research and ensure high standards of menopausal care in women living with HIV. This literature review found significant variation in menopause data collection and nomenclature globally, although some rating scales and definitions were more frequently used. Standardized methods should be preferred to ensure scientific accuracy and comparability between studies. Further research into the validity of menopause symptom scoring and staging tools in women living with HIV is warranted.

AUTHOR CONTRIBUTIONS

Emma Eileen Graham, Anna Hatchfeld, and Ellen Moseholm were involved in the literature review topic design, and Emma Eileen Graham led the review of articles with contributions from Anna Hatchfeld and Ellen Moseholm. All authors contributed to the drafting of the manuscript, critically revised the manuscript, and approved the final version.

CONFLICT OF INTEREST STATEMENT

EM has received grants paid to her institution from The Novo Nordisk Foundation and Gilead and personal fees from Gilead and Merck Sharp & Dohme, outside the submitted work, and honorarium paid to her institution. LM has received a travel grant from ITF Greece and personal fees from Unipharma, unrelated to this work. AH's institution has received travel grants and congress and advisory fees from MSD, ViiV Healthcare, and Gilead, unrelated to this work. EEG declares no conflict of interests.

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