Menopausal hormone therapy for women living with HIV

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People living with HIV are ageing, and a growing number of women living with HIV are entering menopause. Women living with HIV commonly have bothersome vasomotor symptoms and onset of menopause at earlier ages; both factors go on to affect quality of life and systemic health. Vasomotor symptoms and early menopause are both indications for menopausal hormone therapy; however, current evidence suggests that this therapy is seldom offered to women living with HIV. Additionally, women living with HIV have several risks to bone health and are likely to benefit from the bone-strengthening effects of menopausal hormone therapy. We present an assessment of the benefits and risks of menopausal hormone therapy in the context of HIV care and propose a practical approach to its prescription. If considered in the appropriate clinical context with discussion of risks and benefits, menopausal hormone therapy might provide substantial benefits to symptomatic menopausal women living with HIV and improve health-related quality of life.

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Introduction

Available and effective antiretroviral therapy (ART) has caused a shift in the age demographic of women living with HIV. As a result, an increasing number of these women will go through menopause, defined as at least one year without menstruation with no other obvious pathologic or physiological cause.[1] Current evidence suggests that women living with HIV experience a high burden of hot flushes and night sweats (collectively called vasomotor symptoms), and are at increased risk of primary ovarian insufficiency (menopause at an age younger than 40 years) and early menopause (at an age younger than 45 years).[2–5] Although premature reproductive ageing and severe vasomotor symptoms are guideline-approved indications for menopausal hormone therapy (MHT), this therapy is seldom offered to women living with HIV even in the setting of comprehensive, available health care.[2,6–8] As we see growing numbers of women living with HIV entering their symptomatic midlife, it becomes increasingly important to optimise clinical care for these women, including consideration of MHT when appropriate. Herein, we review the potential benefits and risks of MHT in the setting of HIV to open the dialogue about treatment of symptomatic women living with HIV and those experiencing premature reproductive ageing (panel 1).

MHT: a therapy fraught with controversy

MHT generally consists of biosimilar or synthetic oestrogen and progestogen, two ovarian steroids with beneficial and complementary effects in maintaining reproductive and non-reproductive tissues.[7,9] The clinical benefits or harms of MHT have been a topic long since debated in the medical community, particularly following the Women's Health Initiative (WHI). The WHI was a large series of studies including randomised controlled trials (RCTs) of two hormone therapies (conjugated oestrogen alone versus placebo, and oestrogen–progestin versus placebo) for asymptomatic menopausal women. The results of the oestrogen–progestin RCT were first published in 2002 showing a small but concerning increased risk of cardiovascular disease (including blood clots and embolism) and breast cancer.[10] A follow-up oestrogen-only trial was later published in 2004 showing increased risk of strokes and embolism, but breast cancer risk was not increased.[11] Results from these trials were widely disseminated in the media and reported as relative risk rather than absolute risk.[12] The surprising evidence of harm from what was then routine hormone replacement therapy led to an abrupt decrease in MHT use, even for highly symptomatic women, that has persisted for decades. One important consequence has been that many physicians trained in the last two decades have not acquired expertise in treatment of symptomatic menopause.[12]

Although the WHI data remain the largest evidence-based evaluation of MHT, these data should not be applied to women with early menopause, primary ovarian insufficiency, and problematic vasomotor symptoms for

Panel 1: Overview of MHT in women living with HIV

- MHT is effective and safe for the treatment of problematic night sweats and hot flushes (collectively referred to as vasomotor symptoms) in healthy women early in menopause (ie, 1 year or more and less than 10 years without menstrual flow)
- Menopausal women living with HIV frequently have vasomotor symptoms and, even when highly symptomatic, are rarely offered MHT
- Primary ovarian insufficiency (ie, menopause onset at an age younger than 40 years) and early menopause (ie, menopause onset at an age younger than 45 years) are more common in women living with HIV—these women are missing years of ovarian hormones and most likely will benefit from MHT
- Increasing life expectancy for women living with HIV means more women are entering midlife and experiencing symptoms that negatively affect quality of life
- Pragmatic controlled trials of MHT with women living with HIV as partners and participants are urgently needed to assess effectiveness and safety

MHT=menopausal hormone therapy.

several reasons. First, the WHI studied MHT as the primary prevention for chronic diseases in asymptomatic rather than symptomatic menopausal women. Thus, the findings are not directly applicable to the current practice of using MHT in menopausal women only when they are symptomatic.[6] Second, the WHI used animal-derived or synthetic hormones (conjugated equine oestrogen–medroxyprogesterone) rather than the currently available biosimilar preparations (transdermal 17β-estradiol and oral micronised progesterone), the biosimilar preparations being pharmacologically and physiologically similar to endogenous hormones, and probably safer.[13,14] Furthermore, although cardiovascular disease risk was reported in the WHI trial as elevated for all women (older than 50 years) on MHT, subsequent analyses of WHI data showed little to no increased cardiovascular disease risk in women who were less than 10 years beyond the onset of menopause or younger than 60 years.[15–17] In a 2015 Cochrane meta-analysis, MHT did not increase coronary heart disease risk in all women, even when initiated more than 10 years after menopause; however, the risk of venous thrombosis and stroke did increase in the older group.[18] Finally, the WHI included older women (mean age of 63 years) with the majority on MHT for more than 5 years into menopause; this further limits its generalisability to the current practice of starting MHT for symptoms earlier in menopause. Taken together, since the WHI data were published in the early 2000s, improved pharmacology, changes in evidence-based prescribing practices, and a greater appreciation of the need for treatment of symptoms has caused the landscape of MHT use to evolve. As such, for most women waking more than twice a week with night sweats, the benefits of symptom relief outweigh the small absolute increased risk of harm when MHT is initiated early, in lower doses and with biosimilar hormones. Over the past decade, expert groups in endocrinology and gynaecology have updated guidelines recommending physiological MHT as first-line therapy for vasomotor symptoms and for early menopause.[6,7,19]

MHT is underused in menopausal women living with HIV

Menopause care for women living with HIV is of growing importance worldwide as the demographic shifts towards older ages. In high-income countries, approximately a third of women living with HIV are in their menopausal years (aged 50 years or older), a number that is projected to double in the coming decade.[20] Similar ageing trends are being seen in low-income and middle-income countries where the global majority of women living with HIV reside.[20] Despite these growing numbers, studies from North America and Europe suggest that care providers often do not address important aspects of menopause care.[2,8,21] This trend is also likely to be prominent in resource-poor settings where suboptimal menopause training for providers has previously been noted.[22] One aspect of menopause care that has been particularly neglected is the management of vasomotor symptoms. Studies published over the past decade suggest that women living with HIV are infrequently offered MHT despite their high prevalence of severe vasomotor symptoms and the effect of MHT on quality of life.[8,23,24] A 2018 study showed that only 12% of menopausal women living with HIV were offered MHT and even fewer (5·5%) reported being on this therapy.[2] In addition to management of vasomotor symptoms, women living with HIV commonly have other guideline-recommended indications for therapy.[7] In fact, women living with HIV disproportionally experience three (vasomotor symptoms, early menopause or primary ovarian insufficiency, and bone loss) of the four indications for MHT recommended by the North American Menopause Society (table 1).[7]

Underuse of MHT in women living with HIV most likely relates to several factors. Given the relative novelty of managing menopause in HIV, many providers are not yet comfortable with menopause care in this group. This sentiment is evident in a 2017 survey of primary care providers in the UK where 85 (97%) of 88 respondents reported having concerns with menopausal management in the context of HIV, despite being comfortable with menopause care for HIV-negative women.[21] Alternatively, when primary care is provided by infectious disease specialists, these experts often do not have background knowledge and expertise in treating women's symptomatic menopause transition.[25,26] Therefore, menopause care in the context of HIV lies outside the traditional boundaries of expertise for both specialists and generalists, putting symptomatic midlife women with HIV at risk of being overlooked.

In addition to the minimal training for providers, several other factors might contribute to the low rates of

	Health outcomes of women living with HIV	Effect of menopausal hormone therapy
Vasomotor symptoms	Approximately 70% of women have hot flushes, and half reported flushes as moderate to severe	Reduces moderate to severe hot flushes in 64% of women
Early menopause and primary ovarian insufficiency	High rates of early menopause and primary ovarian insufficiency in women living with HIV	Mitigates effects of shorter lifetime exposure to estradiol and progesterone
Prevention of fracture*	Fracture prevalence higher in women living with HIV than age-matched population-based controls	Preserves bone mineral density and reduces risk of fracture

*In conjunction with numerous lifestyle interventions and other bone-strengthening therapies for prevention of fragility fracture.

Table 1: **Indications for menopausal hormone therapy related to health risks of menopausal women living with HIV**

MHT uptake. Drug interactions between MHT and ART are common and, although these interactions are not a contraindication to treatment, they might discourage the provider and patient from pursuing therapy. Pill burden might also be a deterrent to MHT use, as many women living with HIV are reluctant to take additional medications;[27] offering transdermal instead of oral estradiol might help to negotiate this barrier. The values and preferences of women living with HIV related to MHT are key considerations and have not been adequately explored. In a small study of MHT use in women living with HIV, discontinuation rates were relatively high (17%) and for unclear reasons;[8] this finding underscores the importance of future studies evaluating reasons for discontinuation to adapt therapy to address patient-identified preferences. A final barrier to MHT use might be driven by fear of adverse events, and is partly based on valid concerns, as further studies are essential to find the optimal benefits and fewest harms of MHT for women living with HIV. However, this concern can be navigated in a patient-centred manner in collaboration with experts in symptomatic menopause transition. Adaptations for comorbid diseases, lifestyles, and accentuated risks are readily available. Ultimately, optimal care for women living with HIV during symptomatic reproductive ageing and menopause is contingent upon providers having a clear understanding of the underlying physiology, unique HIV or HIV-drug-related risks, and a woman-centred focus on improving quality of life.

Women living with HIV experiencing menopausal vasomotor symptoms would benefit from MHT

Vasomotor symptoms manifest as night sweats or hot flushes that arise due to acute downward swings in estradiol that begin during perimenopause.[28] Menopausal women who frequently wake with night sweats (ie, more than twice a week) or who are bothered by frequent vasomotor symptoms generally benefit from MHT.[7,29] Menopausal women living with HIV frequently have vasomotor symptoms, with up to 70% reporting hot flushes, more than half of which were of moderate to severe intensity.[2,4,30] MHT remains the most effective management for menopausal vasomotor symptoms. Both combination oestrogen–progesterone and daily micronised progesterone alone are effective for moderate to severe symptoms.[6,7,19] The downstream effects of managing severe vasomotor symptoms might be far-reaching, as these symptoms are well established to negatively affect sleep, mood, and quality of life.[7,23,31] Furthermore, increasing evidence shows that severe symptoms in women living with HIV are also associated with poor ART adherence; thus an absence of effective vasomotor symptoms treatment might negatively affect HIV management.[2,32] Given the potential effect of vasomotor symptoms on holistic health and HIV care, management of vasomotor symptoms is an important aspect of care for the menopausal woman living with HIV.

When treating vasomotor symptoms, a distinction must be made between perimenopause and menopause due to the physiological hormonal differences between these normal reproductive phases. Perimenopausal women (who have had a menstrual flow in the past year) often have sporadically high and erratic estradiol levels, whereas those who are menopausal (no flow in the past year), tend to have stable, low estradiol and progesterone levels.[28] Variations in circulating ovarian hormones have meant that perimenopausal women, often among the most symptomatic, were usually excluded from MHT trials, due to valid concerns about increasing already elevated estradiol levels.[33–35] Unfortunately, we are then left with little evidence to guide symptomatic management during the perimenopause, although an RCT (n=189, 4 months) suggests that oral micronised progesterone might be of benefit for perimenopausal vasomotor symptoms, especially night sweats.[36] Another RCT, of an oral contraceptive preparation (20 µg ethinylestradiol with 1 mg norethindrone acetate) in 132 perimenopausal women documented no statistically significant improvement in hot flushes or quality of life versus placebo, but did show increased abnormal vaginal bleeding, which improved in the final three cycles.[37] For women who have primary ovarian insufficiency, hormonal fluctuations of perimenopause often extend even longer than for those experiencing early or natural menopause; specialist consultation might be helpful in prescribing treatment for their many symptoms. Taken together, current evidence only guides MHT use for the symptomatic menopausal woman and emphasises the pressing urgency of research evaluating treatment options for perimenopausal symptoms.

MHT is indicated for early menopause, a common entity for women living with HIV

One of the groups of women most likely to benefit from MHT are those that reach early menopause, an entity commonly overlooked, yet over-represented in populations of women living with HIV. Early onset of menopause can occur either naturally or surgically and is known as early menopause (onset at an age younger than 45 years) or primary ovarian insufficiency (onset at an age younger than 40 years). In all instances, early menopause results in decreased lifetime exposure to ovarian hormones and loss of their protective effects on multiple organ systems.[38] Clinically, early menopause is associated with increased rates of cardiovascular disease, dementia, fractures, mood changes, and even all-cause mortality.[38,39] Given the potential of MHT to prevent these multisystem premature ageing effects, current guidelines suggest use of MHT in women with menopause who are younger than 45 years if they are without contraindications, even if they are asymptomatic. MHT should be continued at least until the average age of menopause

(ie, aged 51 years in Canada).[7] Evidence supports these guidelines by showing sexual, cognitive, bone, and possibly cardiovascular benefit with MHT in early natural or surgical menopause.[40–42]

MHT use for early or premature menopause is relevant for women living with HIV, as the literature suggests that early menopause and primary ovarian insufficiency might be more frequent in this group. Several studies indicate that a large proportion (up to a quarter) of women living with HIV reach menopause at ages earlier than 45 years,[3,5,43] although other studies do not show this finding.[44,45] The true prevalence of early menopause for women living with HIV is difficult to confirm because the majority of current studies do not have biochemical confirmation of menopause (ie, follicle-stimulating hormone level). Two tests for elevated follicle-stimulating hormone levels done 6 weeks apart are needed to separate menopause from prolonged amenorrhoea in women aged 45 and younger,[6] a distinction that is particularly important since prolonged amenorrhoea is also more frequent with HIV.[46,47] Although the exact frequency of early menopause in this group remains unknown, frequent observation of lower age-adjusted anti-Müllerian hormone levels in women living with HIV suggests some degree of advanced reproductive ageing.[48] Taken together, women living with HIV warrant close assessment and biochemical evaluation for early menopause if suspected. If early menopause or primary ovarian insufficiency are confirmed, women should be strongly advised to take MHT given its beneficial effects on age-related comorbidities and potential to reduce long-term mortality.

MHT use in the context of comorbid disease for women living with HIV

Given the over-representation of ageing-related diseases in women living with HIV, MHT must be considered in the context of these comorbidities.[49] Although the effect of MHT on some risks, such as osteoporotic fracture, might be relatively predictable, the effect on other risks (ie, cardiovascular disease) remains unknown and is a pressing research priority. It is beyond the scope of this Viewpoint to consider all health risks; however, we address some risks, and refer the reader to important guideline recommendations for others.[7]

Breast cancer

Breast cancer is important to consider because MHT increases its risk, especially with use early in menopause and longer durations of therapy.[50,51] A 2019 meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer includes individual data from over 100 000 women (>55 000 MHT users) to show that all types of MHT, except vaginal oestrogens, promote breast cancer.[51] From this analysis, 5 years of combination oestrogen and continuous progestin, started at age 50 years, increased the 20-year breast cancer risk from 6·3% to 8·3% (one in every 50 users). The risk of breast cancer might be lower than this figure when micronised progesterone is used, because only a small number of women in this analysis used micronised progesterone, which has a better breast cancer safety profile than progestins.[13]

Although yet to be directly evaluated, the risk of breast cancer for women living with HIV using MHT will most likely be similar to that of the general population. Importantly, incident breast cancer risk is not increased for women living with HIV compared with HIV-negative women; these women might have a lower incidence despite a high prevalence of relevant risk factors.[52,53] A recent study by Coburn and colleagues,[54] re-examined breast cancer rates for women living with HIV adjusting for changes in life expectancy and age to find that incidence was as low as 3·2% compared with the lifetime risk of approximately 12% in the general population. Although discussions of breast cancer risk should always accompany MHT prescription, the lower baseline incidence observed among women living with HIV might reduce breast cancer concerns for those who need MHT for vasomotor symptoms or early menopause.

Cardiovascular disease

The question of how MHT might modulate cardiovascular risk is not a trivial one. Cardiovascular disease is the leading cause of morbidity and mortality in North American menopausal women and this risk is increased in women living with HIV.[55,56] Despite early concerns of increased cardiovascular disease risk with MHT in the WHI trial,[10] follow-up studies have established that risk is low for women who have no history of cardiovascular events and when MHT is initiated early in menopause.[16,17] Subsequent studies have gone on to assess whether early initiation of MHT might provide subclinical cardiac benefit but results have been inconsistent. A placebo-controlled RCT found benefit of early MHT in preventing progression of subclinical atherosclerosis;[17] however, another well designed RCT found no difference in measures of subclinical cardiovascular disease.[57] Given that women living with HIV are at increased cardiovascular risk at baseline,[58] it should be a research priority to evaluate changes in cardiovascular disease events over time in those taking MHT.

Until further evidence is available, we suggest an approach to MHT prescription similar to that used in other chronic diseases that augment cardiovascular disease risk, such as diabetes.[59] Here, individual cardiovascular disease risk should be assessed with the special consideration that standard risk calculators do not capture HIV-associated increased cardiovascular risk. Reversible cardiac risk factors should be optimised and, if risk is elevated, evidenced-based therapies are recommended. Increased cardiovascular disease risk is not a contraindication to MHT. However, this risk should be integrated into risk and benefit discussions,

including favouring transdermal estradiol regimens and consideration of non-hormonal alternative therapies. For women who have history of a previous cardiovascular event (ie, myocardial infarction), several expert guidelines suggest avoiding MHT.[6,7]

Venous thromboembolism and cerebrovascular disease are also important given their increased age-associated risk with MHT.[18] In general, MHT is estimated to result in an additional six strokes and eight venous thromboembolism events per 10 000 users; although, estimates vary based on age, MHT composition, and treatment duration.[7] For women living with HIV, observational studies suggest possible higher rates of ischaemic stroke[60] and venous thromboembolism[61] than in the general population. Evaluation of how MHT might modulate these risks is an important avenue of future study. Until further evidence is available, similar to cardiovascular risk, these risks should be incorporated into counselling, and risk and benefit discussions, before MHT initiation.

Fracture prevention

Fracture prevention is a particularly important topic for midlife women living with HIV given the combined deleterious effects of HIV, ART, and physiological ovarian hormonal changes on skeletal integrity. For all women, complementary actions of oestrogen and progesterone are crucial to maintain bone health: oestrogen prevents osteoclastic bone resorption and progesterone promotes osteoblast-mediated bone formation.[9] Erratic estradiol and declining progesterone levels during perimenopause and the decline of estradiol and progesterone in menopause result in accelerated rates of bone loss.[28,62] In cases of early menopause and primary ovarian insufficiency, shorter lifetime exposures to estradiol and progesterone compromise bone health even further.[40] A known benefit of MHT is prevention of bone loss, and MHT has been shown to reduce fractures, even in women without osteoporosis.[63,64] Although MHT is not recommended for primary menopausal fracture prevention in asymptomatic women,[65] when it is used for vasomotor symptoms or for early menopause, its bone protective effects provide an additional benefit.[7] Women living with HIV are particularly positioned to benefit from the bone-strengthening effects of MHT as increased rates of osteoporosis (measured by bone mineral density) and fractures have long been recognised in people living with HIV due to the combined negative effects of HIV and ART on bone health.[66–69] Furthermore, among people living with HIV, menopausal women have the highest rates of annual bone loss, almost double that of men and four times that of premenopausal women living with HIV.[70] Therefore, together with management of problematic vasomotor symptoms and early menopause and primary ovarian insufficiency, the fracture prevention effects of MHT add to its benefits for women living with HIV.

***Panel 2*: Contraindications to menopausal hormone therapy**

General contraindications

- Unexplained vaginal bleeding
- Acute or severe liver dysfunction
- History of stroke
- Coronary heart disease
- Dementia
- Hypertriglyceridaemia (more than two times upper limit of normal)
- Oestrogen-dependent cancer
- High venous thromboembolism risk

Relative contraindication

- Older than 60 years, and more than 10 years since menopause onset

A practical approach to MHT prescription in HIV care

HIV care providers must adapt to the evolving demographic of women living with HIV and be comfortable providing women-centred menopause care. Providers should engage in conversations about peri-menopause and menopause with women living with HIV and either be able to prescribe treatment or have clear management pathways for symptomatic women. Providers should use a shared-decision approach regarding MHT, including an individualised review of indications, contraindications (panel 2), and evaluation of the absolute risks for adverse events.[7]

Drug interactions between MHT and ART are common and should be reviewed before initiating therapy. Unfortunately, little to no pharmacokinetic data directly evaluating drug interactions between MHT and ART exists, and extrapolating interaction data from hormonal contraceptives, while sometimes helpful, has its limitations.[71,72] MHT uses different oestrogen formulations than hormonal contraceptives (17β-estradiol or conjugated oestrogens *vs* ethinylestradiol), which are metabolised by different pathways and have different interaction potential;[72] such important differences underscore the need for further research evaluating drug interactions specific to MHT formulations. Until more detailed data are available, we have summarised what is currently known about common drug interactions between ART and MHT (table 2). In general, these drug interactions are not contraindications to MHT, but should be incorporated into management decisions regarding dosing, titration, and monitoring. Efavirenz, etravirine, and nevirapine can decrease levels of coadministered oestrogens and progestins, so increased doses of MHT might be required for symptomatic relief. By contrast, unboosted atazanavir and cobicistat-boosted elvitegravir might lead to an increase in oestrogen and progestin levels when given together, so a lower starting dose of

	MHT formulations	Antiretroviral therapy					
		Non-nucleoside reverse transcriptase inhibitors		Protease inhibitors		Integrase inhibitors	
		Efavirenz, etravirine, and nevirapine	Doravirine and rilpivirine	Unboosted atazanavir; protease inhibitor plus cobicistat	Protease inhibitor plus ritonavir	Bictegravir, cabotegravir, dolutegravir, and raltegravir	Elvitegravir plus cobicistat
Oestrogen	Conjugated equine oestrogen (oral, +/- bazedoxifene); micronised 17B-estradiol (oral); 17B-estradiol (patch*, combination patch with progesterone or gel)	Decreases oestrogen	No interactions	Increases oestrogen	Decreases or increases oestrogen	No interactions	Increases oestrogen
Progesterone	Micronised progesterone* (oral); medroxyprogesterone (oral); norethindrone (oral combination, patch); drospirenone (oral combination)	Decreases progesterone	No interactions	Increases progesterone	Increases progesterone	No interactions	Increases progesterone
Progesterone	Levonorgestrel intrauterine device	No interactions	No interactions	No interactions	No interactions	No interactions	No interactions

MHT=menopausal hormone therapy. *MHT that we recommend as first-line therapy.

Table 2: **Common drug–drug interactions between MHT and antiretroviral therapy**

Panel 3: Knowledge gaps and areas of future research for use of MHT in women living with HIV

- Current rates of use, adherence, and reasons for discontinuation of MHT among women living with HIV
- Rates of adverse events, especially coronary artery disease, venous thromboembolism, cerebrovascular disease, and breast cancer for women living with HIV who use MHT
- Effect of MHT on quality of life and bone health for women living with HIV
- Pharmacokinetic and pharmacodynamic studies of drug interactions between antiretroviral therapy and MHT of different formulations (oral, transdermal, and topical; biosimilar and synthetic)
- Evaluation of values and preferences of women living with HIV regarding symptomatic relief compared with the risks of adverse events with MHT
- Prevalence of hormonally confirmed early menopause in women living with HIV

MHT=menopausal hormone therapy.

MHT might be warranted. For more details on the drug interactions described, we recommend using a drug interaction tool specific to antiretrovirals.[73,74]

If a woman living with HIV would like to trial MHT, we suggest starting with a combination of transdermal 17B-estradiol and oral micronised progesterone. We favour use of transdermal estradiol due to its superior safety profile, particularly in terms of venous thromboembolism risk, and micronised progesterone due to lower breast cancer risk compared with progestins.[13,75,76] Unopposed oestrogen must be avoided in women with a uterus due to increased risk of endometrial cancer. Progesterone can be dosed either cyclically or continuously, with sequential regimens generally used for recently menopausal women who might have a higher risk of breakthrough bleeding.[6] If breast tenderness develops on MHT, we suggest estradiol dose reduction or cessation, or a change to oral micronised progesterone if not already taking this formulation.[6] In general, MHT should be prescribed at the lowest dose that is effective at controlling vasomotor symptoms and continuing therapy reassessed at least annually.

In addition to MHT, physicians should also consider other evidence-based ways of managing symptoms. For genitourinary symptoms, vaginal hormonal preparations are first-line therapy and, although absorption might be lower than oral preparations, drug interactions with ART are also relevant for these therapies. For vasomotor symptoms and sleep problems, lifestyle counselling, non-hormonal treatments, cognitive behavioural therapy, and progesterone-only therapy might also be effective.[77,78] Systemic testosterone shows promise as a potential therapy for low libido in surgically menopausal women. However, further studies evaluating its use in women living with HIV and assessing its long-term safety profile are warranted before broad clinical uptake.[79] Finally, other aspects of holistic health including a balanced diet with sufficient vitamin D and calcium, regular exercise, weight management, support for smoking and other addictions, and review of bone and cardiovascular health are essential parts of each clinical visit for menopausal women living with HIV.

Conclusion

Worldwide HIV care is shifting towards a focus on preserving health-related quality of life during ageing, as evidenced by the proposal to add quality of life to the 90-90-90 UNAIDS targets.[80] Menopausal women living with HIV are an important part of the HIV community; these women have a high prevalence of moderate to severe vasomotor symptoms and early menopause, both of which can affect the quality of life. Due to its controversial past and the collective lack of training in its use, MHT is rarely considered for women living with HIV, despite this group being disproportionately affected by health risks that such treatment will most likely benefit. Further studies are needed to address several knowledge gaps that remain about MHT use in women living with HIV (panel 3). However, while awaiting appropriate studies, providers should be ready to engage in candid conversations about MHT with menopausal women living

with HIV, covering its benefits, risks, and unknowns. Neglecting to consider an important management option such as MHT in the appropriate clinical context might lead to missed opportunities to improve health-related quality of life for women living with HIV during this important and often symptomatic midlife transition.

Contributors

EMK, JCP, NP, MK, JvS, ST, ML, and MCMM were responsible for the conceptualisation of this Viewpoint. EMK, JCP, ST, MK, and MCMM were responsible for the literature search. MCMM, ML, and JCP were responsible for the supervision. EMK was responsible for the visualisation of this Viewpoint. EMK, JCP, and MCMM were responsible for writing the original draft. EMK, JCP, NP, MK, JvS, ST, ML, and MCMM were responsible for reviewing and editing. All authors approved the final version of the manuscript and have agreed to be personally accountable for any questions related to the accuracy or integrity of any part of the work.

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