

Menopause and metabolic risk in women with HIV: beyond antiretroviral therapy

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As women with HIV live longer, the convergence of reproductive aging and metabolic disease has become a defining challenge of contemporary HIV care. The success of antiretroviral therapy (ART) has transformed HIV into a chronic, manageable condition, but it has also unmasked an array of noncommunicable diseases that threaten long-term quality of life and survival. Among these, insulin resistance and diabetes have emerged as particularly important – and complex – risks for women with HIV (WWH) [1,2].

In this issue of *AIDS*, Abelman *et al.* [3] provide valuable evidence that menopause represents a critical metabolic turning point. Their longitudinal analysis reveals that insulin resistance rises more steeply in WWH during late perimenopause and menopause compared with women without HIV, independent of ART regimen, integrase inhibitor exposure, or tenofovir formulation.

Menopause is a universal milestone in women's lives, but its physiological consequences are far from uniform. The decline in estrogen and progesterone alters lipid metabolism, fat distribution, vascular tone, and insulin sensitivity [4]. In women without HIV, these changes are already linked to increased cardiometabolic risk. In WWH, menopause unfolds against a background of chronic immune activation, inflammation, and cumulative ART exposure, factors that may magnify the metabolic consequences of hormonal decline [5,6].

Despite these biological intersections, menopause remains understudied in HIV research. Historically, women –

especially those in midlife – have been under-represented in clinical trials [5]. As a result, guidelines for metabolic monitoring in WWH are often extrapolated from data in men or younger women. The study by Abelman and coll. represents a meaningful step toward closing this knowledge gap. Using data from the MACS-WIHS Combined Cohort Study [7], the authors show that WWH experience faster increases in insulin resistance during late perimenopause and menopause compared with women without HIV, independent of ART regimen or body composition.

For many years, discussions of metabolic risk in HIV have focused primarily on ART, first the lipodystrophy of early regimens, and later the weight gain associated with integrase inhibitors and tenofovir alafenamide [2]. These drug effects are real and clinically relevant, but they represent only part of the story. HIV itself, even when virologically suppressed, exerts persistent effects on immune and metabolic systems through residual inflammation, altered adipocyte signaling, and mitochondrial stress [6].

At the same time, menopause does not occur in isolation from the immunovirological context of HIV. Immune reconstitution, persistent low-level viraemia, and chronic inflammation remain defining features of treated infection [8]. These processes intersect with estrogen deficiency in complex ways: both influence adipose tissue biology, hepatic lipid metabolism, and insulin signaling [9]. Although HIV RNA and CD4⁺ cell counts were included as covariates, their relationship with insulin

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resistance was not directly explored. Understanding how immune reconstitution and residual viraemia influence these metabolic changes remains an important question for future research.

The authors suggest that estrogen depletion in the context of chronic HIV-associated inflammation could amplify metabolic dysregulation, highlighting the need for mechanistic studies on hormone-immune-metabolic interactions [3].

From a clinical perspective, these findings should prompt renewed attention to metabolic monitoring in midlife women with HIV. Current diabetes screening guidelines, often derived from male or HIV-negative cohorts, may underestimate risk in this population. Menopause should be recognized as a period of heightened vulnerability that justifies earlier and perhaps more frequent screening for insulin resistance, dyslipidemia, and cardiovascular disease.

The path forward requires studies that bridge disciplines and methodologies. Three priorities stand out:

- (1) Immunometabolic stratification. Future research should evaluate whether viral control, immune activation, and CD4⁺ recovery modify metabolic outcomes. Stratified analyses by HIV RNA and CD4⁺ levels could reveal subgroups of women at particularly high risk.
- (2) Clinical end-points. Longitudinal studies must move beyond surrogate measures such as HOMA-IR to include incident diabetes, cardiovascular events, and mortality. Only then can physiological findings be translated into tangible clinical risk.
- (3) Mechanistic insight. Basic and translational research should explore how estrogen depletion interacts with chronic HIV-associated inflammation. Understanding the molecular dialogue between sex hormones, immune activation, and metabolism could guide targeted interventions.

The story of HIV and ageing is increasingly a story of women. As more women live long enough to experience menopause, the metabolic consequences of reproductive aging will shape the next phase of HIV care. The study published in this issue underscores the urgency of a comprehensive, sex-specific approach, one that views

menopause not as the end of reproductive life, but as the beginning of a new frontier in chronic disease prevention.

The challenge for clinicians and researchers alike is to move from documenting risk to mitigating it. Understanding how hormones, immunity, and ART converge to influence insulin resistance is not merely a scientific question, it is central to ensuring healthy longevity for women with HIV. Longitudinal cohorts such as MACS-WIHS offer unique opportunities to explore these mechanisms, particularly if future data collection captures hormonal therapy use, inflammatory markers, and cardiovascular outcomes alongside virological and immunological variables.

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Conflicts of interest

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