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Does menopause transition influence viral suppression and adherence in Women living with HIV?

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Viral suppression and adherence during menopause transition

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Author contribution statement

Anna Hachfeld, Karoline Aebi-Popp and Andrew Atkinson developed and designed the study. Andrew Atkinson planned and performed the statistical analyses. Anna Hachfeld wrote the manuscript with inputs from Karoline Aebi-Popp and Andrew Atkinson. Petra Stute, Alexandra Calmy, Philip E. Tarr, Katharine Darling, Baharak Babouee Flury, Christian Polli, Leila Sultan-Beyer and Irene A. Abela contributed with their professional expertise, critically reviewed and discussed the analyses and the manuscript.

Conflicts of interest statement

None of the authors has declared a possible conflict of interest related to this study. A. Hachfeld's institution has received travel grants, congress and advisory fees from MSD, Viiv and Gilead, unrelated to this work. B. Babouee Flury has undertaken Advisory Boards or ad-hoc consultancy for Merck/MSD, Melinta/Menarini, Shionogi and Pfizer, and has received research grants from Melinta/Menarini unrelated to this work. K.E.A. Darling's institution has received research funding unrelated to this publication from Gilead and offered expert testimony for MSD. Philip Tarr's institution has received grants, advisory fees, and educational grants from Gilead, MSD, and ViiV, outside the submitted work. K. Aebi-Popp`s institution has received travel grants and advisory fees from MSD, Gilead and ViiV healthcare unrelated to this work. I.A. Abela is supported by the Promedica Foundation.

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Abstract

Background: Increasing numbers of women living with HIV transition through menopause. It is unclear if this transition has an impact on treatment adherence, viral suppression, psychiatric comorbidities or drug use. We aimed at examining adherence and viral suppression during the perimenopausal period and explored the influence of psychiatric comorbidities and active injection drug use (IDU).

Setting: Retrospective Swiss HIV Cohort Study analysis from 01/2010 to 12/2018.

Methods: We explored peri- and postmenopausal trends of viral blips, low-level viremia,

viral failure, adherence, psychiatric comorbidities and IDU using interrupted time series (ITS) models.

Results: Rates of depression and psychiatric care increased during perimenopause before decreasing afterwards. Negative treatment outcomes such as viral blips, low-level viremia, viral failure and low adherence steadily declined while transitioning through menopause – this was also true for subgroups of women with depression, psychiatric treatment and active IDU.

Conclusions: Increased rates of depression and psychiatric care while transitioning through menopause do not result in lower rates of adherence or viral suppression in women living with HIV in Switzerland.

Keywords

HIV, menopause, viral suppression, adherence

Introduction

As a consequence of longer life expectancy and the ageing of people living with HIV, a growing number of women living with HIV experience transition through menopause (1DDI. An increasing body of evidence shows that menopause might occur at an earlier age compared to HIV-negative women, and that many women living with HIV experience severe menopause symptoms (4DDI. Independently of the HIV status, menopause transition has been associated with an elevated risk for depression, which has been shown to decrease adherence (8DDIN. However, it is still unclear if and how menopause impacts adherence and treatment outcomes such as the occurrence of viral blips, low-level viremia or viral failure.

We investigated trends in self-reported treatment adherence, HIV-RNA viral blips, low-level viremia and viral failure in women transitioning through menopause, as well as the occurrence of depression, psychiatric care and active injection drug use (IDU).

Methods

Study population and data collection

We included all cis-women with onset of menopause between 01/2010 and 12/2018 registered in the Swiss HIV Cohort Study (SHCS) and excluded those with hysterectomy prior to menopause onset. The SHCS is a national prospective cohort study covering at least 75% of people living with HIV in Switzerland (13). SHCS data is collected twice yearly during routine visits, including information on menopause onset, self-reported adherence, HIV-RNA measurements, drug use and comorbidities. Local ethics committees of all participating study sites approved the study and written informed consent was obtained from all participants.

Definitions

In this study menopause onset was determined as the first report of presumed menopause defined by the treating physician at a 6 monthly visit in a woman with amenorrhea. In order to assess peri- and postmenopausal trends and due to the difficulties of exact determination of perimenopause, we chose an observation period of eight years prior and eight years after the first menopause report. Self-reported low adherence was defined as missing ART doses once every two weeks or more often. Depression diagnosis was made by the treating physicians or psychiatrists, who used standard diagnostic tools. Psychiatric treatment was defined as being in psychiatric (in- or outpatient) care.

Women were allocated to: A. the depression subgroup if they had at least once a diagnosed depression within +/- eight years of menopause onset, B. the psychiatric treatment subgroup if

they had at least once been in psychiatric care within +/- eight years of menopause onset, C. the active IDU subgroup if they had at least once consumed drugs via injection within +/- eight years of menopause onset.

The following definitions were used to determine HIV-RNA trends: A. Viral suppression: Having at least two consecutive HIV-RNA measurements of <50 copies/ml. Due to different limits of quantification, the included HIV-RNA measurements at exactly 100, 200, 300 or 400 copies/ml before 2005 were also defined to be virally suppressed. B. Viral blip: viral suppression followed by a single measurement of HIV-RNA ≥ 50 copies/ml, followed again by viral suppression. C. Low-level viremia: having more than one consecutive HIV-RNA measurement ≥ 50 copies/ml and <200 copies/ml, including single measurements < 50 copies/ml. D. Viral failure: having more than one consecutive HIV-RNA measurement of ≥ 200 copies/ml.

Statistical analyses

Descriptive statistics were used to characterise the study population. Group comparisons of categorical variables were investigated using the $\chi 2$ test, with continuous variables assessed using the Wilcoxon rank-sum test. Plots of the incidence per year provided an indication of the trends over time. For these plots, the numerator was defined as the occurrence of the respective event in the respective year (*maximally* once per year per patient, even if the event was measured at multiple visits during that year), and the denominator defined as the number of women in follow-up for that year. The definition was slightly different for viral blips; here, we counted the number of blips per year per patient, so that multiple events per patient year were possible.

To confirm peri- and post-menopausal trends, we fitted patient-level interrupted time series (ITS) logistic regression models with the respective event as dependent variable, with the "interruption" defined as the estimated time of menopause onset. Sandwich-type standard errors were calculated to adjust for intra-patient correlation. A subgroup analysis focussed on

differences in trends between women with depression, psychiatric treatment and active IDU. A sensitivity analysis was performed to account for women with inconsistent bleeding patterns after the report of menopause onset.

All statistical analyses were performed with R. Version 3.6.1. (14).

Results

Patient characteristics

1130 postmenopausal women were included. Median age at menopause onset was 50 years (IQR 32, 55) 10% experienced an early menopause (menopause onset <45 years) and 2% a premature ovarian insufficiency (menopause onset <40 years). 67% of the participants were of Caucasian and 25% of Black ethnicity. At menopause onset 13% had a detectable viral load, 5% a CD4 count below 200/µl, 27% had been diagnosed with depression and/or were in psychiatric care but only 3% reported IDU (Supplementary table, http://links.lww.com/QAI/C16 and (1),).

Peri- and postmenopausal trends in viral (non)suppression and adherence

We identified a number of trends in the timeframe eight years prior to and eight years following the first menopause report. Viral blips declined slightly but constantly over the 17-year period (Figure 1A). Episodes of low-level viremia decreased significantly over the whole period (slope OR 0.95 per year, 95% confidence interval (CI) [0.93, 0.97], p<0.001), with a slightly steeper decline after menopause onset (0.89 per year, 95% CI [0.83, 0.96], p=0.002, Figure 1B). Viral failures exhibited a steeper decline over the whole period (OR 0.80 per year, 95% CI [0.78, 0.82], p<0.001) compared to the episodes of low-level viremia, but this trend flattened after menopause onset (Figure 1C). Similarly, self-reported low adherence episodes

decreased over time (OR 0.97 per year, 95% CI [0.95, 0.99], p=0.004), with a slight stabilization after menopause onset (Figure 1D).

A sensitivity analysis excluding 130 women with inconsistent bleeding patterns confirmed the reported trends (results not shown).

Peri- and postmenopausal trends of psychiatric events and active drug use

We observed a modest increase in depression diagnoses until menopause onset (OR 1.04 per year, 95% CI [1.00, 1.08], p=0.03, Figure 1A), when 27% of women had been diagnosed with depression, and a stabilization without significant decrease afterwards. The rate of women attending psychiatric care increased slightly until menopause onset to 17% (OR 1.02 per year, 95% CI [0.99, 1.05], p=0.26), but subsequently decreased in the postmenopausal period to rates similar to before menopause (OR 0.95 per year, 95% CI [0.91, 1.01], p=0.08, Figure 2B). Active IDU events were rare with no apparent trend until menopause onset. After menopause onset, the rate of women reporting IDU declined steeply (OR 0.85, 95% CI [0.85, 0.97], p=0.01, Figure 2C). “For non-IDU, there was a rather steep increase in the years up to approximately 4 years prior to the estimated menopause year (p value for slope 0.001), followed by stabilisation (Supplementary figure S1, http://links.lww.com/QAI/C15).”

Peri- and postmenopausal trends of viral (non)suppression in different subgroups

Subgroup analyses of women diagnosed with depression, being in psychiatric care or injecting drugs showed no significant differences in the overall rates of viral non-suppression. The only difference was noted in women with active IDU and women in psychiatric care who experienced a slight increase of low-level viremia prior to menopause onset. After menopause onset, the trajectories realigned with the other patient groups (Supplementary figure S2, http://links.lww.com/QAI/C15).

Discussion

Women living with HIV in Switzerland experience a steady decline in viral blips, low-level viremia, viral failure and low adherence while transitioning through menopause. In contrast, rates of depression and psychiatric care increase during perimenopause before decreasing afterwards. Nonetheless, women with depression and/or psychiatric care do not experience decreased viral suppression during their menopause transition.

Viral suppression and adherence during menopause transition

Estrogens have a protective role in the course of HIV-infection with 17beta-Estradiol being able to reduce HIV transcription (15–17), HIV susceptibility of CD4+ T cells and macrophages, and by regulating the HIV reservoir through the Estrogen receptor-1 (18). Gianella et al. found a slower HIV reservoir decline in women compared to men and more inducible HIV-RNA+ cells in peri- and postmenopausal women compared to premenopausal (19). However clinical studies show that ART response to HIV seems not to be negatively influenced by menopausal status with low estradiol levels (20–22). Moreover, disregarding menopause, adherence and viral suppression improve in both sexes over time being on ART and increasing age (23–25). Our results not only confirm this, but also show that viral suppression is not significantly affected by menopause transition. Our findings are supported by Okhai et al. who also reported higher viral suppression rates and fewer viral rebounds in perimenopausal women compared to younger women (23). The steeper decline of LLV after menopause onset compared to before is difficult to interpret. It could theoretically be that the natural decline of non-suppressed episodes is slowed during menopause transition but there havn't been any studies with the respective study design to confirm this and we didn't observe this trend regarding the viral blips and viral failure.

Three recent studies indicated that women with severe menopausal symptoms are less likely to engage in medical care and to take their ART (26–28). Data on its effect on virological

control are only provided in one study, which found a non-significant trend towards lower viral suppression rates in women with severe menopausal symptoms (26). Unfortunately, information on menopause symptoms in our patients are lacking, and we are not able to determine if adverse virologic events occur more often in this subset of patients.

Psychiatric comorbidities and IDU during menopause transition

Our observation of increasing depression during peri- and postmenopause is in line with other studies showing increased depressive symptoms during menopause transition in HIV-positive and HIV-negative women with already diagnosed depression, as well as in those without (8–10). Cohen et al. found that women with an early menopause transition had a higher risk for depression (9). This is of importance regarding the earlier menopause onset in women living with HIV reported in our cohort compared to HIV negative women living in Switzerland (1). The very high prevalence of psychiatric comorbidities at time of menopause onset in our cohort highlights the need of routine mental health screening and treatment possibilities in this population. To the best of our knowledge, there are no reports of menopause and its association with IDU.

Viral suppression and adherence in patients with psychiatric comorbidities or IDU

Drug use and psychiatric comorbidities including depression have been associated with lower adherence and less viral suppression (8,11,27). Although rates of depression, psychiatric treatment and IDU increased until menopause, this did not translate into higher rates of detectable viral loads in the entire study population or in the respective subgroups. Based on the assumption that having a psychiatric illness or injecting drugs are frequently chronic conditions - we used generous inclusion criteria for the subgroups, and might have missed a signal of increased viral detection in those with more pronounced psychiatric problems.

Strengths and limitations

This is the first analysis exploring viral load trajectories around menopause in women living

with HIV in Switzerland. The study provides important information around treatment adherence and success in ageing women living with HIV, which has direct implications for healthcare providers. However, the study has several limitations.

Our dataset didn't allow to define the reproductive stages according to the STRAW +10 or SWAN criteria (29,30). Furthermore defining menopause onset as a single time point is problematic as the reproductive stages including peri- and postmenopause are time periods whose beginning and end may be blurred. We have addressed these challenges in two ways: By using the first report of presumed menopause reported by the treating physician we have based our analysis on a clinical assessment and byusing the time series analysis over a period of 16 years we assert that peri- and post-menopausal as well as premenopausal trends are captured". Moreover we performed a sensitivity analysis excluding women with inconsistent bleeding patterns which showed similar results.

HIV-RNA detection is prone to several biases. First, increasingly sensitive HIV assays detect more viral blips and low-level viremia. Second, the introduction of more potent and better tolerable ART combinations over time resulted in better HIV-suppression rates. Third, the decline of viral reservoirs over time, as well as the time on ART and age, also influence viral suppression rates (19,24,25).

The definitions of viral blips, low-level viremia and viral failure are not used consistently between published studies, making comparisons difficult. Our rather high rates of low-level viremia and viral failure are partly due to our conservative definitions based on the official IAS definitions (31). Moreover, we counted low-level viremia and viral failure events which span two calendar years as two separate events, and might have overestimated its incidence. Of importance, neither the definition nor the possible overestimation have an influence on the slope of viral suppression over time, and thus do not influence our overall findings.

Recall and desirability bias may limit the self-reported adherence informations.

The findings concerning women with IDU need to be interpreted with caution due to the low

numbers of included women and consequently, the wide confidence intervals.

Conclusion.

Increased rates of depression and psychiatric care while transitioning through menopause do not result in lower rates of adherence or viral suppression in women living with HIV in Switzerland.

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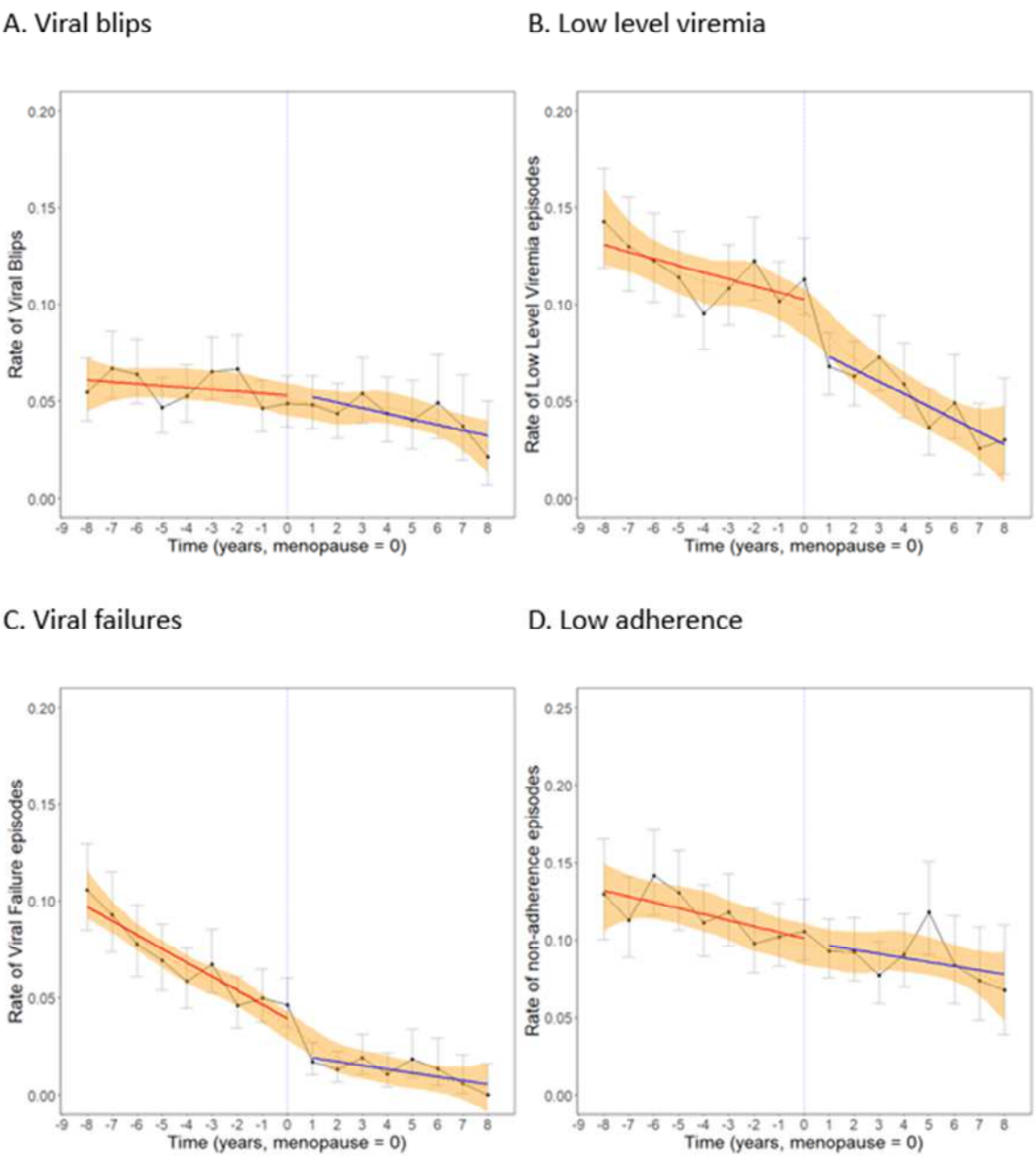
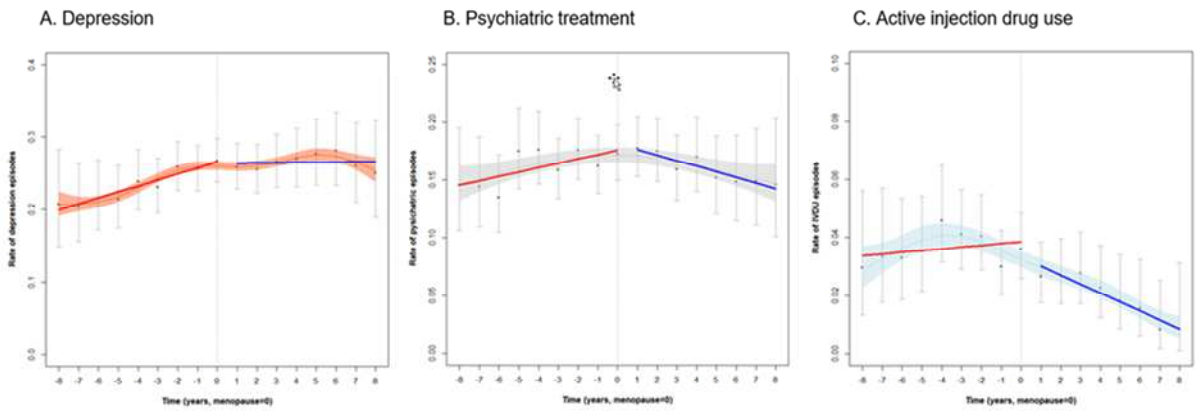
Figures caption

Figure 1: Peri- and postmenopausal trends of A. Viral blips B. Low level viremia C. Viral failures and D. Low adherence.



Rate of events over time (black solid), point-wise 95% confidence intervals (grey), LOESS smoother in orange (with 95% confidence intervals shaded), interrupted time series for peri- (red) and post-menopause (blue)

Figure 2: Peri- and postmenopausal trends of patients with depression diagnosis (A.), psychiatric care (B.), active injection drug use (C.) during eight years before and after menopause onset.



Rate of events over time (black solid), point-wise 95% confidence intervals (grey), fitted cubic spline (6 knots, orange, grey and blue) dashed with 95% confidence intervals shaded), interrupted time series for peri- (red) and post-menopause (blue).

Supplementary Figure S1: Peri- and postmenopausal trends of patients with active non-injection drug use (non-IDU) during eight years before and after menopause onset.

Supplementary Figure S2: Peri- and postmenopausal trends in viral (non)suppression in women with depression (B.), women being in psychiatric care (C.) and women with active injection drug use (D.) during eight years before and after menopause onset.