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Tryptophan-kynurenine metabolic pathway and daytime dysfunction in women with HIV

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Abstract

Sleep disturbances are prevalent in women with HIV (WWH). Tryptophan-kynurenine (T-K) pathway metabolites are associated with alterations in actigraphy derived sleep measures in WWH, although may not always correlate with functional impairment. We investigated the relationship between T-K pathway metabolites and self-reported daytime dysfunction in WWH and women without HIV (WWoH). 141 WWH on stable antiretroviral therapy and 140 demographically similar WWoH enrolled in the IDOze Study had targeted plasma T-K metabolites measured using liquid chromatography-tandem mass spectrometry. We utilized the daytime dysfunction component of the Pittsburgh Sleep Quality Index (PSQI) to assess functional impairment across HIV-serostatus. Lower levels of 5-hydroxytryptophan and serotonin were associated with greater daytime dysfunction in all women. In WWH, daytime dysfunction was associated with increased kynurenic acid ($R = 0.26$, $p < 0.05$), and kynurenic acid-tryptophan (KA-T) ratio ($R = 0.28$, $p < 0.01$). WWH with daytime dysfunction had a 0.7 log fold increase in kynurenic acid compared to WWH without daytime dysfunction. Kynurenic acid levels and the KA-T ratio were associated with daytime dysfunction in WWH but not in WWoH. Longitudinal studies are needed to establish a causal relationship and directionality between T-K metabolic changes and sleep impairment in WWH.

Keywords HIV infection · Metabolomics · Sleep · Women · Tryptophan · Kynurenine

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Introduction

Quality of sleep has been shown to influence medication adherence, mental health, quality of life and life satisfaction in people with HIV (PWH) (Saberi et al. 2011; Rogers et al. 2020, 2021). Sleep disturbances are reported to occur in 58% of PWH with women particularly affected (Wu et al. 2015). In the Women's Interagency HIV Study (WIHS), women with HIV (WWH) were 17% more likely to report symptoms of insomnia compared to women without HIV (WWoH)(Jean-Louis et al. 2012). Historically, poor sleep in PWH has been associated with viremia and the use of efavirenz based antiretroviral regimens(Allavena et al. 2016). In the current era of effective antiretroviral therapy (ART) and reduced use of efavirenz, it remains uncertain why WWH continue to experience sleep disturbances (Rogando et al. 2022).

Two key regulators of the sleep-wake cycle that may contribute to sleep disturbances in WWH are serotonin and melatonin, both of which are metabolic products arising from the amino acid tryptophan(Kokturk and Kanbay 2015). Lower levels of tryptophan and higher levels of kynurenine (an alternate downstream product of tryptophan) have been observed in PWH, particularly in those with progressive HIV disease (Werner et al. 1988; Huengsberg et al. 1998; Qi et al. 2018). Potential mechanisms may relate to the HIV Trans-Activator of Transcription (Tat) protein and higher levels of interferon-gamma (IFN-γ) in HIV, both of which induce the enzyme indoleamine-2,3-dioxygenase (IDO) promoting the conversion of tryptophan to kynurenine (Huengsberg et al. 1998; Campbell et al. 2014).

In the IDOze study, our group demonstrated that a higher kynurenine-tryptophan ratio, an indicator of IDO activation, was associated with wrist actigraphy measures of poorer sleep efficiency and poorer sleep continuity in WWH [4]. Objective sleep metrics are often difficult to obtain and sometimes do not correlate with subjective sleep complaints or daytime functional impairment (Goelema et al. 2019; Benz et al. 2023). It remains unknown whether T-K pathway metabolites or the kynurenine-tryptophan ratio is increased in WWH reporting poorer subjective sleep.

Methods

Eligibility and recruitment

We analyzed women enrolled in the IDOze study that were recruited from the Chicago and New York City sites of the Women's Interagency HIV Study (WIHS) and HIV care clinics between October 2018 and January 2020. The WIHS is a longitudinal study of WWH and demographically similar WWoH and has been previously described (Bacon et al. 2005; Adimora et al. 2018).

In the IDOze study eligible WWH were: English-speaking, aged 35–70, on stable antiretroviral therapy (ART) excluding efavirenz, with an HIV RNA level < 200 copies/ml and CD4 + T Lymphocyte count ≥ 200 cells/μL in the 6 months before enrollment. Ineligible participants were those with severe chronic or acute medical or psychiatric illness, narcolepsy, illicit drug use (> 1 day/week of self-reported use), use of psychotropic medication (prescription hypnotics, over the counter sleeping aids > 2 nights per week, melatonin supplementation), and those who were night shift workers. We also excluded pregnant or lactating women, those who had given birth within three months of the study, were using estrogen-containing contraceptives, or were taking hormone replacement therapy. Further eligibility criteria for the IDOze study have been detailed previously (Rogando et al. 2022).

Written informed consent was obtained from all participants in accordance with Department of Health and Human Services guidelines and institutional review board approval from each site.

Participant demographic and clinical data

Demographic information, including age, race, menopausal status, and substance use (alcohol, cigarettes, marijuana, and illicit drugs) were extracted from the most recent WIHS research or clinical visit or newly collected if not available within the past six months. Participant height and weight were measured to obtain body mass index (BMI, in kg/m^2). In this study we define HIV viremia as HIV RNA level ≥ 20 copies/mL.

Daytime dysfunction

Self-reported daytime dysfunction was assessed using the Daytime Dysfunction component score of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989) which is the sum of two subcomponents (staying awake and maintaining enthusiasm). Each subcomponent was assessed with the following question and respondents provided self-reported responses based on a 4-point Likert scale, scored as 0 to 3: (i) "During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?" with the following response options: 0 = not during the past month, 1 = less than once a week, 2 = once or twice a week, 3 = three or more times a week; and (ii) "During the past month, how much of a problem has it been to keep up enough enthusiasm to get things done?" with the following response options: 0 = no problem at all, 1 = only a very slight problem, 2 = somewhat

of a problem, 3 = A very big problem. The overall daytime dysfunction score was calculated by summing the scores from the two subcomponents (i) and (ii), and ranges from 0 to 3: 0 = summed score of 0, 1 = summed score of 1 or 2, 2 = summed score of 3 or 4, 3 = summed score of 5 or 6. To compare individuals with daytime dysfunction to those without, the scores are dichotomized as follows: A daytime dysfunction score of 0 is considered "absence of daytime dysfunction"; a daytime dysfunction score of 1 or higher is considered "presence of daytime dysfunction".

Confounding covariates

Depressive symptoms, which can confound assessments, were measured using the Center for Epidemiological Studies Depression Scale (CESD). We utilized the affective component of the CESD score (CESD affect) which measures the non-somatic component of depression and excludes questions regarding sleep that may overlap with the PSQI, particularly the daytime dysfunction subcomponent, maintaining enthusiasm. Seven of the original twenty questions in the CESD are related to somatic symptoms, once excluded, the revised score range for CESD-affect was 0–39. Additional variables controlled for in the multivariate analyses were age, race, and menopausal status.

Laboratory methods for plasma metabolite measurement

Blood samples were processed within 24 h of collection; plasma aliquots were stored at -70 °C until batch testing. Targeted hydrophilic interaction liquid chromatography/positive ion mode (targeted HILIC-pos) mass spectrometry (MS) was used to measure metabolite quantities of the following metabolites in the Tryptophan-Kynurenine pathway: tryptophan, 5-hydroxytryptophan, 5-methoxytryptophol, serotonin, N-methylserotonin, kynurenine, kynurenic acid, xanthurenic acid, 3-hydroxyanthranilic acid, quinolinic acid.

HILIC analyses of metabolites in the positive ionization mode were conducted at the Broad Institute using an LC-MS system comprised of a 1290 Infinity II U-HPLC (Agilent) coupled to a triple quadrupole mass spectrometer (Agilent 6495). Plasma samples (10 µL) were prepared via protein precipitation with the addition of nine volumes of 74.9:24.9:0.2 v/v/v acetonitrile/methanol/formic acid containing stable isotope-labeled internal standards (valine-d8, Sigma-Aldrich; St. Louis, MO; and phenylalanine-d8, Cambridge Isotope Laboratories; Andover, MA). The samples were centrifuged (10 min, 9,000 x g, 4 °C), and the supernatants were injected directly onto a 150 × 2 mm, 3 µm Atlantis HILIC column (Waters). The column was eluted isocratically at a flow rate of 250 µL/min with 5% mobile phase A (10 mM ammonium formate and 0.1% formic acid in water) for 0.5 min followed by a linear gradient to 40% mobile phase B (acetonitrile with 0.1% formic acid) over 10 min. MS analyses were carried out using electrospray ionization (AJS ESI source) and dynamic multiple reaction monitoring scans in the positive ion mode. To create the method collision energies were optimized for each metabolite by infusion of reference standards. The ion spray voltage was 3.0 kV and the gas temperature was 200 °C. The nozzle voltage was 500 V and the gas flow was 14 L/min. Nebulizer pressure was 40psi. Raw data from the 6495 QTRAP MS system were processed using MassHunter B.07.00 software (Agilent). Metabolite identities were confirmed using authentic reference standards.

Statistical methods

WWH were compared to demographically similar WWoH using χ^2 measures of association for categorical variables, Wilcoxon rank-sum to compare means of non-parametric continuous variables, and one-way ANOVAs to compare parametric continuous variables. Due to skewed distributions all plasma metabolites were log transformed. The kynurenine-tryptophan and kynurenic acid-tryptophan ratios were calculated after the log transform. Multivariate linear regressions models using Spearman's rank correlation coefficient were utilized to identify relationships between metabolites and PSQI Daytime Dysfunction while controlling for age, race, menopausal status, and non-somatic depressive symptoms (CESD affect score). All analyses were conducted using R software (version 4.2.2, R Foundation for Statistical Computing), and significance was taken at $p < 0.05$ based on 2-tailed measurements.

Results

Participants

Data was available on 141 WWH and 140 WWoH. The WWH had a slightly higher median age than WWoH (55 vs. 52) and were less likely to consume alcohol, and smoke tobacco and marijuana. The groups did not differ by race, menopausal status, or other demographic variables (Table 1). WWH had higher total CESD scores, but similar non-somatic CESD affect scores to WWoH. Daytime dysfunction (PSQI daytime dysfunction score > = 1) was similar between WWH (35%) and WWoH (33%). There were no differences in perceived stress, PTSD symptomatology, housing stability, or the number of children in the house between the groups.

Table 1 Participant demographics comparing women with HIV (WWH) to HIV-negative matched controls (WWoH)

Characteristic	WWoH, $N=140$	WWH, $N=141$	p-value[1]
Age, Median (IQR)	52 (46–57)	55 (48–59)	**0.036**
Race, n (%)			0.079
Black	106 (77)	106 (75)	
Hispanic	30 (22)	25 (18)	
Other	0 (0)	5 (3.5)	
White	2 (1.4)	5 (3.5)	
Post-menopausal, n (%)	60 (55)	69 (63)	0.21
BMI, Median (IQR)	31 (27–35)	31 (27–36)	0.68
Diabetes, n (%)	24 (19)	38 (28)	0.12
Fasted at metabolite blood draw, n (%)	125 (91)	126 (89)	0.73
BQSA High Sleep Apnea Risk, n (%)	27 (51)	32 (49)	0.85
Daytime Dysfunction, n (%)	47 (34)	50 (35)	0.74
CESD total score (Depression), Median (IQR)	5 (3–11)	8 (3–16)	**0.043**
CESD affect score (Non-somatic Depression), Median (IQR)	2.0 (0.0–5.0)	3.0 (0.0–6.0)	0.37
Perceived Stress Scale (PSS10), Median (IQR)	14 (7–20)	12 (7–18)	0.69
PCL Civilian PTSD Score, Median (IQR)	26 (19–36)	25 (19–33)	0.61
Presence of children at home, n (%)	40 (36)	33 (25)	0.067
Partner or roommate in same bed, n (%)	52 (37)	45 (32)	0.36
Alcohol use during study	50(53)	35(31)	**0.001**
Current smoker, n (%)	62 (49)	44 (32)	**0.004**
Current marijuana use, n (%)	33 (29)	26 (19)	0.079
Illicit drug use in prior 6 months, n (%)	5 (5.1)	4 (3.3)	0.73
CD4 Count, Median (IQR)	NA (NA– NA)	708 (514–893)	
Nadir CD4 Count, Median (IQR)	NA (NA– NA)	194 (101–322)	
Viremic, n (%)	0 (NA)	25 (18)	>0.99

[1]Wilcoxon rank sum test; [2]Viremia defined as >20 copies/ml of HIV RNA in serum. Pearson's Chi-squared test; IQR = interquartile range; HIV = human immunodeficiency virus; BMI = body mass index; CESD = Center for Epidemiological Studies– Depression Scale; BQSA = Berlin Questionnaire for Sleep Apnea

We found that log-transformed kynurenine and kynurenine-tryptophan (K-T) ratio were higher in WWH compared to WWoH, p's < 0.01 (Table 2). Kynurenine and the K-T ratio was also significantly higher in viremic ($n=25$) compared to aviremic ($n=116$) WWH

Associations between T-K pathway and daytime dysfunction

We next examined the associations between T-K metabolites and daytime dysfunction, after controlling for age, race, menopausal status, and CESD-affect. Low serotonin and 5-hydroxytryptophan levels were associated with increased daytime dysfunction in both WWH and WWoH **(**Fig. 1**).** The same association was observed in the aviremic subgroup of WWH, but not in the viremic subgroup (although limited by sample size).

In WWH, but not WWoH, higher levels of kynurenic acid were associated with increased daytime dysfunction ($R=0.26$, $p<0.05$). Similarly, the kynurenic acid-tryptophan (KA-T) ratio predicted daytime dysfunction only in WWH ($R=0.28, p<0.01$). The associations with kynurenic acid and the KA-T ratio were only statistically significant in the aviremic subgroup however the trend for these associations in the viremic subgroup was similar.

Within the WWH and HIV-negative groups, we compared those with versus without daytime dysfunction (dichotomized by PSQI daytime dysfunction score > = 1) **(**Fig. 2). In WWH, we found that there was a 1.2-log fold decrease in the serotonin and 5-hydroxytryptophan level (p's < 0.01) in those with daytime dysfunction compared to without daytime dysfunction (multivariate analysis controlled for CESD-affect, age, race, menopausal status, and alcohol consumption). WWoH with daytime dysfunction also had significant decreases in serotonin and 5-hydroxytroptophan. In WWH, those with daytime dysfunction had a 0.71 log fold increase in kynurenic acid ($p<0.01$) compared to those without daytime dysfunction. No such relationship was observed in the WWoH. While our data hint at a potential influence of HIV serostatus on the relationship between T-K pathway metabolites and daytime dysfunction, incorporating HIV serostatus as an interaction term in our multivariate analyses did not yield statistically significant results.

Discussion

We compared the relationships between daytime dysfunction and metabolites in the T-K metabolic pathway in women with HIV (WWH) and women without HIV (WWoH). These groups were similar, however WWH were slightly older (median age of 55 vs. 52), were less likely to smoke tobacco, and were less likely to consume alcohol during the study. We speculate that these differences are the result of WWH receiving more regular health monitoring and doctor visits, and therefore were more regularly advised about the harms of alcohol and tobacco. After including these possible confounders as covariates in our multivariate analyses, we

Table 2 Tryptophan-kynurenine pathway metabolites across serostatus and viremic status in WWH and WWoH

Metabolite	WWoH, $N=140$	WWH, $N=141$	p-value[1]	Aviremic[3] WWH, $N=116$	Viremic WWH, $N=25$	p-value[2]
Tryptophan, Mean (SD)	13.59 (0.31)	13.54 (0.32)	0.24	13.54 (0.31)	13.56 (0.36)	0.75
5-hydroxytryptophan, Mean (SD)	9.46 (1.85)	9.66 (2.07)	0.40	9.66 (2.12)	9.63 (1.84)	0.94
5-methoxytryptophol, Mean (SD)	9.44 (0.32)	9.44 (0.30)	0.93	9.46 (0.30)	9.38 (0.31)	0.24
Serotonin, Mean (SD)	9.37 (1.83)	9.55 (2.08)	0.44	9.54 (2.13)	9.59 (1.87)	0.91
N-methylserotonin, Mean (SD)	3.83 (2.25)	4.01 (2.34)	0.50	4.12 (2.38)	3.48 (2.06)	0.22
Kynurenine, Mean (SD)	8.91 (0.41)	9.06 (0.42)	**0.004**	9.00 (0.40)	9.35 (0.42)	**< 0.001**
Xanthurenic acid, Mean (SD)	10.42 (0.65)	10.33 (0.62)	0.24	10.32 (0.66)	10.41 (0.41)	0.53
Kynurenic acid, Mean (SD)	12.73 (0.96)	12.69 (0.93)	0.74	12.69 (0.94)	12.71 (0.93)	0.93
3-hydroxyanthranilic acid, Mean (SD)	2.75 (1.01)	2.85 (1.00)	0.40	2.76 (0.98)	3.31 (1.01)	**0.012**
Quinolinic acid, Mean (SD)	9.98 (0.67)	10.09 (0.69)	0.18	10.13 (0.71)	9.92 (0.58)	0.17
K-T Ratio, Mean (SD)	0.656 (0.030)	0.669 (0.029)	**< 0.001**	0.665 (0.026)	0.690 (0.034)	**< 0.001**
KA-T Ratio, Mean (SD)	0.94 (0.08)	0.94 (0.07)	> 0.99	0.94 (0.07)	0.94 (0.08)	0.97

All metabolites were log transformed. [1]One-way ANOVA between WWoH; [2]One-way ANOVA between aviremic and viremic WWH;[3]Viremia defined as > 20 copies/ml of HIV RNA in serum. HIV = human immunodeficiency virus; K-T = kynurenine-tryptophan; KA-T = kynurenic-acid-tryptophan; SD = standard deviation

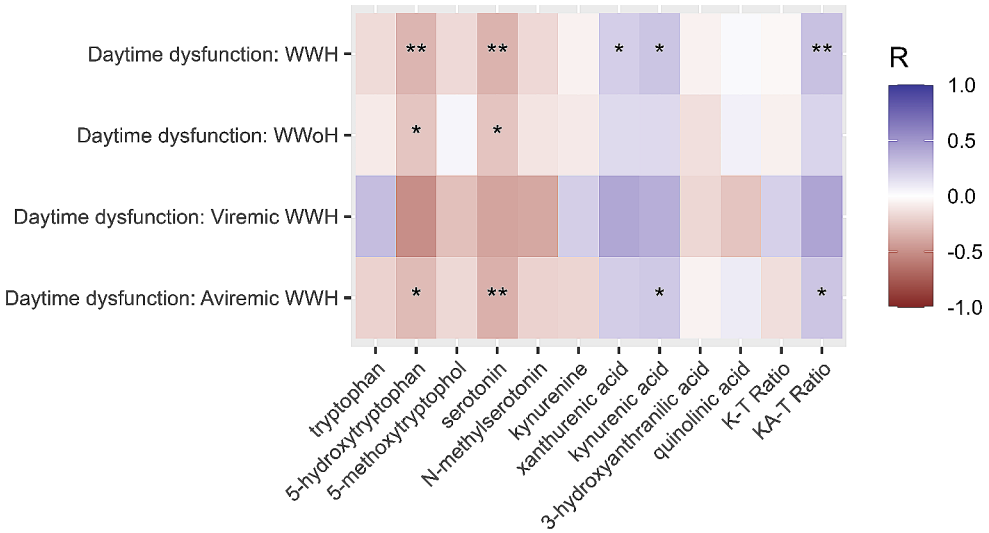

Fig. 1 Heatmap of correlations between daytime dysfunction and metabolites in the tryptophan-kynurenine pathway for women with HIV (WWH), WWoH, viremic WWH and aviremic WWH. Daytime dysfunction scores on the Pittsburgh Sleep Quality Index (PSQI) were correlated to log metabolite abundances in the T-K pathway in WWH ($n=141$), WWoH ($n=140$), viremic WWH ($n=25$) and aviremic WWH($n=116$). Viremia was defined as > 20 copies/ml of HIV RNA in serum. Spearman's R was used to calculate the correlation coefficient for multivariate analysis controlling for age, race, menopausal status, CESD-affect score, and alcohol use. Tiles with no stars indicate no statistical significance, * = $p<0.05$, ** = $p<0.01$. HIV = human immunodeficiency virus; CESD = Center for Epidemiological Studies– Depression Scale; K-T = kynurenine-tryptophan; KA-T = kynurenic-acid-tryptophan

found no significant difference between WWH and WWoH regarding the prevalence of daytime dysfunction measured with the PSQI. We did however identify distinct T-K metabolite profiles associated with daytime dysfunction across HIV status.

Predictors of insomnia in HIV include the presence of mental health disorders, cognitive impairment, efavirenz treatment, and AIDS-defining illnesses (Reid and Dwyer 2005; Jean-Louis et al. 2012; Daubert et al. 2022). Our IDOze study comparison groups had no differences in depressive symptoms, were not using efavirenz, and participants with AIDS-defining or severe mental illnesses were excluded. Therefore, it is unsurprising to find no serostatus differences for prevalence of daytime dysfunction in our cohort.

In both WWH and WWoH, lower levels of serotonin and 5-hydroxytryptophan were associated with daytime dysfunction, independent of affective depressive symptoms. The log-difference in the serotonin levels in those with and without daytime dysfunction was similar across serostatus groups. Serotonin itself acts to facilitate sleep, as well as being the precursor to melatonin which regulates the sleep/wake cycle (Portas et al. 2000). Irrespective of serostatus,

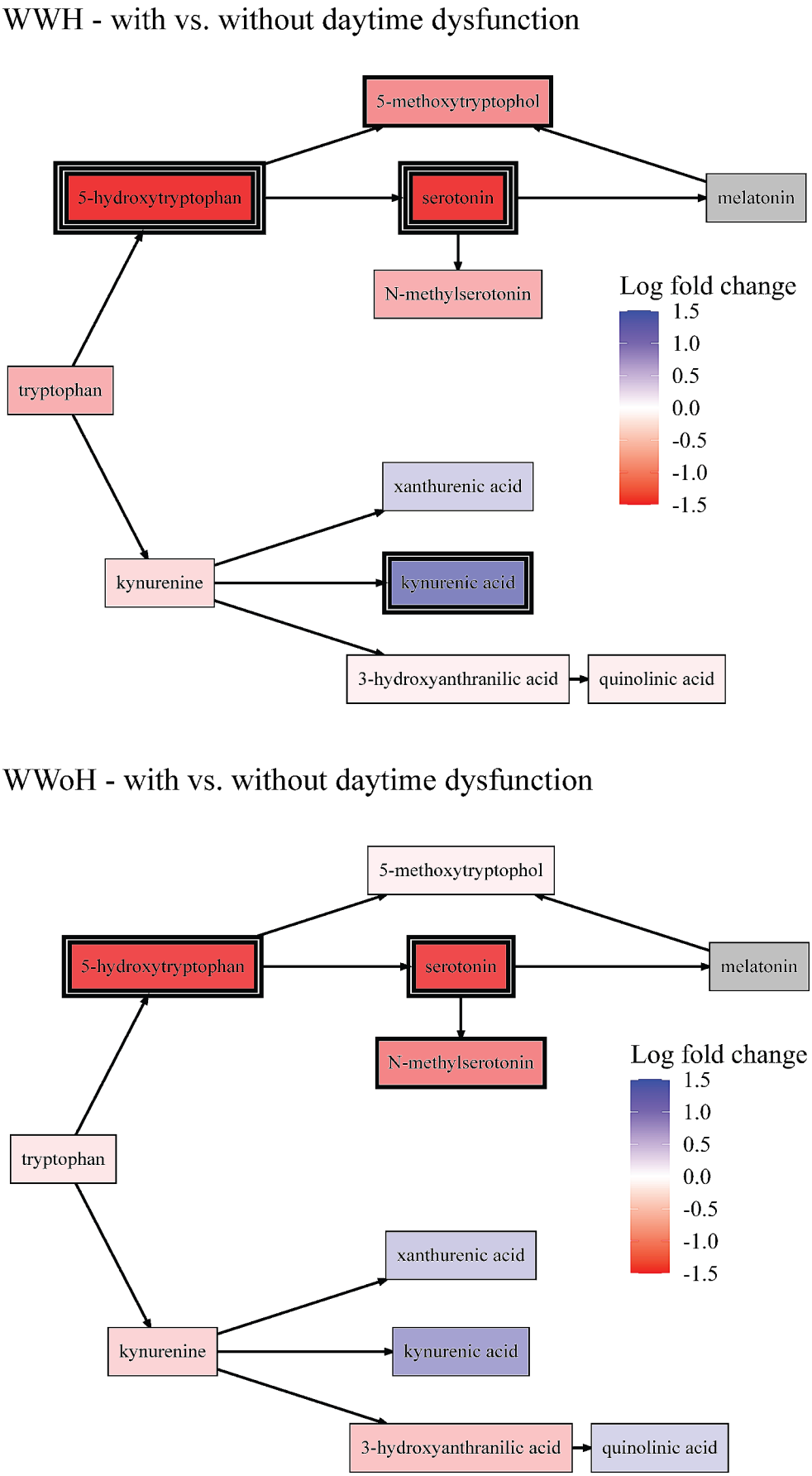

Fig. 2 Log fold differences in metabolite abundances for those with versus without daytime dysfunction in women with HIV (WWH) and without HIV (WWoH). Presence of daytime dysfunction considered if PSQI daytime dysfunction score was >=1. Comparison within WWH ($n=141$) group shown in top panel, comparison within WWoH ($n=140$) shown in bottom panel. Metabolites are colored based on the log fold relative abundance differences in those with versus without daytime dysfunction. Melatonin is colored grey as it was not measured. Single bold border represents statistical significance at $p<0.05$, double bold border represents significance at $p<0.01$, triple bold border represents significance at $p<0.001$. All associations were adjusted for age, race, menopausal status, and CESD-affect score. Not all metabolites in the T-K pathway are shown here. HIV = human immunodeficiency virus; PSQI = Pittsburgh Sleep Quality Index; CESD = Center for Epidemiological Studies–Depression Scale

the depletion of serotonin could explain the lack of restorative sleep in those reporting daytime dysfunction.

In WWH, but not in WWoH, elevated kynurenic acid, and kynurenic acid-tryptophan (KA-T) ratios, were associated with greater subjective PSQI daytime dysfunction. In our prior IDOze study we showed associations between the kynurenine: tryptophan (K-T) ratio and objective actigraphy-based sleep disturbances in WWH (Rogando et al. 2022). The K-T ratio has been shown to increase with HIV disease progression (Huengsberg et al. 1998) as well as in other conditions such as multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer's disease (Chen and Guillemin 2009; Hestad et al. 2022).

A speculated mechanism for the increase in kynurenine or downstream kynurenic acid is via the induction of the IDO (indoleamine-2,3-dioxygenase) enzyme which shunts tryptophan away from melatonin and towards kynurenine. Induction of IDO can occur via interferon-gamma (IFN-γ) which would be expected to be elevated in those with viremia or those with HIV-related inflammation or immune activation (Fuchs et al. 1991; Huengsberg et al. 1998; Samikkannu et al. 2009; O'Connor et al. 2009; Davies et al. 2010; Kandanearatchi and Brew 2012). HIV viremia has previously been correlated to sleep disturbances, mental health disorders and cognitive dysfunction in HIV (Ning et al. 2019; Leone et al. 2021; Daubert et al. 2022; Pujasari and Chung 2022). In our viremic subgroup of WWH we did not find that daytime dysfunction was predicted by increased kynurenine levels, however we believe this is likely due to our limited sample size ($n = 26$ viremic participants).

In our previous IDOze study the K-T ratio was associated with worse objective sleep, while in this study a higher KA-T ratio, was associated with worse subjective sleep (daytime dysfunction). Several studies have shown discordance between objective sleep metrics and subjective perception of sleep quality (Åkerstedt et al. 2016; Kaplan et al. 2017). Subjective reporting of sleep quality appears to be more influenced by personal disposition, comorbid depression as well as other mental health conditions. Although there is a relationship between subjective and objective sleep, they are two separate constructs and we therefore might not expect the metabolic changes associated with subjective sleep disturbance to mimic the metabolic changes seen with objective sleep disturbance.

We assessed limited aspects of daytime dysfunction with PSQI, as only 2 questions with 4 item Likert scales were used. Likert scales with 5 items would allow subjects to select neutral options. Moreover, the PSQI queries subjective daytime dysfunction over the prior month which is prone to reporting bias. Our sample is not truly representative of WWH and WWoH as the parent study was designed to eliminated sleep related confounders that are common including alcohol, drug use, and mental illness. Additionally, we did not account for specific ART regimens, or quantify inflammatory biomarkers, which are known to activate IDO and alter kynurenine-tryptophan ratios (Lukehart et al. 1988; Zangerle et al. 2002; Schwarcz et al. 2012; Routy et al. 2015; Spitsin et al. 2021). Another possible confounder is sleep timing and chronotype which may affect metabolite levels (Xiao et al. 2017).

Tryptophan is an essential amino acid which can only be obtained through diet, however, due to the challenge in controlling for individual diets this factor was not accounted for. Moreover, our group has previously shown that the composition of the gut microbiome differs between WWH and WWoH, and that these differences may impact sleep (Zhang et al. 2023). Antiretrovirals are also known to affect the composition of oral and gut microbiota and therefore the sleep may differ depending on particular ART regimens (Imahashi et al. 2021). As the gut microbiome is an important determinant of tryptophan absorption, the relationship between gut microbiota, T-K metabolites, and sleep are the subject of a future study.

Longitudinal studies with a greater representation of HIV viremic women would help establish causal relationships between T-K metabolites and sleep-related functional impairment as a function of HIV disease status. Assessing this mechanistic link may provide new directions for treating sleep disturbances and thereby reducing daytime dysfunction in WWH. Furthermore, future studies should consider the role of food intake and gut microbiota which can alter metabolite concentrations and in turn lead to sleep disruption and possibly a vicious cycle of poor sleep and metabolic imbalances (O'Mahony et al. 2015).

Daytime dysfunction incorporates the ability to stay awake and maintain enthusiasm and motivation. Increased attention on rectifying sleep disturbances in HIV is needed as quality of sleep and resultant daytime dysfunction has been shown to influence antiretroviral medication non-adherence (Saberi et al. 2011), and is associated to worsening mental health, quality of life, and life satisfaction in PWH over time(Rogers et al. 2020, 2021).

In conclusion we found that kynurenic acid and the KA-T ratio predicted daytime dysfunction in WWH but not in WWoH. These findings complement our previously reported IDOze data showing a relationship between TK pathway metabolites and actigraphy derived sleep measures by HIV status, suggesting the unique role of kynurenine and its metabolites in sleep disruption and daytime dysfunction in WWH.

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R.D., L.R: Patient enrollment and data collection: A.F., A.S., D.G., R.M., T.Y. Metabolomics on plasma samples: C.C., K.B. Wrote the main text and performed analysis: E.S. Provided expert analysis: A.F., K.W., R.D, L.R., E.S., E.D. Critical editing and review: A.R., D.G., A.S., E.D., Q.Q.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The study was performed according to the principles outlined by the Helsinki Declaration. All participants provided informed consent in accordance with Department of Health and Human Services guidelines and with approval from each site's institutional review board: Chicago– Cook County Health IRB #18 – 008; Brooklyn– SUNY Downtown state Health Sciences University IRB and Privacy Board #1280378-8; Bronx– Albert Einstein College of Medicine IRB #2018–9115.

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