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Trauma across the lifespan and multisystem morbidity in women with HIV

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Abstract

Objective: Sexual and physical abuse are highly prevalent among women living with HIV (WLWH) and are risk factors for development of mental health and substance use disorders (MHDs, SUDs), and cognitive and medical co-morbidities. We examined empirically-derived patterns of trauma, MHD, and SUD, and associations with later cognitive and health outcomes.

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Methods: 1027 WLWH (average age=48.6 years) in the Women's Interagency HIV Study completed the World Mental Health-Composite International Diagnostic Interview during 2010–2013 to identify MHDs, SUDs, and age at onset of sexual and physical abuse. Then, cognitive impairment, cardiovascular/metabolic conditions, and HIV disease outcomes were assessed for up to 8.8 years. Latent class analysis (LCA) identified patterns of co-occurring trauma, MHDs, and/or SUDs. Generalized estimating equations determined associations between these patterns and mid-life cognitive and medical outcomes.

Results: Six distinct profiles emerged: no/negligible sexual/physical trauma, MHD, or SUD (39%); preadolescent/adolescent sexual trauma with anxiety and SUD (22%); SUD only (16%); MHD+SUD only (12%); early childhood sexual/physical trauma only (6%); and early childhood sexual/physical trauma with later MHD+SUD (4%). Profiles including early childhood trauma had the largest number of mid-life conditions (i.e., cognitive, cardiovascular, HIV-related). Preadolescent/adolescent sexual trauma with anxiety and SUD predicted both global and domain-specific cognitive decline. Only SUD without trauma predicted lower CD4, while childhood trauma with MHD+SUD predicted increased CD8.

Conclusions: WLWH have complex multisystem profiles of abuse, MHD, and/or SUD that predict midlife cognitive, metabolic/cardiovascular, and HIV outcomes. Understanding the interplay between these factors over time can identify risks and personalize preventative and treatment interventions.

Keywords

Trauma; Women; HIV; Mental Health; Substance Use

Introduction

Traumatic life experiences such as childhood sexual and physical abuse are highly prevalent among people living with HIV (PLWH), particularly women, who comprise 23.4% of HIV cases in the United States (U.S.) (1). The estimated prevalence of childhood sexual abuse among women living with HIV (WLWH) is 39%, adult sexual abuse is 35%, and physical violence is 54% (2, 3), approximately double that of women in the general U.S. population (4–6). Sexual and physical abuse are risk factors for mood, anxiety, post-traumatic stress disorder (PTSD), and substance use disorder (SUD). Both types of abuse also predict poor antiretroviral (ART) adherence, ART treatment failure, HIV disease progression, and mortality in PLWH (7–9). Sexual and physical abuse also have profound implications for cognitive and physical health (10). Understanding the longitudinal interplay between all of these factors for WLWH can help to identify women at risk and personalize preventative and treatment interventions.

There are significant individual differences in development of comorbidities after exposure to trauma, defined here as sexual and physical abuse; the timing of trauma may be key to understanding these differences. Lupien (11) postulates that the effects of trauma at different life stages depend on the brain areas that are developing during those stages. Trauma first occurring in early childhood (age 0–7), may affect the developing hippocampus, a structure involved in learning and memory. Trauma beginning during pre-adolescence

and adolescence (age 8–17) may affect the developing amygdala, involved in emotion processing, and the frontal cortex, involved in higher order cognitive functions (e.g., working memory, fluency). Finally, trauma beginning in young- (age 18–29) and late adulthood (age 30 through 59) may affect brain regions that rapidly decline with age.

This developmental framework linking trauma sequela to stages of brain development may help to account for cognitive impairment, metabolic and cardiovascular conditions, and poor HIV disease outcomes in WLWH. A systematic review of observational studies found that trauma before age 18 was associated with later development of MHD and cognitive impairment, especially declines in memory and executive functions (12). Childhood maltreatment and other early stressors have been associated with adult depression, reduced brain volumes and abnormal brain connectivity (13, 14), and metabolic diseases such as higher body mass index (BMI), glycated hemoglobin, and elevated total cholesterol (15–17). Early childhood trauma was also associated with increased activation of cytokines and dysregulation of the immune system (18), which are implicated in the development of hypertension, liver disease, immune system suppression, and other poor medical outcomes (19, 20). Finally, early childhood trauma was associated with later poor mental health, substance use, and HIV disease progression indicated by decreased CD4 T lymphocytes, increased viral load, greater clinical decline, and mortality (21–24). Remaining unknown are constellations of risk factors and their connection to multisystem morbidity following traumatic life events.

We leveraged the strengths of the Women's Interagency HIV Study (WIHS), including large sample size (n=1027), lengthy follow-up period (mean=8.8 years), and validated diagnostic measures. Our first aim was to identify empirically-identified patterns of sexual/physical trauma, MHDs, and SUDs that constituted potential risk factor profiles for later comorbidities. The second aim was to examine the association of these profiles with midlife cognitive, cardiovascular, metabolic, and HIV disease outcomes in WLWH.

Materials and Methods

Ethical Approval of Studies and Informed Consent

The WIHS was approved by the institutional review board at each site and written informed consent was obtained from all participants.

Study Participants

Detailed information on the WIHS cohort and study design is available in previous publications (25, 26); detailed information on the substudy is also available (27). Substudy participants were WLWH, communicated fluently in English, and completed an in-person behavioral health assessment.

Measures

Trauma (exposure) and behavioral health diagnoses

The World Mental Health Composite International Diagnostic Interview (WMH-CIDI) is a comprehensive, fully standardized assessment of disorders (28) according to the criteria

of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)(29), designed for use by trained and certified, non-clinician research interviewers. Interviews were administered once between 2010–2013. We extracted past 12-month and lifetime *DSM-IV* disorders including mood, anxiety, and SUD. We also extracted information on the age at onset of sexual and physical abuse, given prior research showing that onset is more important than abuse duration or severity in predicting later psychiatric comorbidities (30). Consistent with Lupien and colleagues (11), the timing of trauma onset was classified into four categories: *early childhood* (age 0–7), *preadolescence/adolescence* (age 8–17), *young adulthood* (age 18–29), and *late adulthood* (age 30–59). None of the women were aged ≥60. The occurrence of physical and sexual abuse were not examined beyond the period of onset. Given our interest in physical and sexual abuse, we did not examine other types of trauma.

Cognition Outcome Measures

Beginning in 2009 and biennially, a neuropsychological (NP) test battery was administered, including: Hopkins Verbal Learning Test–Revised (HVLT-R), Trail Making Test (TMT), Stroop Test, Symbol Digit Modalities Test (SDMT), Letter-Number Sequencing (LNS) Test, letter fluency, animal fluency, and Grooved Pegboard (GPEG). NP outcomes were transformed into demographically-adjusted T-scores as described in previous WIHS studies (31, 32). NP outcomes were combined into domain-specific T-scores: learning (HVLT-R total learning), memory (HVLT-R delay free recall), verbal fluency (letter and animal fluency), fine motor skills (GPEG dominant and non-dominant hands), processing speed (TMT-Part A, SDMT), attention/working memory (LNS attention and working memory conditions), and executive function (TMT-Part B, Stroop Trial 3). A global NP score was also computed for individuals with data for ≥4 domains. See details in our previous publication (32). Impairment was defined as a T-score ≤40. Global NP function was examined continuously (T-scores) and categorically (impaired vs. unimpaired); domain-specific cognitive function was examined continuously due to non-convergence of models examining domain-specific cognitive impairment. All NP data were collected subsequent to the WMH-CIDI assessment.

Physical Health Outcome Measures

We used physical health outcome data that were collected bi-annually following the WMH-CIDI assessment. Preclinical cardiovascular disease risk indices included BMI (kg/m^2), and systolic and diastolic blood pressure (mmHg). For metabolic health, we used the Homeostasis Model Assessment of insulin resistance (HOMA-IR) based on fasting specimens (33, 34). For diabetes/pre-diabetes, we used Hemoglobin A1c which indicates average blood sugar levels over a 3-month period. For liver health, we used Fibrosis-4 (FIB-4) Index for Liver Fibrosis (35). Finally, HIV-related clinical outcomes included log HIV RNA (cp/ml), current CD4 count, CD8 count (cells per mm^3), and the ratio of CD4/CD8 count.

Statistical Analysis

We applied latent class analysis (LCA) to identify mutually exclusive profiles of individuals (36) based on responses to measured binary variables. Timing of the first self-reported sexual and/or physical abuse contributed 8 dummy variables to the LCA (4 per abuse

type)[<8 years of age, 8–17, 18–29, ≥30(11)], along with three 12-month MHD variables (mood disorder, anxiety disorder, PTSD), and four SUD variables (AUD and/or drug use disorder [DUD] in the past 12-months and lifetime). As all participants fully completed the WMH-CIDI, there were no missing data on these 15 variables. The number of classes we examined ranged from 2 to 7 with the optimal number of classes determined using model fit statistics (Akaike's Information Criterion [AIC], the Bayesian Information Criterion [BIC], entropy) and predicted probability of individuals' assigned profile while taking into account model interpretability. After identifying the best fitting model, we extracted the probability of an individual's membership in each latent profile, assigning them to the one where their posterior probability of membership was highest. Profiles were then used in a series of generalized linear mixed effects models to examine the link between profile membership and cognitive and physical health trajectories where the generalized estimating equation was used for parameter estimation to account for correlation from repeated measures. As different participants have a different number of cognitive/physical health measurements, this analytic strategy uses the observed complete data of each individual to estimate parameters and did not require missing data imputation for parameter estimation and subsequent statistical inference. Primary predictors included Profile, age time (linear trend), age time*age time (quadratic trend) and two-way interactions between Profile and each trend. Models adjusted for study site, income, initial global NP performance (cognition only), hepatitis C seropositivity, history of clinical AIDS, and current smoking status. The timing of the outcome measure for each individual began subsequent to the date of completion of that person's WMH-CIDI assessment (between 2010 and 2013) LCAs were conducted with Mplus statistical software (version 7.4); ANOVAs and Chi-squares were conducted in SAS (version 9.4, SAS Institute Inc, Cary, NC).

Results

Participant Characteristics

Participants included 1027 WLWH in a nested WIHS substudy of psychopathology (27). Participant characteristics are described in Table 1. Participants had a mean age of 48.6 years (standard deviation [SD]=8.8) and 64% identified as Black, non-Hispanic. Sixty-seven percent completed 12 or more years of education and 45 had annual income <$12,000. Although thirty-eight percent self-reported current smoking, only a small percentage reported heavy alcohol (13%) or illicit substance use (16% marijuana use; 5% crack, cocaine, and/or heroin use). A high percent had cardio-metabolic risk factors (42% hypertension; 23% diabetes; average body mass index of 29.8 (SD=7.9) and 45% were on non-ART medications with known CNS effects with 24% on antidepressants and 24% on opioids. HIV RNA was <20 copies/mL for 71%, the average current CD4 count was 531 cells/mm^3 (SD=409), and 45% had a prior diagnosis of AIDS.

Sexual abuse was reported by 51% and physical abuse by 44%. Onset of sexual abuse was reported by 14% (n=145) in early childhood (age 0–7), 26% (n=267) in pre-adolescence/adolescence (age 8–17), 11% (n=109) in adulthood (age 18–60), and 49% reported no sexual abuse. For physical abuse, 10% (n=106) reported onset in early childhood, 15% (n=153)

in pre-adolescence/adolescence, 19% (n=196) in adulthood, and 56% (n=572) reported no physical abuse.

The most prevalent MHDs in the past 12-months were anxiety (39%), followed by mood (24%), and PTSD (17%). Because 12-month prevalence of SUDs was very low (i.e., DUD at 8% and alcohol use disorder [AUD] at 5%), we also included diagnosis of SUDs at any point in the person's lifetime in our analysis. Prevalence of lifetime AUD was 36% and lifetime DUD was 51%, most of which was polysubstance DUD (64%). The most common lifetime DUDs were cocaine (41%), opioid (22%), cannabis (19%), sedative (11%), and pain medication (10%).

Co-occurrence of trauma, MHD, and SUD among WLWH

Our first aim was to identify empirically-based profiles using LCA combining the following: 1) onset of physical/sexual abuse at a given life stage; 2) existence of current (i.e., 12-month) depressive disorder, mood disorder, or PTSD; and 3) existence of 12-month or lifetime AUD or DUD. Seven LCA models were evaluated with the 6-class solution chosen based on model fit statistics (Supplemental Table 1). This resulted in six risk profiles. The probability of membership was examined and only 28 out of the 1027 participants had a probability of membership <0.50 to their assigned profile. The profiles are presented below and illustrated in Figure 1A with specific exposure types presented in Supplemental Table 2 and sociodemographic, behavioral, and clinical factors presented in Supplemental Table 3.

- **Profile 1 (n=38; 4%)—*Early childhood trauma with later MHD+SUD.*** Women in this profile had high probabilities of early childhood exposure to sexual (87%) and physical abuse (100%) as well as 12-month MHDs including mood (63%), anxiety (56%), and PTSD (55%), and lifetime AUD (71%) and DUD (100%).
- **Profile 2 (n=228; 22%)—*Preadolescent/Adolescent sexual trauma with anxiety disorders and SUD.*** This profile had high probabilities of pre-adolescent/adolescent sexual (but not physical), abuse (100%), 12-month anxiety disorder (56%), and lifetime AUD and DUD (>58%).
- **Profile 3 (n=121; 12%)—*Co-occurring MHD+SUD.*** This profile had low probabilities of trauma exposure at any age (<31%) but high probabilities of 12-month mood or anxiety disorder (>66%) and lifetime AUD and DUD (>68%).
- **Profile 4 (n=169; 16%)—*SUD during lifetime.*** This profile had low probabilities of both trauma exposure and 12-month MHD, but high probabilities of lifetime AUD (54%) and DUD (79%).
- **Profile 5 (n=65; 6%)—*Resilient after childhood trauma.*** This profile had high probabilities of early childhood sexual and physical abuse (≥64%) but low probabilities of MHDs and SUDs (≤39%).
- **Profile 6 (n=406; 39%)—*Control.*** This profile had the lowest probabilities of all 3 exposures (trauma ≤12%, MHDs and SUDs ≤21%), and was the referent to which other profiles were compared.

The 12-month prevalence of AUD and DUD was low in the total sample; however, these variables were retained in the LCA because removal decreased model entropy.

Risk factor sequelae

The second aim was to examine the association of these risk factor profiles with later cognitive, cardiovascular, metabolic, and HIV disease outcomes using generalized linear models adjusting for enrollment site and relevant sociodemographic, behavioral, and clinical factors. On average, participants contributed 8.8 years of outcome data (SD=5.8) following the WMH-CIDI assessment.

Cognitive Health

Global cognitive function.—At the baseline for our observation period (i.e., age 40), there were no significant differences between Profiles 1–5 and Profile 6 (control) in global neuropsychological (NP) function measured continuously (T-scores) or categorically as impairment. However, the longitudinal analysis showed that Profile 1-*Early childhood trauma with MHD+SUD* and Profile 2-*Preadolecent/adolescent sexual trauma with anxiety disorders and SUD* exhibited significantly faster global NP decline (unstandardized beta $[B]_{\text{quadratic trend}}=-0.02$, standard error [SE]=0.01, $P=0.04$; $B_{\text{linaer trend}}=-0.08$, SE=0.03, $P=0.02$, respectively), and greater levels of impaired performance ($B_{\text{quadratic trend}}=0.01$, SE=0.004, $P=0.02$; $B_{\text{linear trend}}=0.04$, SE=0.02, $P=0.01$, respectively) than Profile 6 (Figure 1B). No other profile differed from Profile 6 in patterns of cognitive change.

Domain-specific cognitive function.—At observational baseline, there were no significant differences in motor function between Profiles 1–5 and Profile 6. However, over time, Profile 1-*Early childhood trauma with MHD+SUD* demonstrated faster rates of decline in motor function ($B_{\text{quadratic trend}}=-0.04$, SE=0.01, $P<0.001$) compared to Profile 6 (Figure 1C.A). On average, Profile 1 also tended to perform lower on processing speed compared to Profile 6 across all time points (M=44.89 [SE=1.34] vs M=47.24 [SE=0.69], $P=0.07$). At baseline, Profile 2-*Preadolecent/adolescent sexual trauma with anxiety disorders and SUD* had higher verbal fluency (B=4.21, SE=1.09, $P<0.001$) compared to Profile 6 (Figure 1C.B). Over time, Profile 2 demonstrated faster rates of verbal fluency decline ($B_{\text{linear trend}}=-0.15$, SE=0.07, $P=0.03$) relative to Profile 6. At baseline, there were no differences in attention/working memory between Profile 3—*Co-occurring MHD+SUD* and Profile 6. However, Profile 3 demonstrated faster rates of decline over time in attention/working memory ($B_{\text{quadratic trend}}=-0.02$, SE=0.02, $P=0.003$) compared to Profile 6 (Figure 1C.C). At baseline, Profile 4—*SUD during lifetime* had higher executive functioning (B=4.63, SE=1.52, P=0.002) and processing speed (B=4.26, SE=1.39, P=0.002) than Profile 6 (Figure 1C.D–E). Over time, Profile 4 demonstrated faster rates of decline on executive function ($B_{\text{linear trend}}=-0.20$, SE=0.02, $P=0.03$), processing speed ($B_{\text{linear trend}}=-0.19$, SE=0.09, $P=0.04$), and verbal fluency ($B_{\text{quadratic trend}}=-0.01$, SE=0.007, $P=0.02$) compared to Profile 6. Profile 4 also performed lower on verbal memory compared to Profile 6 across all time points (M=47.60 [SE=0.76] vs M=49.20 [SE=0.67], $P=0.03$). Notably, Profile 5–*Resilient after childhood trauma* did not differ at baseline or over time on any domain-specific cognitive outcomes from Profile 6 (Figure 1C.F–G).

Physical Health

Preclinical Cardiovascular Risk Indices.—At observational baseline, there were no significant differences between Profiles 1–5 and Profile 6 on BMI. However, Profile 5—*Resilient after childhood trauma* demonstrated significant increases in BMI over time compared to Profile 6 ($B_{\text{linear trend}}$=0.10, SE=0.04, *P*=0.04)(Figure 2A). The remaining Profiles 1–4 did not differ from Profile 6. While Profiles 1–5 showed a similar trajectory in systolic and diastolic blood pressure compared to Profile 6, Profile 1-*Early childhood trauma with MHD+SUD* had significantly higher systolic blood pressure (M=127.8 [SE=2.55] vs. M=121.3 [0.98]; B=6.45, SE=3.00, *P*=0.04) and diastolic blood pressure (M=78.4 [SE=1.67] vs. M=74.56 [SE=0.71]; *P*=0.01) over time compared to Profile 6 (Figure 2B–C).

Metabolic outcomes.—At observational baseline, there were no significant differences between Profiles 1–5 and Profile 6 in insulin resistance (HOMA-IR), liver fibrosis (FIB-4) or diabetes, (hemoglobin A1C). However, Profile 5—*Resilient after childhood trauma* demonstrated significant increases in **insulin resistance** over time compared to Profile 6 ($B_{\text{quadratic trend}}$=0.001, SE=0.000, *P*=0.04)(Figure 2D). Profile 5 also had higher insulin resistance levels across all time points compared to Profile 6 (M=1.07 [SE=0.09] vs. M=0.87 [SE=0.05], *P*=0.03). Regarding **liver health**, there were no differences at baseline or over time between Profiles 1–5 and Profile 6 in FIB-4 scores (Figure 2E). Regarding presence of **diabetes or pre-diabetes**, Profile 5 demonstrated significant increases over time in hemoglobin A1C compared to Profile 6 (B_{linear} trend=0.04, SE=0.01, *P*=0.04)(Figure 2F).

HIV-related clinical outcomes.

At observational baseline, there were no significant differences between Profiles 1–5 and Profile 6 in immune health as measured by HIV RNA (Figure 2G) or CD4 count. However, Profile 4—*SUD during lifetime* had significantly lower CD4 counts over time compared to Profile 6 (M=555.54 [SE=22.26] vs. M=590.90 [SE=21.44]; *P*=0.02) (Figure 2H). Regarding immune senescence and chronic inflammation, Profile 1-*Early childhood trauma with MHD+SUD* demonstrated significant increases in CD8 levels over time compared to Profile 6 (B_{qudratic} trend=0.78, SE=0.39, *P*=0.04) (Figure 2I). There were no other longitudinal differences between Profiles 1–5 and Profile 6 on the remaining HIV-related clinical outcomes.

Sensitivity Analyses

All generalized linear mixed effects models were re-run after excluding the 28 individuals whose predicted probability of profile membership was <0.50. The same pattern of results emerged which was to be expected given the small proportion of individuals that were not high probability fits for their assigned cluster.

Discussion

The results of this analysis suggest that WLWH have complex multisystem morbidity profiles characterized by onset of physical and sexual abuse at different life stages, by the development of SUDs, and by the development of depressive disorders, anxiety disorders, and PTSD. These profiles, in turn, are predictors of later cognitive impairment, metabolic

and cardiovascular conditions, and poor HIV disease outcomes. The causal pathways of these multi-morbidities and their linkages to mid- and later-life health are poorly understood. However, our results are suggestive in implicating the important role of brain development that is likely to be influenced by the onset of trauma at different life stages.

The most common constellation of comorbidities, reported by 39% of women, was Profile 6, defined by no-to-negligible trauma exposure, psychiatric disorders, or SUDs. The next most common was Profile 2, reported by 22%, defined by sexual, but not physical, trauma occurring in pre-adolescence/adolescence along with anxiety disorder and SUD. The next most common was Profile 4, reported by 16%, defined by AUD and/or DUD not accompanied by psychiatric disorders or trauma. Profile 3, reported by 12%, was co-occurring MHD and SUD without trauma. Fairly infrequent, at 6%, was Profile 5 with childhood trauma not followed by MHD or SUDs. Finally, lowest in frequency was Profile 1, reported by 4%, with childhood onset of both physical and sexual abuse and later development of mood, anxiety, and PTSD along with lifetime AUD and DUD. Profiles 1 and 5, the two characterized by childhood sexual abuse, had the largest number of poor outcomes although these differed in type. Profile 1 displayed worsening global NP function, declining motor function and processing speed, increasing hypertension, and worsening chronic inflammation. While Profile 5 did not display increases in global NP impairment, it did display increasing BMI, worsening insulin resistance, and greater likelihood of diabetes.

A large and growing body of research outside of HIV has focused on understanding childhood trauma and its psychiatric and psychobiological effects. The main biological systems impacted by childhood trauma include the limbic-hypothalamic-pituitary-adrenal axis and the locus coeruleus/sympathetic nervous systems (37). Other systems implicated in stress response include the serotonin, oxytocin, and immune systems as well as genetic and epigenetic factors, and gene-environment interactions that lead to poor cognitive, behavioral health, and health outcomes (37). These mechanisms are likely to be perturbed by the occurrence of trauma leading to psychiatric and SUD comorbidities and/or mid- and later-life medical outcomes.

Both global and domain-specific NP impairment worsened for Profile 2, which was characterized by sexual trauma alone beginning in pre-adolescence/adolescence with comorbid anxiety and SUD. This finding is confirmed by other studies showing that sexual abuse is a stronger predictor than physical abuse of depression and anxiety (30, 38, 39). Prior cross-sectional and longitudinal findings suggest that adolescents with PTSD exhibit abnormal frontolimbic development, especially reduced gray matter in the prefrontal cortex and decline in hippocampal volume, and disruptions in prefrontal-amygdala and prefrontal-hippocampal connectivity compared to typically developing youth (40). Cisler and Herringa suggest that trauma experienced during adolescence can negatively impact the development of systems underlying emotion regulation, reward processing, learning and decision making, and social cognition (40). These mechanisms may account for the worsening NP functioning we observed in the absence of the development of metabolic or cardiovascular disease found in other profiles. Given that anxiety disorder predominated in Profile 2, it is possible that preadolescent/adolescent sexual trauma followed by development of anxiety and SUD have an especially negative impact on cognition.

Declining NP health was also experienced by Profiles 3 and 4, both of which were characterized by SUDs with the majority being polysubstance DUD. The association between SUDs and poorer cognitive function is well-documented outside of HIV (28–30). In the context of HIV, SUDs are associated with increased vulnerability to specific cognitive deficits associated with dysfunction in prefrontal-striatal and limbic pathways (41). The prefrontal-striatal network is critical for modulating executive functions such as working memory (42) which has been shown to be a core deficit among HIV-seropositive men with polysubstance use disorders (43). We too found this deficit among women in Profile 3, where co-occurring AUD+SUD was associated with faster declines in attention/working memory than the control Profile. Profile 4 demonstrated faster declines in executive function, processing speed, and verbal fluency compared to the control Profile, although this may represent regression to the mean since Profile 4 had significantly higher executive function and processing speed at baseline. Alternatively, compensatory strategies that supported these cognitive abilities for women in Profile 4 early on (in their 40s) may have declined with age due to substance use. Studies also demonstrate that WLWH with SUDs are more cognitively vulnerable than men with SUDs (44–47). WLWH are particularly vulnerable to verbal memory deficits (48) and substance use has been shown to contribute to these deficits in this population (49, 50).

Only Profile 4, defined by SUDs during lifetime without trauma or MHDs, was associated with declining CD4 levels. While *current* drug use has been repeatedly associated with poor CD4+ T cell recovery in viral-suppressive PLWH on ART (51) less is known about the impact of *former* substance use on immune reconstitution. However, prior research suggests that former drug users who were currently abstinent had lower CD4 increases compared to non-users, controlling for adherent ART use (52, 53). This suggests that a history of substance use without current use may continue to impair viral reconstitution even with ART use.

It is also interesting to note that women in Profile 5, exposed to early childhood trauma without later MHDs or SUDs, did not experience declines on global or domain-specific cognitive measures, suggesting that early trauma alone may not predict poor cognitive outcomes in WLWH. This is confirmed by an earlier cross-sectional analysis of WIHS data (44) which found cognitive difficulties only among those reporting both sexual abuse (including childhood exposures) and probable PTSD. Importantly, women in Profile 5 were the only ones to show increases in BMI, HOMA-IR, and A1C over time, while only Profile 1 showed increases in hypertension. Childhood trauma characterizing both Profiles has been linked to obesity (54, 55), and the comorbidities of hypertension, insulin resistance and diabetes (16, 20, 56–59). Activation of biological stress response systems following childhood trauma and consequent inflammation, combined with psychological, and environmental factors, have been implicated in their development (15, 60).

Finally, it is also worth commenting on possible explanations for why the resilient profile, Profile 5, experienced adverse physical but not cognitive health outcomes. It is important to note that Profile 5 had a higher socioeconomic position, education in particular, compared to other profiles including the control profile (Profile 6). Education is an established protective factor for cognitive health; however, education is also generally protective for physical

health, which Profile 5 did not experience (e.g., increases in BMI, HOMA-IR, and A1C over time). One possibility is that this dissociation could be due in part to some form of high-effort coping that is protective against MHD and cognitive decline but comes at a physical cost. There are likely complex interplays that facilitate resiliency. Ioannidis (61) proposed that resiliency is not facilitated by any single biomarker after exposure to early childhood trauma but rather that resiliency following childhood trauma is a result of complex processes stemming from the micro level (e.g., genes, molecules, cells, and brain circuits) to the macro level such as environmental factors (e.g., social support).

With respect to limitations, our use of a longitudinal cohort means that our results may not be generalizable to the U.S. population of WLWH. Second, we were unable to examine data from HIV-negative women because the psychopathology WIHS substudy was limited to WLWH. Third, is the use of self-report for key study variables such as trauma, MHD, and SUD. Another limitation includes our focus on physical and sexual abuse and not other types of trauma, and our focus on age of onset and not persistence of abuse. Finally, we did not consider the effects of receiving treatment for the comorbidities we studied since this is beyond the scope of the present analysis. Study strengths include the large sample size, diversity of geographic site locations, use of behavioral health diagnostic interviews instead of screening tools, and consideration of the effects of early childhood trauma separate from trauma occurring later in life on cognitive function (12) and other important outcomes.

In conclusion, among WLWH, early childhood trauma is associated with the development of mid- and later life cognitive impairment, metabolic and cardiovascular disorders, and poor HIV disease outcomes, both in the presence and absence of MHD and SUDs. In comparison, effects of trauma with pre-adolescent and adolescent onset appear to be linked to impairment in global and domain specific cognitive function and co-occurring MHD and SUDs but not metabolic, cardiovascular or HIV-related outcomes. MHD and SUD in the absence of trauma have some association with rates of decline in certain cognitive domains (but not cognitive impairment) and SUD impacts immune reconstitution even without current use. While the causal pathways underlying these associations remain poorly understood, hopefully future studies will shed light on processes underlying these impacts on WLWH in middle-age and older adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AIC	Akaike's Information Criterion
ART	antiretroviral
AUD	alcohol use disorder
B	unstandardized beta coefficient
BIC	Bayesian Information Criterion
BMI	body mass index
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
DUD	drug use disorder
FIB=4	Fibrosis-4
GPEG	Grooved Pegboard
HOMA-IR	Homeostasis Model Assessment of insulin resistance
HVLT-R	Hopkins Verbal Learning Test–Revised
LCA	latent class analysis
LNS	Letter-Number Sequencing
MHD	mental health disorders
NP	neuropsychological
PLWH	people living with HIV
PTSD	post-traumatic stress disorder
SDMT	Symbol Digit Modalities Test; SE=standard error
SUD	substance use disorders

TMT	Trail Making Test
U.S.	United States
WIHS	Women's Interagency HIV Study
WHM-CIDI	World Mental Health Composite International Diagnostic Interview
WLWH	women living with HIV

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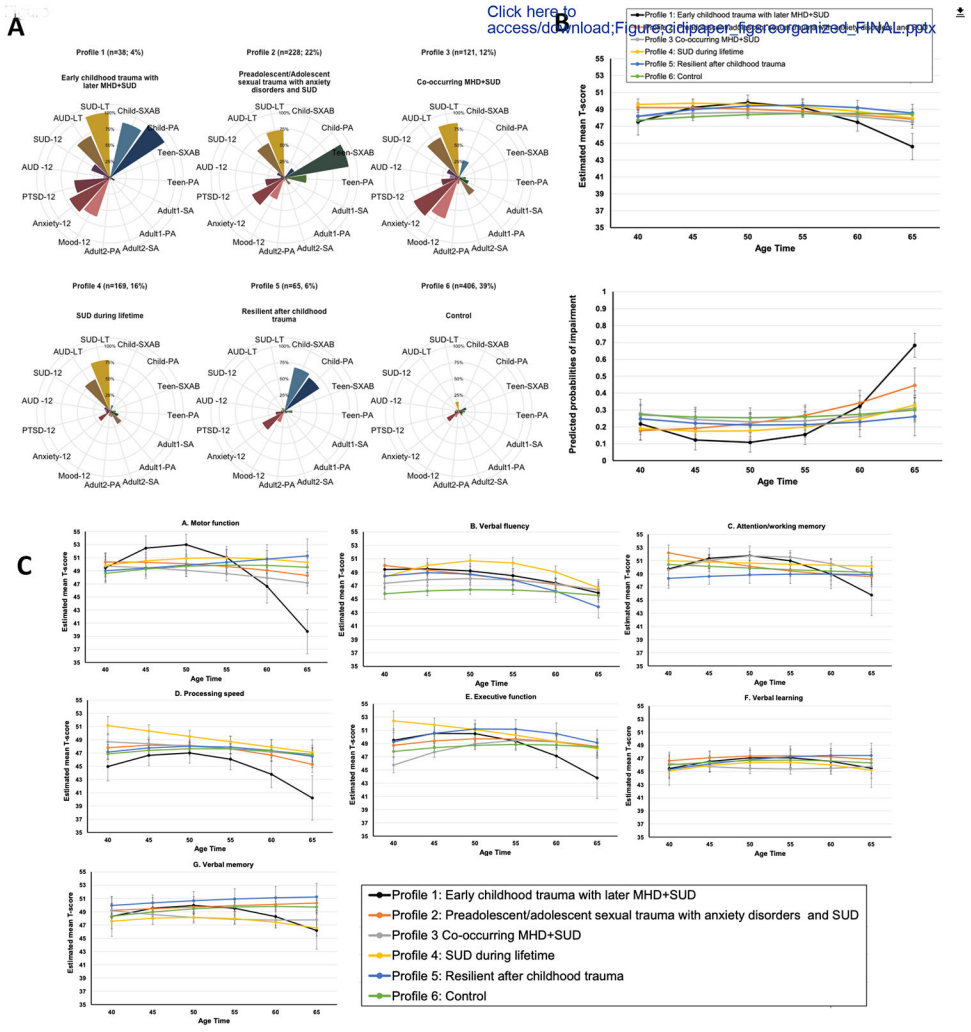

Figure 1.

(A) Six-latent class model of the occurrence of trauma, mental health disorders (MHD), and substance use disorders (SUD) in women living with HIV (WLWH). Probability of age of trauma onset (sexual and physical abuse), MHD, and SUD. −12 past year; -LT=lifetime; PTSD=post-traumatic stress disorder; PA=physical abuse; SXAB=sexual abuse. **(B)** Profile differences over age-time on continuous (A) and impaired (B) global neuropsychological (NP) function in WLWH. **(C)** Profile differences over age-time on domain-specific cognitive function in WLWH.

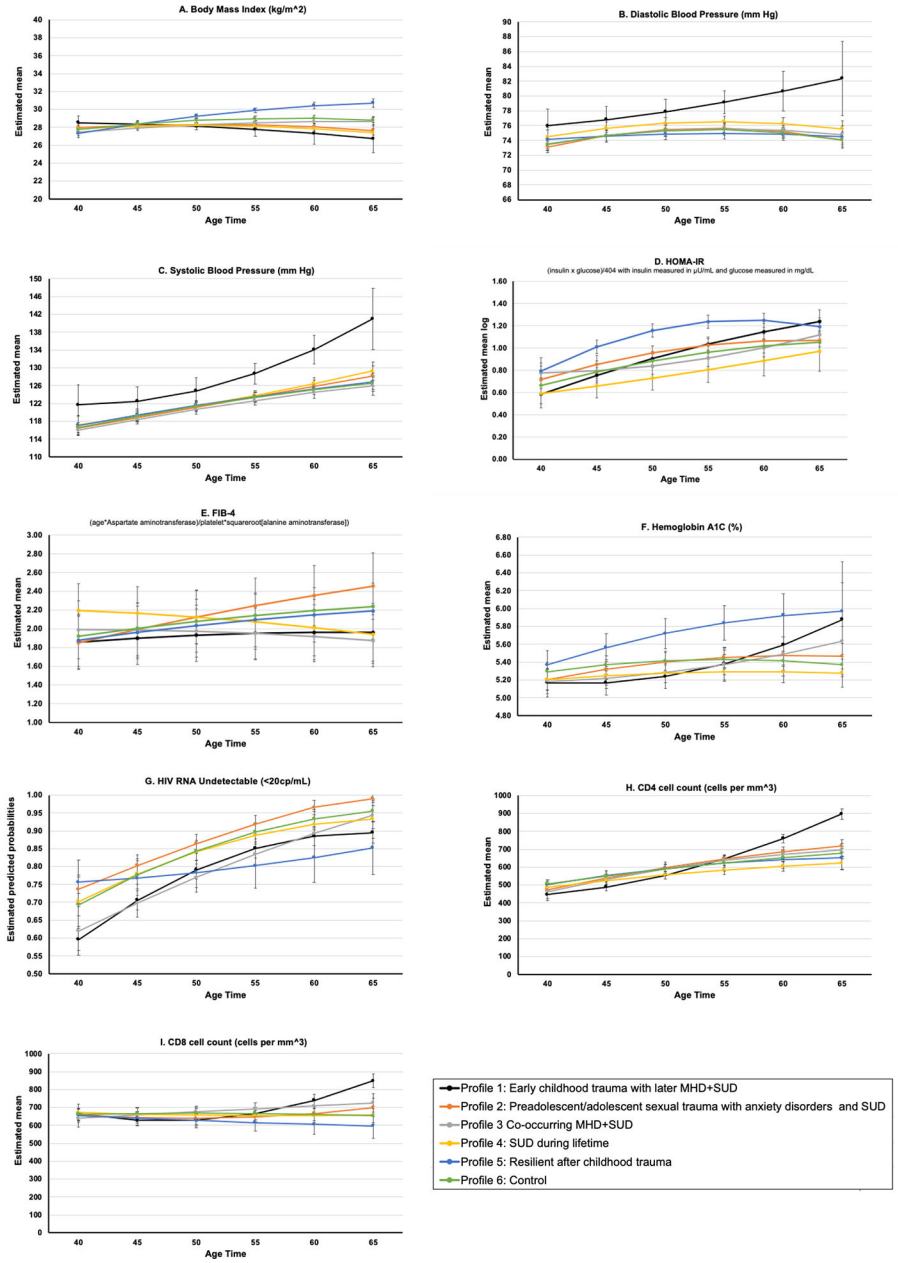

Figure 2.
Profile differences over age-time on medical outcomes in women living with HIV (WLWH).

Table 1.

Sociodemographic, behavioral, and clinical factors of the overall sample of women living with HIV (WLWH) when the World Mental Health-Composite International Diagnostic Interview was conducted.

	N (%)
Sample size	1027
Follow-up time, M (SD)	8.8 (5.8)
Age, M (SD)	48.6 (8.8)
Years of Education	
< high school	339 (33)
high school	327 (32)
> high school	360 (35)
Race/ethnicity	
Black, non-Hispanic	654 (64)
White, non-Hispanic	143 (14)
Hispanic	193 (19)
Other	37 (4)
Marital status	
Married/cohabitate	379 (37)
Previously married	319 (31)
Never married	329 (32)
Annual household income ≤12K/year	466 (45)
Hepatitis C RNA+	223 (22)
Prescribed NC-AE medications	460 (45)
Statin use	156 (15)
Depressive Symptoms, mean (SD)	316 (31)
Antipsychotic use	78 (7)
Antidepressants	128 (12)
Opioid use	239 (24)
Recent	
Heavy alcohol use	132 (13)
Marijuana use	167 (16)
Crack, cocaine, &/or heroin use	51 (5)
Current smoker	388 (38)
Years spent smoking cigarettes, M (SD)	16.8 (14.5)
Body mass index, M (SD)	29.8 (7.9)
Hypertension	435 (42)
Diabetes	232 (23)
cART use+adherence	
yes + ≥95% adherence	678 (66)
yes + <95% adherence	161 (16)
no	187 (18)
Nadir CD4 count in WIHS, median (IQR)	193 (206)

	N (%)
Current CD4 count, mean (SD)	531 (409)
Current CD8 count, mean (SD)	836 (419)
Current CD4/CD8 ratio	0.8 (0.5)
HIV RNA, undetectable	731 (71)
cART duration (years), median (IQR)	12.3 (5.0)
Reported AIDS diagnosis	460 (45)

Note. Depressive symptoms=CES-D ≥16; cART=combined antiretroviral therapy; IQR=interquartile range