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Integrase Inhibitors are Associated with Neuropsychiatric Symptoms in Women with HIV

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Abstract

Objective Women with HIV(WWH) are more likely to discontinue/change antiretroviral therapy(ART) due to side effects including neuropsychiatric symptoms. Efavirenz and integrase strand transfer inhibitors(INSTIs) are particularly concerning. We focused on these ART agents and neuropsychiatric symptoms in previously developed subgroups of WWH that differed on key sociodemographic factors as well as longitudinal behavioral and clinical profiles. WWH from the Women's Interagency HIV Study were included if they had ART data available, completed the Perceived Stress Scale-10 and PTSD Checklist-Civilian. Questionnaires were completed biannually beginning in 2008 through 2016. To examine ART-symptom associations, constrained continuation ratio model via penalized maximum likelihood were fit within 5 subgroups of WWH. Data from 1882 WWH contributed a total of 4598 observations. 353 women were previously defined as primarily having well-controlled HIV with vascular comorbidities, 463 with legacy effects(CD4 nadir < 250cells/mL), 274 aged ≤ 45 with hepatitis, 453 between 35–55 years, and 339 with poorly-controlled HIV/substance users. INSTIs, but not efavirenz, were associated with symptoms among key subgroups of WWH. Among those with HIV legacy effects, dolutegravir and elvitegravir were associated with greater stress/anxiety and avoidance symptoms(P's < 0.01); dolutegravir was also associated with greater re-experiencing symptoms(P = 0.005). Elvitegravir related to greater re-experiencing and hyperarousal among women with well-controlled HIV with vascular comorbidities(P's < 0.022). Raltegravir was associated with less hyperarousal, but only among women aged ≤ 45 years(P = 0.001). The adverse neuropsychiatric effects of INSTIs do not appear to be consistent across all WWH. Key characteristics (e.g., age, hepatitis positivity) may need consideration to fully weight the risk–benefit ratio of dolutegravir and elvitegravir in WWH.

Keywords

HIV; Women; Stress; PTSD; Heterogeneity; Antiretroviral

Introduction

The advent of combination antiretroviral therapy (ART) markedly reduced the incidence of severe central nervous system (CNS) complications such as CNS opportunistic infections and AIDS dementia complex in people with HIV (PWH). As a result of this success, attention has turned to the presence of less severe adverse CNS side effects such as mild cognitive impairment as well as depressive, anxiety, and post-traumatic stress symptoms (e.g., upsetting dreams). In particular, concerns have emerged for the non-nucleoside reverse

transcriptase inhibitor (NNRTI), efavirenz, and the integrase strand transfer inhibitors (INSTI), dolutegravir and raltegravir (de Boer et al. 2016; Bengtson et al. 2017; Borghetti et al. 2017; Elzi et al. 2017; Fettiplace et al. 2017; Hoffmann et al. 2017; Menard et al. 2017; Penafiel et al. 2017; Borghetti et al. 2018; Revuelta-Herrero et al. 2018).

The frequency and severity of developing ART-related CNS adverse events such as depressive symptoms or mild cognitive impairment are highly variable, with differences between ART classes and among individual agents in each class. A number of studies indicate that the impact of INSTIs on cognition for example may not be a class effect. One study demonstrated that starting or switching to dolutegravir or elvitegravir, but not raltegravir, is associated with poorer domain-specific cognitive function in women with HIV (WWH) (O'Halloran et al. 2021). A second study showed that longer dolutegravir exposure, but not other INSTIs, is associated with a poorer cognitive profile in PWH (Amusan et al. 2020).

Although inter-individual variability of drug response and clearance (e.g., variability in DNA sequences of genes critical for drug metabolism) are likely contributors to variability in ART-related CNS adverse events (Abers et al. 2014; Vujkovic et al. 2018), the characteristics of the population under investigation are also likely to be critical. For example, Hoffman et al. (2017) demonstrated higher rates of ART-related CNS adverse events leading to dolutegravir discontinuation were more common in WWH and individuals 60 years of age and older. With respect to efavirenz, sociodemographic factors such as age (≥ 45 years of age) and economic status, medical comorbidities, as HIV-related clinical characteristics (CD4 count of < 200cells/mm3, advanced disease stage) are more likely to report having a CNS adverse event(Muche et al. 2020). Limitations of these studies are the statistical approaches (simple stratification, multivariable regression) used to examine risk factors for CNS adverse events.

Our group has leveraged advances in computational modeling and bioinformatics to examine effects of ART agents on CNS adverse events, in particular depressive symptoms and cognition (Rubin et al. 2020; Williams et al. 2020). Using data from the Women's Interagency HIV Study (WIHS), a longitudinal multi-site study of the natural and treated history of WWH, we have been able to identify subgroups of WWH with similar socio-demographic and longitudinal behavioral and clinical characteristics which better represents a more personalized medicine approach. These initial studies demonstrate that the links between ART agents including efavirenz and INSTI-based agents on depressive symptoms and cognition depend on key factors including age, Hepatitis C RNA positivity, and longitudinal patterns of vascular and metabolic factors (hypertension, diabetes) as well as HIV-related clinical factors (CD4 count, HIV RNA, prior AIDS diagnosis)(Rubin et al. 2020; Williams et al. 2020).

Despite our initial work examining effects of ART agents on depressive symptoms and cognition, other CNS adverse events warrant study. In particular, less is known about the associations between ART agents and anxiety and post-traumatic stress symptoms which include feelings of re-experiencing (e.g., upsetting dreams, flashbacks), avoidance (e.g., thoughts, feelings, people), and changes in arousal (e.g., irritability, difficulty sleeping or

concentrating). In general, these symptoms are risk factors for mood and anxiety disorders which are known to be highly prevalent in PWH, particularly women with HIV (WWH) (Penza et al. 2003; Neigh et al. 2009; Heim et al. 2010). However, to date, there are no studies that have evaluated anxiety and post-traumatic stress symptoms as an adverse CNS effect of INSTIs in WWH using a more personalized medicine approach.

Here we examined efavirenz and INSTIs in relation to anxiety and post-traumatic stress symptoms in previously identified subgroups of WWH defined by key sociodemographic and longitudinal behavioral and clinical factors (Rubin et al. 2020; Williams et al. 2020). We hypothesized that these ART agents would be associated with greater symptomatology (anxiety, post-traumatic stress) in some but not all subgroups of WWH. In our prior work, we have seen INSTI drugs to relate to cognition among women with profound legacy effects (CD4 nadir < 250 cells/μL), those primarily aged 36–55 years of age, and among substance users with poorly controlled HIV (Rubin et al. 2020). Efavirenz related to cognition but only among younger individuals (< 45 years of age) with hepatitis C virus. With respect to anxiety and post-traumatic stress symptoms, it is difficult to predict which groups efavirenz and INSTIs would have the greatest effects on these symptoms.

Methods

Study Population

WWH were enrolled in the Women's Interagency HIV Study (WIHS); details of the study design and data collection have been described in detail previously (Barkan et al. 1998; Bacon et al. 2005; Adimora et al. 2018). Briefly, the first three waves of study enrollment occurred between October 1994 and November 1995, October 2001 and September 2002, and January 2011 and January 2013 from Brooklyn NY, Bronx NY, Chicago IL, Washington DC, and Los Angeles and San Francisco CA. A more recent wave of enrollment occurred at sites in Chapel Hill NC, Atlanta GA, Miami FL, Birmingham AL, and Jackson MS) between October 2013 and September 2015. Participants complete semiannual visits which includes physical examinations, biospecimen collection, and a face-to-face interview for the collection of clinical, behavioral, and demographic characteristics.

Administration of two stress measures were initiated in the WIHS in 2008 and subsequently, every 2 years from 2008 through 2016. Therefore, using 2008 as a baseline, a maximum of ten stress measures were available for each WWH.

In the present analysis, only WWH who contributed to data that were collected at all WIHS study visits where ART and stress measures were collected are included. Participants were excluded from analysis if reported ART use "at study visit" and "since last study visit" (~ past 6 months) were discordant, as we wanted to ensure stability on ART drugs for the previous 6 months. Excluded were 3191 of 7789 (41%) observations, thus leaving 4598 observations provided by 1882 WWH for analysis. Not all women contributed the same number of visits (mean number of visits per participant = 2.4; range 1 to 6).

Study participants were previously classified into several subgroups (Williams et al. 2020). Specifically, subgroups were developed by applying parametric latent class trajectory

modelling to sociodemographic (e.g., age) and longitudinal behavioral (e.g., substance use) and clinical data (e.g., CD4 count). This was an essential first step as factors such as age, body mass index, and compliance may differentially affect the neuropsychiatric correlates of ART drugs in WWH. Of the 1882 WWH, 353 women contributing 655 observations were previously identified (Williams et al. 2020) and were from Subgroup 1, a group with the highest frequency of women with undetectable HIV RNA (49% had < 500cp/mL) and vascular and metabolic comorbidities (46% with hypertension; 11% with diabetes). There were 453 women contributing 1239 observations from Subgroup 2, a group with the highest frequency (61%) of women with CD4 nadir < 250cells/μL. There were 274 women contributing 736 observations from Subgroup 3, a group where 90% were ≤ 45 years of age and had the highest prevalence of hepatitis C (31%). There were 453 women contributing 1056 observations from Subgroup 4, a group where 68% were between 36 and 55 years of age. Finally, there were 339 women contributing 912 observations from Subgroup 5, a group that had the highest percentage of crack, cocaine, and/or heroin use (21%), current smokers (56%) and the worst HIV-related clinical characteristics (67% CD4 nadir < 250cells/μL, 70% current CD4 count < 250cells/μL, 56% with HIV RNA > 5000 cp/mL, and 30% with a prior AIDS diagnosis). Thus, the names of each subgroup were: Subgroup 1 (controlled HIV with vascular comorbidities), Subgroup 2 (HIV legacy effects), Subgroup 3 (younger individuals [≤ 45 years] with hepatitis C), Subgroup 4 (primarily 36–55 years), and Subgroup 5 (>substance use and poorly controlled HIV). Supplemental Tables 1 and 2 provides characteristics of the WWH by subgroup.

Study Outcomes: Anxiety and Post-traumatic Stress Symptoms

Perceived Stress Scale (PSS-10)—The PSS-10 is a widely used self-report instrument measuring the degree to which situations occurring during the *previous month* in one's life are appraised as stressful and anxiety provoking (Cohen et al. 1983; Cohen and Williamson 1988). Items assess the degree to which respondents have found their lives unpredictable, uncontrollable, and overloaded in the last month. Each of 10 items is rated on a five-point Likert scale (0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often). A total score is computed by summing item responses (reverse scored when needed), with higher scores indicating greater perceived stress/anxiety (scores range from 0 to 40). The Cronbach Alpha in the present sample was 0.87 which indicates excellent internal consistency.

PTSD Checklist-civilian Version (PCL-C)—The PCL-C is a widely used 17-item self-report measure of the DSM-IV symptoms of PTSD (Weathers et al. 1991). The PCL-C asks about symptoms (re-experiencing, avoidance, hyperarousal) in relation to "stressful experiences". Thus, PTSD symptoms may reflect multiple events. The PCL-C is reliable and valid in civilian populations (Ruggiero et al. 2003) and the Cronbach's Alpha in the present sample was 0.94. A total symptom severity score (range = 17–85) is obtained by summing the scores from each of the 17 items. Five of the items assess re-experiencing trauma symptoms (e.g., nightmares or flashbacks concerning the trauma), seven assess avoidance symptoms (e.g., avoidance of thoughts or feelings about the trauma), and five items assess hyperarousal symptoms (e.g., difficulty concentrating, trouble falling or staying asleep). We used the total score on re-experiencing, avoidance, and hyperarousal as primary outcomes.

Covariates

Covariates were selected based on our previous stress-related work in WWH (Rubin et al. 2015, 2016, 2017) and ART study (Williams et al. 2020) and included clinic site, enrollment wave, and sociodemographic (age, race/ethnicity, years of education, employment status, average annual household income, and marital status), behavioral (smoking status, recent alcohol use, marijuana use, crack, cocaine, and/or heroin use), clinical (Hepatitis C antibody positive), and cardiometabolic factors (body mass index, hypertension, diabetes). HIV-related clinical factors included HIV RNA, current and nadir CD4 count, previous AIDS diagnosis, and other ART agents that women were taking that were not of primary interest.

Statistical Analyses

Prior to our primary analyses, we examined all ART agent-covariate interactions on our neuropsychiatric outcomes of interest after running the linear regressions with lasso penalty for all cross-sectional data. In brief, for each ART agent and stress/anxiety and post-traumatic stress symptoms, there were always covariates that significantly interacted (P's < 0.05) with the ART agent thus suggesting effect modification. The number of interactions identified motivated the subgrouping method used in our prior ART studies (Rubin et al. 2020; Williams et al. 2020) and here. We stratified participants into groups with similar sociodemographic, behavioral, and clinical characteristics. Then we examined the association between ART agents and outcomes within each subgroup. The subgrouping is based on longitudinal covariates, not a covariate value at a single point in time. Specifically, among five subgroups of WWH that were previously identified (Williams et al. 2020), a constrained continuation ratio (CCR) model via penalized maximum likelihood was fit (via R package glmnetcr, version 1.0.4) using ART use information as independent variables (X) as well as other covariates (e.g., age, BMI) and each neuropsychiatric outcome as a dependent variable (Y). The Lasso penalty was used in the model for variable selection to enhance the prediction accuracy and interpretability of the model. We searched through a sequence of values to identify the best regularization parameter in the lasso penalty through cross-validation. For robustness of the inference on ART drug and symptoms and the adjustment of multiple comparisons, we employed a bootstrap aggregation procedure to control the false discovery rate (Benjamini and Hochberg 1995). Specifically, we generated 100 bootstrapping datasets by randomly sampling half of the number of observations without replacement. Subsequently, we applied the CCR model to the 100 datasets separately and obtained significant ART-symptom associations for each of the datasets. The association of one specific ART-symptom pair was claimed significant if that drug was selected as an important predictor for that symptom in more than 90 bootstrapping datasets (90%).

Results

On average, each of the subgroups of women had similar scores on the total PSS-10 and on the PCL-C subscale scores (P's > 0.05).

Associations Between ART Drugs and Stress/Anxiety and Post-traumatic Stress Symptoms in WWH

INSTIs, but not efavirenz, were associated with neuropsychiatric symptoms (Table 1). Among those with *HIV legacy effects* (Subgroup 2), use of dolutegravir and elvitegravir were associated with greater stress/anxiety and avoidance symptoms; dolutegravir was also associated with greater re-experiencing symptoms ($P = 0.005$). Elvitegravir also related to greater re-experiencing and hyperarousal symptoms among those women with well-controlled HIV with vascular comorbidities (P's < 0.022). Raltegravir was associated with less hyperarousal, but only among younger women (< 45 years; $P = 0.001$). Notably, none of the INSTIs were associated with stress symptoms among primarily *36–55 year olds* (Subgroup 4) or *substance users with poorly controlled HIV* (Subgroup 5).

Although not of primary interest, other ART drugs used as part of the current first or second line regimens were associated with neuropsychiatric symptoms. Use of NRTIs were associated with less symptoms among some subgroups of WWH (Subgroups 4 and 5). The use of abacavir was only associated with lower hyperarousal among *younger women* (Subgroup 4) whereas tenofovir disoproxil fumarate was associated with lower stress/anxiety only among *substance users with poorly controlled HIV* (Subgroup 5). PIs were also associated with symptoms. Among WWH and *HIV legacy effects* (Subgroup 2), use of atazanavir was associated with lower avoidance and hyperarousal. Conversely, use of atazanavir was associated with higher stress/anxiety and higher avoidance and re-experiencing among *substance users with poorly controlled HIV* (Subgroup 5). None of the NNRTIs were associated with symptomatology.

Discussion

To our knowledge, there are no large-scale studies examining associations between recent ART use and stress/anxiety and post-traumatic stress symptoms in WWH. In the present investigation, we identified associations as expected between each INSTI (elvitegravir, raltegravir, dolutegravir).

and neuropsychiatric symptoms. Also as expected, the association between INSTI drugs and symptoms were not uniform across all WWH. The most vulnerable group of WWH to dolutegravir and elvitegravir were those defined by longitudinal patterns in vascular and metabolic factors and/or HIV-related clinical factors (CD4 nadir, HIV RNA). WWH defined by age (≤ 45 years) showed less symptoms at least with respect to raltegravir. In general, these findings suggest that the variability in ART-related adverse neuropsychiatric events are dependent on key sociodemographic and longitudinal clinical factors.

Our findings are consistent with a number of previous studies demonstrating that INSTIs have been linked to psychiatric symptoms. Specifically, studies report that INSTIs are associated with anxiety, depression, insomnia, nightmares, abnormal dreams, and affect liability following INSTI initiation and thus have been one of the main reasons why individuals stop INSTIs medications (Cohen et al. 2011; Teppler et al. 2011; Madeddu et al. 2012; Abers et al. 2014; de Boer et al. 2016; Fettiplace et al. 2017; Hoffmann et al. 2017; Hoffmann and Llibre 2019). Notably, the majority of previous studies focused

on were men with HIV who self-identified as White or samples of predominately men. Given that the effects of ART depend on factors such as biological sex, age, Sub-Saharan African descent and health status, many of these initial findings cannot be generalized to WWH (Hoffmann et al. 2017; Senneker and Tseng 2021). Based on the present findings, we provide preliminary evidence that use of dolutegravir and evitegravir are associated with greater symptoms, whereas raltegravir is associated with less symptoms. Importantly, the type of symptoms linked to these specific ART agents depends on key factors such as age, vascular and metabolic factors, HIV-related clinical factors, and Hepatitis C positivity, which need to be taken into account.

Unexpectedly, use of efavirenz was not associated with either higher or lower neuropsychiatric symptoms in any of the subgroups. Efavirenz is one of the most common ART agents associated with adverse neuropsychiatric affects including vivid dreams, fatigue, insomnia, and dizziness (Mollan et al. 2014; Bengtson et al. 2017; Arenas-Pinto et al. 2018). Additional work is warranted in WWH to determine whether these findings hold in longitudinal analyses examining cumulative efavirenz exposure, as well as analyses accounting genetic variations in the enzyme CYP2B6 which affect the levels of efavirenz (Ward et al. 2003). CYP2B6 is highly polymorphic and has differing enzyme levels, function, and associated toxicities among individuals from differing racial/ethnic backgrounds (Klein et al. 2005; Zanger et al. 2007; Li et al. 2012). This is particularly important as 64% of WIHS women self-identify as African American. Notably, studies of populations with African American ancestry do not always demonstrate the link between CYP2B6 and neurotoxicity, compared studies of those of European Ancestry (Gounden et al. 2010; Ribaudo et al. 2010). As in the present study, it is critical for racial/ethnic demographic information to be included in analyses evaluating associations between ART and adverse CNS effects.

Secondarily, we also identified that the NRTIs abacavir and tenofovir disoproxil fumarate were associated with less neuropsychiatric symptoms among specific subgroups of WWH. The PI atazanavir was also associated with symptoms albeit the directionality of associations depended on subgroup. These findings are hypothesis generating and warrant further study.

Despite a novel approach to address the association of ART drugs on neuropsychiatric symptoms in the largest female cohort to date over eight years, there are some limitations to the present study. The main limitation is that given the calendar time span of the study, not all WWH had the opportunity to be evaluated on all of the ART agents at all visits, and it is possible that the dynamics between specific patient characteristics and likelihood of exposure to a specific ART agent varied over the course of follow-up. This concern is somewhat mitigated as the distribution of enrollment periods and follow-up time/dropout was not substantially different between the identified cluster groups. Additionally, our findings are only generalizable to WWH and the pattern of associations may not be the same among men with HIV, which we plan to examine in future analyses.

Similar to our previous findings associating ART to depressive symptomatology and cognitive function (Rubin et al. 2020; Williams et al. 2020), we also demonstrate heterogeneity in INSTI-related effects on stress/anxiety and post-traumatic stress symptoms

among WWH. Our findings provide initial, preliminary insights into the importance of key sociodemographic and longitudinal clinical factors when weighing the risk–benefit ratio of dolutegravir and elvitegravir in WWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Edge weights (magnitude of ART drugs and stress-related symptoms score) for each subgroup of women with HIV (WWH)

Drug Class	Edge	Subgroup	Symptom	Weight	Hedges' g method	Cohen's f^2
Primary						
INSTI	Elvitegravir (EVG)	1	Re-experience	1.23	0.66	0.021
			Arousal	0.68	0.51	0.013
		2	Perceived stress	2.56	0.53	0.005
			Avoidance	1.44	0.40	0.003
	Raltegravir (RAL)	3	Arousal	−0.65	0.11	0.001
	Dolutegravir (DTG)	2	Perceived stress	2.27	0.56	0.007
			Avoidance	1.14	0.47	0.005
			Re-experience	0.91	0.44	0.005
Secondary						
NRTI	Abacavir (ABC)	4	Arousal	−0.39	0.17	0.004
	Tenofovir disoproxil fumarate (TDF)	5	Perceived stress	−1.03	0.23	0.012
PI	Atazanavir (ATV)	2	Avoidance	−0.58	0.16	0.004
			Arousal	−0.31	0.15	0.004
		5	Perceived stress	1.18	0.30	0.014
			Avoidance	1.11	0.36	0.020
			Re-experience	0.48	0.26	0.010

NRTI nucleoside reverse-transcriptase inhibitors, *INSTI* integrase strand transfer inhibitor, *PI* protease inhibitor, Positive weight values indicate that the ART agent is associated with more symptomatology whereas negative weight values indicate that the ART agent is associated with less symptomatology. Hedges' g method and Cohen's f^2 are both measures of effect size. Hedges' g method computes the effect size by the standardized group difference (e.g., on an ART agent vs. not), while Cohen's f^2 computes the local effect size, i.e., one variable's effect size within the context of a multivariate regression model