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ORIGINAL PAPER

Starting or Switching to an Integrase Inhibitor-Based Regimen Affects PTSD Symptoms in Women with HIV

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Abstract

As the use of Integrase inhibitor (INSTI)-class antiretroviral medications becomes more common to maintain long-term viral suppression, early reports suggest the potential for CNS side-effects when starting or switching to an INSTI-based regimen. In a population already at higher risk for developing mood and anxiety disorders, these drugs may have significant effects on PTSD scale symptom scores, particularly in women with HIV (WWH). A total of 551 participants were included after completing ≥ 1 WIHS study visits before and after starting/switching to an INSTI-based ART regimen. Of these, 14% were ART naïve, the remainder switched from primarily a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen. Using multivariable linear mixed effects models, we compared PTSD Civilian Checklist subscale scores before and after a "start/switch" to dolutegravir (DTG), raltegravir (RAL), or elvitegravir (EVG). Start/switch to EVG improved re-experiencing subscale symptoms (P's < 0.05). Switching to EVG improved symptoms of avoidance ($P = 0.01$). Starting RAL improved arousal subscale symptoms ($P = 0.03$); however, switching to RAL worsened re-experiencing subscale symptoms ($P < 0.005$). Starting DTG worsened avoidance subscale symptoms ($P = 0.03$), whereas switching to DTG did not change subscale or overall PTSD symptoms (P's > 0.08). In WWH, an EVG-based ART regimen is associated with improved PTSD symptoms, in both treatment naïve patients and those switching from other ART. While a RAL-based regimen was associated with better PTSD symptoms than in treatment naïve patients, switching onto a RAL-based regimen was associated with worse PTSD symptoms. DTG-based regimens either did not affect, or worsened symptoms, in both naïve and switch patients. Further studies are needed to determine mechanisms underlying differential effects of EVG, RAL and DTG on stress symptoms in WWH.

Keywords HIV1 · PTSD · Stress · Antiretroviral · Integrase inhibitors · Women

Introduction

Early intervention with effective antiretroviral therapy (ART) after HIV diagnosis can improve neuropsychiatric outcomes over the lifespan [1–4]. However, older age, ART-related side effects, and viral mutations may cause clinical providers to change ART regimens, which may alter the relationships between neuropsychiatric functioning, viral suppression, and comorbid risk factors [5–7]. Integrase inhibitors (INSTIs), are a newer class of antiretroviral (ART) medications to sustain viral suppression in people living with HIV (PLWH), by interrupt the insertion of HIV-DNA into the host cell's genome [8, 9]. Patients often transition onto INSTI-based regimens from more

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widely used combination regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitor (PI) medications, and these newer regimens have shown improved tolerability and efficacy [10, 11], as well as lower potential of developing resistance [12–14]. However, several early clinical trials of the three available INSTI medications; raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) may affect neural functioning [15]. RAL and DTG in particular tend to be associated with more significant neurocognitive side-effects relative to EVG, and DTG has also been associated with a higher risk of neuropsychiatric side-effects [16], such as sleep disruption [17, 18], and worse symptoms of depression and anxiety [19, 20], often resulting in interruption or discontinuation of the treatment, which jeopardizes continued viral suppression.

Along with increased symptoms of depression and anxiety in PLWH, these individuals area also at higher likelihood of exposure to stressful life experiences, and an enhanced risk of developing symptoms of post-traumatic stress disorder (PTSD) compared to HIV-uninfected individuals [21–24]. Up to 30% of women with HIV (WWH) who experience trauma will be diagnosed with PTSD, an anxiety disorder characterized by three symptom clusters: hyperarousal, re-experiencing, and avoidance [25]. The neurobiological changes underlying these stress symptoms in women generally, include increased amygdala sensitivity [26, 27], increased circulating cortisol [28, 29], and dysregulated frontal-limbic signaling [30]. Early life exposure to chronic stress is associated with decreases in regional brain volumes [31–33] and increases in neuroinflammation [34, 35], both of which have been associated with poorer clinical neuropsychiatric outcomes, particularly in WWH [36, 37].

Taken together, the evidence suggests INSTI medications may potentially exacerbate PTSD symptoms in certain PLWH through multiple factors. The effects of stress exposures, ART-related neurological effects, and interactions with other medications (ART and non-ART) which may interact with the effects of the drugs to alter brain functioning in WWH, particularly those with a history of stress and trauma exposure. The goal of this study was to examine the effects of starting or switching to (start/switch), an INSTI-based ART regimen, and to better understand the potential differential associations of the individual INSTI drugs, RAL, EVG, and DTG, on prevalence and severity of PTSD symptoms in middle-aged and older WWH. We hypothesized that the differences observed in individual side-effect profiles of these drugs, particularly DTG and RAL, may alter the incidence and severity of PTSD symptoms in WWH. The goal of this study was to better characterize optimal treatment strategies for WWH with a history of stressful life experiences, to understand how ART regimens impact existing neuropsychological symptoms of stress.

Methods

Study Population

Participants were enrolled in the Women's Interagency HIV Study (WIHS); details of the study design and data collection are described in https://wihshealth.org. 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, Bronx, Chicago, DC, Los Angeles, and San Francisco. 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 include physical examinations, biospecimen collection, and a face-to-face interview for the collection of clinical, behavioral, and demographic characteristics. Two stress measures, the PTSD Checklist-Civilian (PCL-C) and Perceived Stress Scale (PSS) were added to in the WIHS battery in 2008, and subsequently every two years thereafter through 2016.

Outcome Measures

PTSD Checklist-Civilian version is a widely used 17-item self-report measure of the DSM-IV symptoms of PTSD [38]. Five of the 17 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). Items within each symptom category were summed to create a total symptom severity score for each subscale, re-experiencing, avoidance, and hyperarousal, which comprised the three primary outcomes.

Statistical Analysis

We first compared the mean and standard error for each item in the PTSD Checklist-Civilian version (PCL-C) and three subscale scores (re-experiencing, avoidance, hyperarousal) before and after a "start/switch" to any (combined) INSTI or to a specific INSTI (DTG, EVG, RAL). Using linear mixed effects models (LMEMs), we first compared PCL-C subscale scores before and after a "start/switch" to any INSTI, controlling for relevant covariates (e.g., age, race, BMI, HIV-RNA). Next, we examined the effects of each INSTI separately (DTG, EVG, RAL) using the same statistical approach. LMEMs were fitted in R 3.5.2, and a P-value < 0.05 was statistically considered significant.

Covariates

Covariates of primary interest that were available across the duration of WIHS were included in this analysis. Self-reported sociodemographic factors included age, race/ethnicity, years of education, employment status, annual household income, and marital status, current smoking status, recent alcohol use, marijuana, and crack, cocaine, and/or heroin use. Clinical factors such as Hepatitis C antibody status, body mass index (BMI), hypertension (systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90, self-report or use of anti-hypertensive medications), and diabetes (self-reported anti-diabetic medication or any of fasting glucose ≥ 126 or HgbA1C > 6.5% or self-reported diabetes) were also included. HIV-related variables included HIV RNA (copies/ml), CD4 + T cell count (current and nadir; cells per mm^3), and previous self-reported AIDS. In addition, an indicator variable for all INSTIs as a combined drug class was included in the analysis.

Results

Of 3567 WWH enrolled in Women's Interagency HIV Study (WIHS) from 2006 to 2019, 1036 participants completed at least one study visit before and after starting/switching to an INSTI-based ART regimen. Of these, 551 WWH were included in this sub-analysis. Fourteen percent (14%) of the sample were ART naïve before initiation of an INSTI-based regimen ("Start"), and the remaining 86% "Switched" to an INSTI-based regimen from primarily either a combined protease inhibitor (PI) + nucleoside reverse transcriptase (NRTI) –based regimen, or a combined NNRTI + nucleoside reverse transcriptase (NRTI) –based regimen.

Detailed demographic, clinical, and screening characteristics of these 551 subjects can be found in Tables 1, 2, stratified by ART status (ART-naïve *versus* not ART-naïve) before starting, or switching to an INSTI-based regimen. Prior ART regimens (if any) of the analytic subsample are detailed in Table 3. The mean age of the sample was 48 years old, and approximately 64% identified as black or African-American. Approximately 60% of the sample reported a lifetime exposure to physical violence, and 45%, a lifetime exposure to sexual abuse. The majority of the sample (83%) had a current median CD4 count of ≥ 250 cells/mL, while only 31% of the sample had a median CD4 nadir count of ≥ 250 cells/mL. Approximately 27% of the sample had an undetectable HIV viral load (< 50 copies/mL) at their initial study visit, and half (50%) of the sample reported a prior AIDS diagnosis.

ART-Naïve to INSTI-Based Regimen ("Start")

In the subset of participants (14%) who were ART-naïve before their first WIHS visit, 23% of the sample had a PCL-C total score indicating a presumptive PTSD diagnosis before initiating any INSTI-based regimen, and 18% after. Starting an EVG-based regimen in particular, resulted in a smaller proportion having a presumptive PTSD diagnosis (9%, P < 0.08). Starting an ART regimen including RAL was associated with a trend-level improvement (decreased incidence or severity) of re-experiencing sub-scale scores ($P = 0.091$), and a significant improvement in hyperarousal sub-scale scores ($P = 0.037$) (Fig. 1a). Starting an ART regimen including DTG was associated with a trend of worsening of "re-experiencing" sub-scale scores ($P = 0.073$) and a significant worsening of arousal sub-scale scores ($P = 0.039$).

NNRTI + NRTI-Based to INSTI-Based Regimen ("Switch")

In the subset of participants (29%) who were stable on an NNRTI + NRTI-based regimen before their first WIHS visit, 16% of the sample had a PCL-C total score indicating a presumptive PTSD diagnosis before initiating and any INSTI-based regimen, and 18% after. None of the individual drugs had any effect on PTSD symptoms in any group after switching onto an INSTI-based regimen. Those Switching to an ART regimen based on RAL was associated with a worsening of re-experiencing sub-scale scores ($P = 0.005$), and a trend-level worsening of symptoms in the avoidance cluster ($P = 0.061$) (Fig. 1b). DTG was not associated with changes in PCL-C scores across any of the three sub-scales (P's > 0.400); and EVG was associated with a trend-level improvement in hyperarousal sub-scale scores ($P = 0.076$).

Of participants using a NNRTI + NRTI-based regimen before the switch, the majority of these (73%) were on a previous regimen including efavirenz (EFV). Due to existing data showing significant neuropsychiatric side-effects of this drug [39–42], we conducted a sub-analysis to evaluate the effects of switching from EFZ in particular, to any INSTI-based regimen. In this subset, switching to an EVG-based regimen was still associated with trend-level improvement on the avoidance sub-scale ($P = 0.053$). Switching from an EFZ-based to a RAL-based regimen however, significantly worsened symptoms on the re-experiencing sub-scale ($P = 0.019$), with a large effect size (d = 1.405) relative to the other subgroups (Fig. 2). Switching to RAL also resulted in a trend-level worsening in avoidance sub-scale scores ($P = 0.085$). Switching from EFZ-based regimen to a DTG-based regimen still had no significant effects on any PCL-C symptom sub-scale (P's > 0.100).

Table 1 Demographic, behavioral, and clinical characteristics of art-naïve participants before "start" of integrase inhibitor-based regimen

Variable	INSTI overall (n = 79) N (%)	EVG (n = 22) n (%)	RAL (n = 29) n (%)	DTG (n = 28) n (%)
Age, median (IQR)	46 (17)	47 (17)	46 (14)	45 (17)
Years of education				
Less than high school	25 (32)	3 (14)	12 (41)	10 (36)
High school	24 (30)	10 (45)	6 (21)	8 (29)
College or above	29 (37)	8 (36)	11 (38)	10 (36)
Race/ethnicity				
White, non-hispanic	12 (15)	3 (14)	4 (14)	5 (18)
White, hispanic	4 (5)	1 (5)	2 (7)	1 (4)
Black, non-hispanic	53 (67)	16 (73)	15 (52)	22 (79)
Black, hispanic	1 (1)	0 (0)	1 (3)	0 (0)
Other, hispanic	8 (10)	2 (9)	6 (21)	0 (0)
Asian or Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
Native American or Alaskan	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (1)	0 (0)	1 (3)	0 (0)
Average annual household income				
< $6000	18 (23)	5 (23)	7 (24)	6 (21)
$6001–12,000	33 (42)	6 (27)	10 (34)	17 (61)
$12,001–18,000	4 (5)	0 (0)	3 (10)	1 (4)
$18,001–24,000	4 (5)	3 (14)	1 (3)	0 (0)
$24,001–30,000	4 (5)	1 (5)	1 (3)	2 (7)
$30,000–36,000	3 (4)	2 (9)	1 (3)	0 (0)
$36,001–75,000	8 (10)	4 (18)	2 (7)	2 (7)
> $75,000	5 (6)	1 (5)	4 (14)	0 (0)
Currently employed	28 (35)	11 (50)	10 (34)	7 (25)
Married	23 (29)	7 (32)	10 (34)	6 (21)
Currently smoking	33 (42)	5 (23)	12 (41)	16 (57)
Recent use				
Alcohol, drinks/week, median (IQR)	0.1 (1.8)	0 (0.4)	0 (2.5)	0.5 (6.3)
Marijuana, median (IQR)	19 (24)	2 (9)	8 (28)	9 (32)
Crack, cocaine, and/or heroin	5 (6)	0 (0)	1 (3)	4 (14)
Hepatitis C RNA positive	16 (20)	1 (5)	6 (21)	9 (32)
Body Mass Index (kg/m^2), median (IQR)	27.6 (11)	32.3 (11)	26.5 (8)	26.8 (11)
Hypertension	28 (35)	8 (36)	10 (34)	10 (36)
Diabetes	21 (27)	3 (14)	10 (34)	8 (29)
CD4 count, median (IQR)				
Current	335 (355)	364 (262)	265 (302)	354 (417)
Nadir	223 (269)	269 (233)	134 (205)	248 (300)
HIV RNA (copies/mL), median (IQR)	7776 (32,913)	168 (17,347)	22,000 (80,783)	6670 (25,055)
Prior AIDS diagnosis	27 (34)	2 (9)	17 (59)	8 (29)
PCL-C total (before), mean (sd)	32.5 (15.2)	30.4 (15.8)	30.7 (12.5)	36.0 (17.2)
PCL-C total (after), mean (sd)	31.8 (14.2)	26.5 (11.3)	28.0 (10.2)	39.8 (16.4)
Presumptive PTSD Dx (before)	18 (23)	5 (23)	4 (14)	9 (32)
Presumptive PTSD Dx (after)	14 (18)	2 (9)	3 (10)	9 (32)
Monocyte efficacy score (after) mean (sd)	52.8 (21.2)	62.5 (0)	54.6 (22.6)	43.2 (24.4)
CNS penetrance effectiveness Score (after), mean (sd)	7.6 (1.6)	6.1 (0.6)	7.4 (1.5)	8.8 (1.1)

ART antiretroviral therapy, *INSTI* integrase inhibitors, *RAL* raltegravir, *EVG* elvitegravir, *DTG* dolutegravir, *PI* protease inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *CNS* central nervous system, *PCL-C* PTSD checklist-civilian

Table 2 Demographic, behavioral, and clinical characteristics of sample before "switch" to integrase inhibitor-based regimen

Variable	INSTI Overall (n = 472) N (%)	EVG (n = 132) n (%)	RAL (n = 130) n (%)	DTG (n = 210) n (%)
Age, median (IQR)	49 (12)	48 (12)	48 (11)	50 (12)
Yeas of education				
Less than high school	154 (33)	38 (29)	46 (35)	70 (33)
High school	148 (31)	47 (36)	39 (30)	62 (30)
College or above	170 (36)	47 (36)	45 (35)	78 (37)
Race/ethnicity				
White, non-hispanic	69 (15)	11 (8)	24 (18)	34 (16)
White, hispanic	25 (5)	7 (5)	10 (8)	8 (4)
Black, non-hispanic	311 (66)	97 (73)	80 (62)	134 (64)
Black, hispanic	6 (1)	1 (1)	0 (0)	5 (2)
Other, hispanic	39 (8)	7 (5)	11 (8)	21 (10)
Asian or Pacific Islander	3 (1)	2 (2)	1 (1)	0 (0)
Native American or Alaskan	4 (1)	2 (2)	0 (0)	2 (1)
Other	15 (3)	5 (4)	4 (3)	6 (3)
Average annual household income				
< $6000	48 (10)	14 (11)	15 (12)	19 (9)
$6001–12,000	173 (37)	48 (36)	50 (38)	75 (36)
$12,001–18,000	77 (16)	24 (18)	21 (16)	32 (15)
$18,001–24,000	47 (10)	15 (11)	9 (7)	23 (11)
$24,001–30,000	19 (4)	6 (5)	4 (3)	9 (4)
$30,000–36,000	25 (5)	5 (4)	6 (5)	14 (7)
$36,001–75,000	54 (11)	18 (14)	16 (12)	20 (10)
> $75,000	29 (6)	2 (2)	9 (7)	18 (9)
Currently employed	165 (35)	47 (36)	44 (34)	74 (35)
Married	146 (31)	33 (25)	42 (32)	71 (34)
Currently smoking	172 (36)	54 (41)	53 (41)	65 (31)
Recent use				
Alcohol: drinks/week, median (IQR)	0 (0.9)	0 (1.7)	0 (0.2)	0 (1.0)
Marijuana	85 (18)	25 (19)	20 (15)	40 (19)
Crack, cocaine, and/or heroin	26 (6)	8 (6)	7 (5)	11 (5)
Hepatitis C RNA positive	89 (19)	14 (11)	31 (24)	44 (21)
Body Mass Index (kg/m^2), median (IQR)	29.3 (9.5)	30.9 (9.7)	28 (9.2)	30 (10.2)
Hypertension	220 (47)	68 (52)	48 (37)	104 (50)
Diabetes	103 (22)	27 (20)	22 (17)	54 (26)
CD4 count, median (IQR)				
Current	594 (412)	630 (376)	493 (409)	622 (397)
Nadir	214 (251)	283 (271)	409 (145)	397 (227)
HIV RNA (copies/mL), median (IQR)	20 (69)	< 20 (28)	49 (1562)	< 20 (28)
Prior AIDS diagnosis	179 (38)	27 (20)	70 (54)	82 (39)
PCL-C Total (before), mean (sd)	32.0 (14.3)	32.9 (14.0)	30.4 (13.9)	32.6 (14.8)
PCC-C Total (after), mean (sd)	31.2 (13.9)	30.1 (13.2)	31.6 (13.3)	31.6 (14.8)
Presumptive PTSD Dx (before)	77 (16)	19 (14)	19 (15)	39 (19)
Presumptive PTSD Dx (after)	75 (16)	17 (13)	21 (16)	37 (18)
Monocyte efficacy score (before) mean (sd)	87.8 (32.4)	92.0 (31.4)	86.3 (36.1)	86.0 (30.3)
Monocyte efficacy score (after) mean (sd)	52.8 (24.1)	63.7 (9.8)	53.2 (28.4)	45.8 (25.1)
CNS penetrance effectiveness Score (before) mean (sd)	7.8 (1.6)	7.4 (1.2)	8.0 (1.9)	7.8 (1.5)
CNS penetrance effectiveness Score (after) mean (sd)	8.1 (1.8)	6.3 (0.9)	8.7 (2.0)	8.8 (1.2)

ME score is calculated according to Table 1 in [44]

ART antiretroviral therapy, *INSTI* integrase inhibitors, *RAL* raltegravir, *EVG* elvitegravir, *DTG* dolutegravir, *PI* protease inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor

Table 3 Participant ART regimens in use before INSTI-based regimen start or switch

Previous ART therapy	INSTIs overall (n = 551) N (%)	EVG (n = 154) N (%)	RAL (n = 159) N (%)	DTG (n = 238) N (%)
NNRTI based	160 (34)	69 (52)	24 (18)	67 (32)
PI based	278 (58)	54 (41)	88 (68)	136 (65)
Others	34 (8)	9 (7)	18 (14)	7 (3)
EFV before switch/start				
EFV	117 (25)	54 (41)	19 (15)	44 (21)
No EFV	355 (75)	78 (59)	111 (85)	166 (79)

INSTI integrase inhibitors, *RAL* raltegravir, *EVG* elvitegravir, *DTG* dolutegravir, *EFV* efavirenz, *PI* protease inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *EI* entry inhibitor

NNRTI + PI-Based to INSTI-Based Regimen ("Switch")

The majority of the sample (50%) were stable on an NNRTI + PI-based regimen before their first WIHS visit (Fig. 1c). Switching to an EVG-based regimen was associated with improvement in re-experiencing sub-scale scores ($P = 0.020$), but neither RAL nor DTG produced significant changes in any PCL-C sub-scale score (P's > 0.100).

We additionally evaluated the effects among participants (n = 48) who started or switched to the INSTI regimen DTG + tenofovir alafenamide (DTG + TAF). Aside from a trend-level increase in the arousal sub-scale score in the participants who started DTG + TAF ($P = 0.096$), there were no statistically significant effects on any of the three composite sub-scale scores (P's > 0.100).

We additionally analyzed our data to evaluate CNS Penetrance Effectiveness Score (CPE) [43] and Monocyte Efficacy (ME) Score [44], to determine whether these measures may be related to changes in PSTD symptoms seen in our participants who were switching from a previous ART regimen. We found a significant decrease in ME in all participants who switched to an INSTI based regimen (Ps < 0.001), regardless of drug (RAL, EVG, or DTG). There was also a significant effect of switching and INSTI-based regimen on CPE score, which was significantly higher after the switch (Ps < 0.001). However, these significant changes in ME and CPE were not correlated with any PTSD measure (Ps > 0.1) (Supplemental Figs. 1 & 2).

Discussion

Individual ART regimens are often as heterogeneous as the individuals who take them, in some cases complicating the careful balance between the intended effects of the drug on the HIV virus and unintended side-effects on the CNS and periphery. In this study, we determined that start or switch to a regimen including at least one INSTI medication, affected PTSD symptoms in WWH, depending on the drug in question. EVG was associated with improved re-experiencing symptom scores in WWH who started or switched to an INSTI-based regimen, and improved avoidance symptom scores in WWH who switched to an INSTI-based regimen from other regimens (mainly PI- and NNRTI-based). RAL's effects on symptoms were more modest, associated with improved arousal symptom scores only in the formerly ART-naïve participants, and was associated with worsening symptom scores in the participants switching from other regimens. DTG, however stood out, having either no significant relationships, or being associated with worse avoidance symptom scores. This variable pattern of effects of this drug class, suggests there may be subtle neurochemical differences in the mechanisms underlying these medications' off-target effects, warranting further studies.

Early initiation and stability of ART is well known to be associated with better psychiatric and neurological outcomes in PLWH [45, 46], compared to those on less effective combinations and those less medically adherent patients. Even in those who diligently take their ART, despite best practices, side-effect profiles can still change over time, in particular in those individuals more vulnerable to the added effects of stressful or traumatic experiences over the lifespan. Inevitably, there may be multiple reasons to change a given ART regimen to maintain suppression, and better understanding of how these drugs affect neurological and psychiatric outcomes is crucial to prevent exacerbating these symptoms unnecessarily.

Initiation of an INSTI based regimen in a treatment-naïve individual, could potentially avoid some of the challenges associated with older NNRTI- or PI-based regimens: higher chance of developing drug resistance [5, 47, 48], increased pill burden, [49, 50], or peripheral and systemic side effects on cardiovascular, kidney or liver function [11]. Similarly, switching to an INSTI-based regimen from a different, less effective ART regimen, may also change side-effect profiles even in long-term HIV-patients. However, these changes may be better attributed to the withdrawal of the effects of the prior regimen than effects of the new regimen, at least in the short-term, particularly those including the NNRTI, efavirenz (EFZ). EFZ has

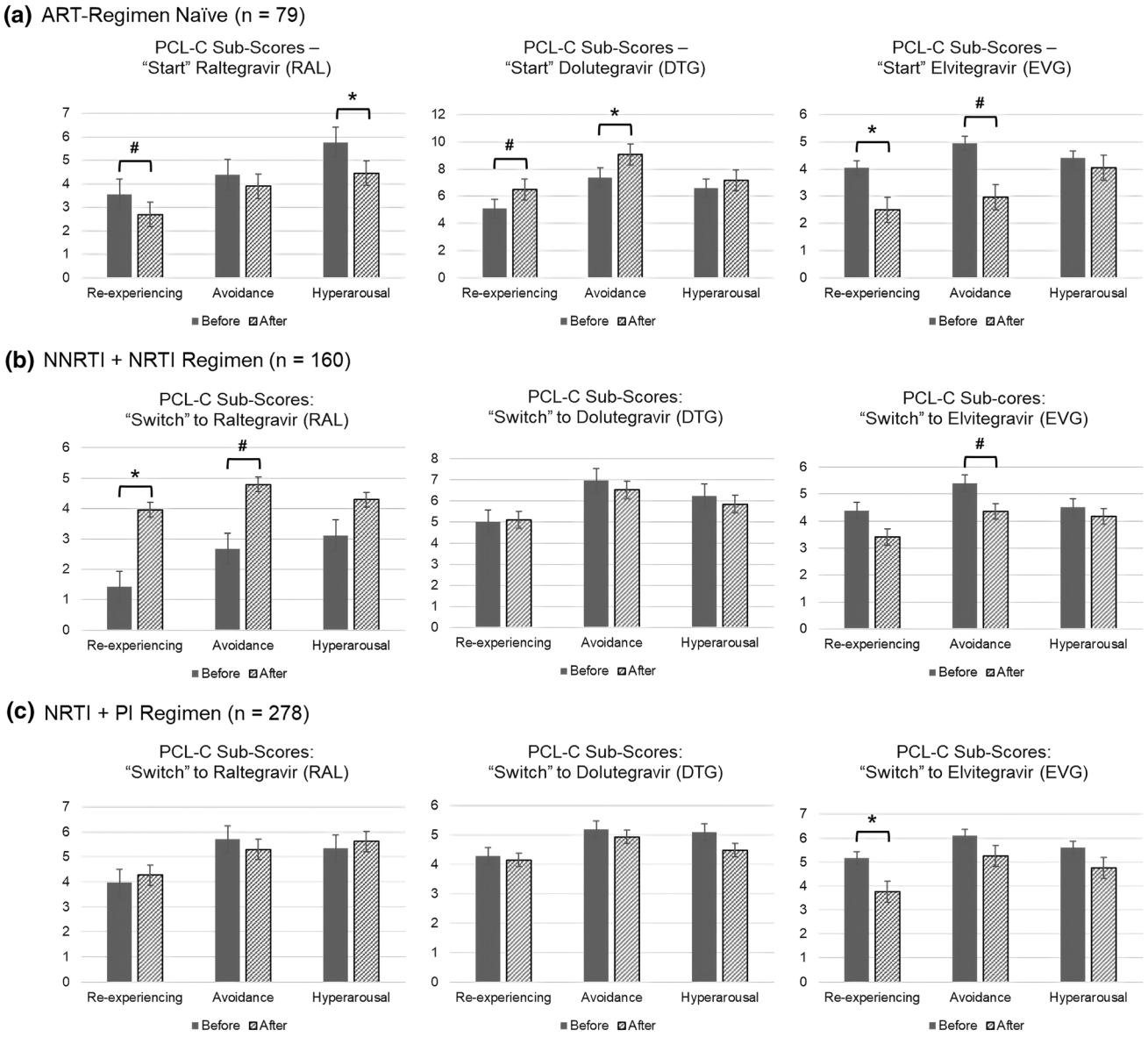

Fig. 1 PCL-C subscale scores: before and after INSTI start/switch, by drug. # = $p < 0.10$, * = $p < 0.05$

previously been associated with significant neurological side-effects [40, 51–56], particularly in older PWH [57, 58]. This theory may explain our results in the subset of participants who switched off a regimen based on EFZ, rather than attributing that change in subscale scores necessarily to starting the INSTI medication.

Women with HIV consistently report higher levels of trauma exposure [22, 59–61] and poorer cognitive and psychiatric outcomes due to the CNS effects of those traumatic experiences [62, 63]. We elected to focus on women in this study, because there have been numerous studies giving evidence that the neurological mechanisms underlying stress and trauma reactivity is subject to sex differences in pre-frontal amygdala and limbic processing [64–66]. Our research group has previously also shown evidence of subtle differences in the effects of ART switches on cognitive performance in men [67] and in women [68]. This current study contributes to that literature, better characterizing the relationship between ART and PTSD symptoms specifically in women with HIV, which may interact with existing HIV-related CNS dysfunction, ultimately influencing cognitive performance as well.

Our data correspond with at least one prior study done in WWH, showing that DTG was associated with nearly a threefold increase in number of neuropsychiatric adverse events relative to EVG or RAL, subsequently leading to

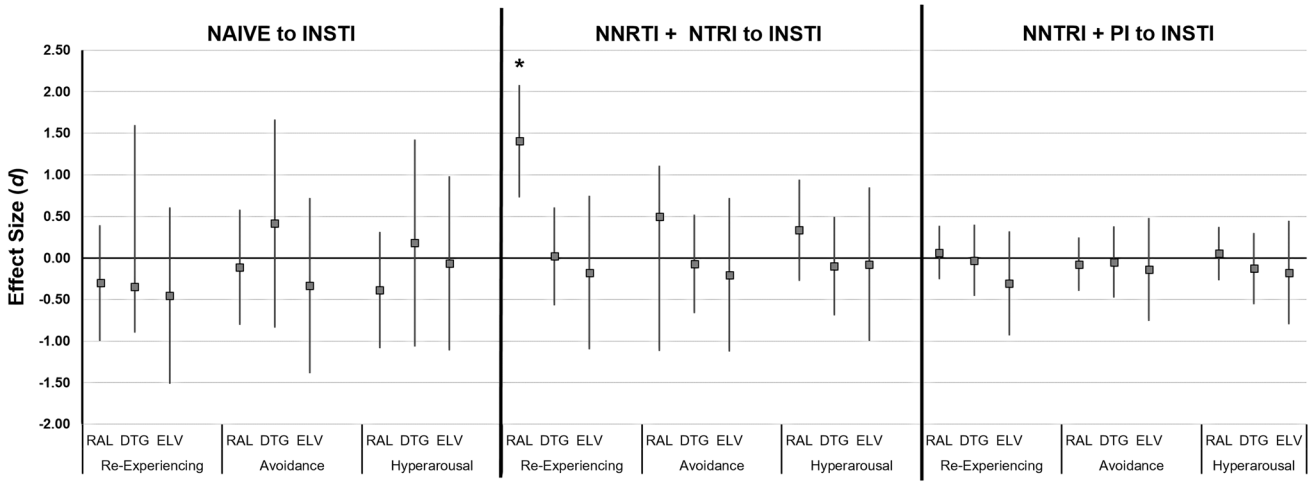

Fig. 2 Effect sizes of PCL-C subscale change scores, by prior regimen. * = $p < 0.05$

discontinuation of that regimen and a switch to another drug class [16]. RAL has also been shown to highly penetrate the CNS [69], as well as cause insomnia in a small number of cases [70], but this potential mechanism does not explain why hyperarousal sub-scale symptoms in our sample improved (decreased in severity/incidence) after start or switch to a RAL-based regimen.

While EVG has been demonstrated to be highly effective, convenient (taken once-daily as opposed to multiple doses per day), with a low incidence of neurological side-effects [71], it is unclear why this particular medication was so successful in symptom improvement, relative to DTG and RAL. The additional effect of prior trauma experience in our sample may potentially confound the adverse effects of this medication on mood and neurological outcomes. In our cohort, the majority of the participants who switched to a regimen including EVG were previously on a NNRTI + NRTI regimen including EFZ, which may explain why this subset of participants experienced the most significant symptom improvements after the switch.

Our exploratory analysis of CPE Score and ME Score before and after switching to an INSTI-based regimen yielded significant effects of INSTIs on both, though these dramatic changes had no impact on any PTSD measure recorded in this cohort. This is a clear mechanistic difference in how INSTIs function peripherally and centrally compared to other regimens, but may not impact mood symptoms. Both of these metrics have been previously associated with cognitive performance [43, 44] but we did not evaluate cognitive performance in this small study.

Limitations

The primary limitation of this study was the relatively small sample size. Data collection in the WIHS Cohort is ongoing, and as additional data points of mood and neurological symptoms before and after regimen starts and switches continue to be analyzed, a clearer understanding of the neurological impact of INSTI medications over time will be able to be better characterized. It is also worth noting that the INSTI class of ART medications is a relatively novel therapeutic approach (developed and approved in the last 5–10 years) relative to NRTI, NNRTI, or PI medications that have been in use for much longer. This may also contribute to the relatively smaller N's of individuals starting or switching to INSTI-based regimens. As larger proportions of PLWH are prescribed INSTI medications as first-line regimens, more answers will be available to better characterize the positive and negative attributes of this drug class. A larger study would also allow us to address the potential that these INSTI effects on PTSD symptom score may be related to the type of trauma (sexual, emotional, physical), or whether these changes in symptoms are clinically significant. We also did not control for the timing of drug regimen switches in these participants: participants were scheduled for two [2] follow-up WIHS visits per year, and though their current regimens were recorded at each WIHS visit, the amount of time between study visits and changes to individual participant's prescriptions were not accounted for. This study design was able to account for acute effects of an ART switch (within approximately 6 months), though evaluation of these effects longitudinally are also warranted.

While we incorporated numerous factors into our analytical modeling for these data to understand the subtle effects of INSTI medications on stress symptoms, the potential additional effects of polypharmacy, or individual variability in both ART and non-ART medications cannot be disregarded. The effects of cobicistat, for instance (PI-class booster co-prescribed with EVG) may also interact positively or negatively with other medications, though to-date there have

been no studies determining whether this medication alone may improve or worsen neuropsychiatric side-effects. Participants in this study were also not blinded or randomized to their change in ART, and it cannot be determined whether this knowledge that they were being put on a potentially better regimen, may have influenced their perception of symptoms after starting or switching to an INSTI-based regimen.

Conclusions

The more significant risk of mood disorders such as PTSD in WWH necessitates a better understanding of the potential neurological and psychiatric effects of changing ART medications, in the interest of successful adherence and sustained viral suppression. The clinical advantages of the INSTI class of medications: efficacious, well-tolerated, reduced pill burden; compared to older NNRTI- or PI-based regimens, may not always necessarily correspond with the most successful profile of CNS side-effects, and this success may also vary from person to person depending on their individual HIV-related and psychiatric history. Future studies to determine the complex relationships between these comorbid factors in WWH, particularly focused on CNS side-effects, will ultimately help to improve adherence and longer-term neurological and behavioral outcomes in persons living with HIV.

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