Common antiretroviral combinations are associated with somatic depressive symptoms in women with HIV

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Objective: While modern antiretroviral therapy (ART) is highly effective and safe, depressive symptoms have been associated with certain ART drugs. We examined the association between common ART regimens and depressive symptoms in women with HIV (WWH) with a focus on somatic vs. nonsomatic symptoms.

Design: Analysis of longitudinal data from the Women's Interagency HIV Study.

Methods: Participants were classified into three groups based on the frequency of positive depression screening (CES-D $\geq$16): chronic depression ($\geq$50% of visits since study enrollment), infrequent depression (<50% of visits), and never depressed (no visits). Novel Bayesian machine learning methods building upon a subset-tree kernel approach were developed to estimate the combined effects of ART regimens on depressive symptoms in each group after covariate adjustment.

Results: The analysis included 1538 WWH who participated in 12 924 (mean = 8.4) visits. The mean age was 49.9 years, 72% were Black, and 14% Hispanic. In the chronic depression group, combinations including tenofovir alafenamide and cobicistat-boosted elvitegravir and/or darunavir were associated with greater somatic symptoms of depression, whereas those combinations containing tenofovir disoproxil fumarate and efavirenz or rilpivirine were associated with less somatic depressive symptoms. ART was not associated with somatic symptoms in the infrequent depression or never depressed groups. ART regimens were not associated with nonsomatic symptoms in any group.

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Conclusions: Specific ART combinations are associated with somatic depressive symptoms in WWH with chronic depression. Future studies should consider specific depressive symptoms domains as well as complete drug combinations when assessing the relationship between ART and depression.

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Introduction

More than three decades after the approval of the first antiretroviral (ART) drug, the treatment of HIV has substantially evolved. The development of safer and potent compounds such as the integrase strand transfer inhibitors (INSTIs) has changed the life course of people with HIV (PWH) who receive treatment. Similarly, the challenges that PWH face in modern times have also changed, with age-related comorbidities and drug toxicities becoming new priorities.

In an aging population of PWH, the longer exposure to ART and the availability of multiple effective treatment options calls for rigorous surveillance of possible drug-related toxicities and side effects. While ART use overall often reduces depressive symptoms [1,2], there is a growing body of research exploring the neuropsychiatric adverse effects (NPAEs) of ART medications, some of which have been associated with depression [2–6]. Depression is about three-times more common in PWH compared to those without HIV [7]. Additionally, depression and other patient-related outcomes are known to be associated with treatment failure in PWH [8,9]. Moreover, the detrimental effect of depression on treatment outcomes may be independent of ART adherence [10] and is associated with cardiovascular outcomes [11,12] mortality [13] and worse cognitive function [14]. In addition, multiple studies have described an association between depression and immune activation [15–17], and more recent evidence suggests that somatic depressive symptoms may contribute more to immune activation in PWH than cognitive/affective (nonsomatic) symptoms [18].

Recent studies suggest that INSTIs are associated with NPAEs including sleep disorders, anxiety, depression, poor concentration, headaches, and slow thinking [19–22]. Cohort studies found higher rates of INSTI discontinuation due to NPAEs in real-life scenarios compared to clinical trials [23–28]. Some studies compared the risk between different INSTIs and found that NPAEs were highest with dolutegravir (DTG) but also seen with elvitegravir (EVG) or raltegravir (RAL) [20]. Moreover, effectiveness data of the fixed-drug combination bictegravir/emtricitabine/tenofovir alafenamide (BIC, FTC, TAF) in treatment-experienced people shows rates of discontinuation of around 10% with NPAEs occurring in two-thirds of cases [27].

While there has been significant progress with respect to ART-related AEs, there is still a significant knowledge gap about how different drug regimens affect the overall risk of individual patients to experience any potential long-term complication. Considering the need to use multiple drugs for the treatment of HIV and the availability of various effective combinations, it is essential to understand the risk that specific, common ART regimens convey. This is exemplified in the context of ART and weight changes. Multiple randomized studies now support the influence that different drugs among INSTIs, EFV, TAF, and TDF can have on weight trajectory, but the eventual weight outcome will depend, among other factors, on the specific combination used [29–32].

In the same way, it is important to examine the effect of different drug combinations on the risk of NPAEs in PWH. For example, observational studies suggest that the co-administration of abacavir and dolutegravir may increase the risk of NPAEs including depression [23,24,33], although this association has not been consistent [26]. Other observational studies have reported associations between TDF and less depressive symptoms [22,34], but these reports did not consider combination regimens as a whole.

In this analysis, we examined the longitudinal relationship between commonly used ART combinations and the frequency of somatic and nonsomatic depressive symptoms in participants from the Women Interagency HIV Study (WIHS). Based on prior literature and observations, we hypothesize that: ART will be associated with depressive symptoms, the magnitude and directionality of the associations will vary according to the specific drug combination used, and INSTI-containing regimens will be associated with more depressive symptoms.

Methods

Study population

Data for the present analysis was obtained from the WIHS. The WIHS study design and procedures have

been described elsewhere in detail [35–37]. Briefly, it is a large multicenter, prospective cohort study of the natural and treated history of women with HIV (WWH). Study enrollment occurred in four waves between October 1994 and September 2015. The first three enrollment waves occurred at five sites in Brooklyn and Bronx, NY; Chicago, IL; Washington, DC; Los Angeles and San Francisco, CA; whereas the final enrollment wave included five additional Southern United States sites in Chapel Hill, NC; Atlanta, GA; Miami, FL; Birmingham, AL; and Jackson, MS.

Participants attended semiannual visits where they self-reported data on sociodemographic status, healthcare utilization, and medical comorbidities. They also underwent a clinical examination, questionnaires [including the Center for Epidemiological Studies Depression scale (CES-D)], and laboratory testing.

We first identified study visits where ART and CES-D information was concurrently collected. There were 3046 participants with a total of 42 777 observations available across WIHS. We only included visits after January 1, 2014 and excluded those that had discordant ART use 'at study visit' and 'since last study visit' (approximately past 6 months) to ensure stability of ART for the previous 6 months. Those with 1–2 visits only were also excluded. A total of 12 924 observations from 1538 participants from January 2014 to September 2016 were included in the final analysis.

ART drugs

For this study, we considered ART drug combinations that were used for 25 or more participants. Medication information was provided by participants via pill bottles or pharmacy print outs.

Depressive symptoms

To measure depressive symptoms, we used the CES-D scale which is a 20-item self-administered questionnaire aimed to measure the frequency of depressive symptoms (somatic, nonsomatic) in the previous week [38]. Somatic symptoms on the CES-D include states of depressive mood with unpleasant or worrisome bodily sensations including changes in sleep, appetite, and concentration [39]. Nonsomatic symptoms include affective symptoms such as anhedonia and negative affect as well as interpersonal symptoms that relate to interpersonal challenges. The CES-D is well validated and commonly used in studies of PWH, often using a score of $\geq$16 to indicate depression [40–44]. Participants were classified into three groups based on the frequency of positive depression screening (CES-D $\geq$16): chronic depression group ($\geq$50% of visits since study enrollment), infrequent depression group (<50% of visits), and never depressed group (no visits).

Covariates

Covariates were selected based, in part, on previous research suggesting association between those covariates and depressive symptoms in WWH [42–45] (Table 1). Those included clinical research site (11 sites), enrollment wave (4 waves), sociodemographic, behavioral, and clinical factors. Sociodemographic factors included age, race, years of education, and annual household income. Behavioral factors included self-reported tobacco use status, and recent alcohol, cannabis, crack, cocaine, or heroin use. Clinical factors included standardized measures of height and weight used to calculate body mass index (BMI), self-reported menopause status, and diabetes (self-reported diagnosis, antidiabetic medication use, or any of fasting glucose $\geq$126 mg/dl or HgbA1c >6.5%). HIV-related factors included HIV RNA (copies/ml), $CD4^+$ T-cell count (current and nadir, cells/μl), and self-reported previous AIDS diagnosis.

Statistical analysis

A novel Bayesian mixed-effects model was developed to estimate the effect of ART drug regimens on depressive symptoms stratified by depression group (chronic depression, infrequent depression, never depressed). Denote Y_{ij} to be the depression score for participant i at visit j, $i = 1, \ldots, n$, $j = 1, \ldots J_i$. Let Z_{ij} denote the drug regimen used by participant i at visit j. For example, Z_{ij} = DTG + TAF + emtricitabine (FTC) if participant i at visit j takes a combination of DTG, TAF, and FTC. Let X_{ij} be a vector including an intercept, time-invariant covariates (e.g., race), and time-varying covariates (e.g., BMI) for participant i at visit j. Denote t_{dij} to be the accumulative exposure time of a single ART drug d for participant i before visit j. We proposed the following mixed-effects model:

$$Y_{ij} = X_{ij}\beta + f(Z_{ij}) + \sum_{d=1}^{D}\gamma_d t_{dii} + b_i \in_{ij},$$

where D is the total number of individual ART drugs that have been used in WIHS. In the proposed mixed-effects model, fixed effects consisted of drug regimens modeled by $f(Z_{ij})$, covariates (see covariates section) effect $X_{ij}\beta$, and accumulative exposure time of all individual ART drugs $\sum_{d=1}^{D}\gamma_d t_{dij}$; while the random effect consisted of a random intercept b_i.

Modeling the effect of drug regimens is challenging due to its high dimensionality. With more than 30 FDA-approved ART drugs, there are thousands of possible drug combinations. Since some drug regimens were frequently used in WIHS but some were rarely used, we did not model drug regimens separately especially for regimens that were only used few times. For example, the drug combination atazanavir (ATV), FTC, and TDF was only used by four participants in nine visits. We proposed a kernel smoother approach to model $f(Z_{ij})$. In particular, we selected a number V of representative drug regimens (e.g. those commonly prescribed in clinical practice), denoted by $z_1, \ldots, z_V$ and defined a drug similarity function $\kappa(Z_{ij}, z_v)$. Then we model

Table 1. Baseline study characteristics in the total study sample and by depression group.

	Total Sample ($N=1538$) mean (SD)	Chronic depression ($N=459$) mean (SD)	Infrequent depression ($N=500$) mean (SD)	Never depressed ($N=579$) mean (SD)	*P*-value
Year of age, *n* (%)					0.307
25–35	158 (10)	44 (10)	62 (12)	52 (9)	
36–45	434 (28)	122 (27)	141 (28)	171 (30)	
45–55	660 (43)	214 (47)	204 (41)	242 (42)	
>55	286 (19)	79 (17)	93 (19)	114 (20)	
Race/ethnicity, *n* (%)					0.031
White (Non-Hispanic)	159 (10)	65 (14)	49 (10)	45 (8)	
African-American (Non-Hispanic)	1113 (72)	319 (69)	356 (71)	438 (76)	
Hispanic	220 (14)	60 (13)	78 (16)	82 (14)	
Other	46 (3)	15 (3)	17 (3)	14 (2)	
Highest level of education: complete high school, *n* (%)	1042 (68)	280 (61)	330 (66)	432 (75)	<0.001
Average household income/year ≤$12 000, n (%)	792 (51)	274 (60)	266 (53)	252 (44)	<0.001
Diabetes, *n* (%)	311 (20)	104 (23)	102 (20)	105 (18)	0.196
HIV RNA > 20 copies/ml, *n* (%)	423 (28)	139 (30)	134 (27)	150 (26)	0.267
Lowest $CD4^+$ (cells/μl), median (IQR)	275 (300.5)	272 (321)	273.5 (296.5)	278 (286.5)	0.980
Current $CD4^+$ (cells/μl), median (IQR)	585 (423.5)	559 (478.5)	574 (397)	613 (411)	0.102
Body mass index (kg/m^2)	31.5 (8.9)	31.5 (9)	31.5 (9)	31.6 (8.8)	0.890
Depressive symptoms (CES-D)	12.5 (11.6)	23.9 (11.3)	11.3 (8.9)	4.4 (4.2)	<0.001
CES-D >16, *n* (%)	464 (30)	340 (74)	124 (25)	0 (0)	<0.001
Recent heavy alcohol use, *n* (%)	253 (16)	89 (19)	90 (18)	74 (13)	0.009
Current smoking status, *n* (%)	579 (38)	226 (49)	173 (35)	180 (31)	<0.001
Recent cannabis use, *n* (%)	296 (19)	124 (27)	85 (17)	87 (15)	<0.001
Recent Crack, cocaine, and/or heroin use, *n* (%)	123 (8)	69 (15)	28 (6)	26 (4)	<0.001

CES-D, Center for Epidemiological Studies Depression scale.

$f(Z_{ij}) = \frac{\sum_{v=1}^{V} \kappa(Z_{ij}, z_v)\alpha_v}{\sum_{v=1}^{V} \kappa(Z_{ij}, z_v)}$. Such a design not only allows sharing of information across different drug regimens so that similar regimens have the similar effect, but also induces parsimony to reduce the high-dimensional regimen space to a manageable size. To incorporate known clinical knowledge (e.g. the drug class information) in the drug similarity function $\kappa(Z_{ij}, z_v)$, we represented each regimen as a tree structure encoding the knowledge such as drug classes and the number of distinct drug classes in each regimen, following our previous work [46]. Lastly, we conduct posterior inference by assigning priors to all unknown parameters and obtaining posterior distributions of all unknown parameters through Markov chain Monte Carlo simulation.

Results

Characteristics of study sample

Our study population included 1538 WWH who participated in 12 924 (mean 8.4) visits from January 2014 through September 2016 (Table 1). At baseline, the mean age was 49.9 years, with 19% of participants >55 years of age. Minority representation was high with 72% of participants identifying as Black and 14% Hispanic. Most participants (68%) completed high school and 51% had an average household income/year of <$12 000. Overall, 16% of participants reported recent heavy alcohol use, 38% current tobacco smoking, 19% recent cannabis use, and 8% recent crack, cocaine, and/or heroin use. The median $CD4^+$ T-cell count at baseline visit was 585 cells/μl, with 60% of participants having a $CD4^+$ cell count >500 cells/μl. The median lowest $CD4^+$ T-cell count was 275 cells/μl. Seventy two percentage of participants had HIV RNA <50 copies/ml at baseline.

Within our study population, 30% ($n=459$) were classified in the chronic depression group, 33% ($n=500$) in the infrequent depression group, and 37% ($n=579$) in the never depressed group. There were significant differences among groups in baseline level of education, average household income, symptoms of depression, and use of tobacco, cannabis, crack, cocaine, and/or heroin as shown in Table 1. Regarding ART, the most common regimens used were: EFV, FTC, TDF (14%); DTG, ABC, 3TC (10%); and RPV, FTC, TDF (8%). Included ART combinations and classifications can be found in Table 2.

Association between ART drug combinations and depressive symptoms in women with HIV

Common ART regimens were significantly associated with depressive symptoms in WWH in the chronic depression group (Fig. 1). No associations were found in the infrequent depression, or never depressed groups. Specifically, the association was present for somatic depressive symptoms, while no associations were found between nonsomatic depressive symptoms and common ART combinations in any group.

Table 2. Common ART regimens.

Regimen	Number of participants ($n = 1538$)	Number of visits ($n = 12\ 924$)
EFV, FTC, TDF	298	1734
DTG, ABC, 3TC	269	1288
RPV, FTC, TDF	194	1056
EVG, COBI, FTC, TAF	323	1046
EVG, COBI, FTC, TDF	206	916
ATV, RTV, FTC, TDF	180	745
DRV, RTV, FTC, TDF	148	636
DTG, FTC, TAF	146	414
DTG, FTC, TDF	112	350
RPV, FTC, TAF	123	343
RAL, FTC, TDF	78	312
BIC, FTC, TAF	129	180
ATV, RTV, ABC, 3TC	37	167
EFV, ABC, 3TC	28	161
DRV, COBI, FTC, TAF	48	129
RAL, ABC, 3TC	25	129
DRV, RTV, ABC, 3TC	29	128
EVG, COBI, DRV, FTC, TAF	36	110
DRV, COBI, FTC, TDF	34	90

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BIC, bictegravir; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand-transfer inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors; PI, protease inhibitors; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

In the chronic depression group, ART combinations including TAF plus COBI-boosted EVG and/or darunavir (DRV) were associated with more somatic symptoms of depression after adjusting for all specified covariates and accumulative exposure time of all individual ART drugs. Specifically, this association was present for: EVG, COBI, FTC, TAF; DRV, COBI, FTC, TAF; and EVG, COBI, DRV, FTC, TAF. No associations were observed with similar regimens that contained TDF instead of TAF (Fig. 1). In addition, no associations were observed for regimens containing DTG or BIC. There were also no significant associations between those receiving boosted regimens containing ritonavir (RTV) as a boosting agent, such as DRV, RTV, ABC, 3TC; ATV, RTV, ABC, 3TC; DRV, RTV, TDF, FTC; and ATV, RTV, TDF, FTC. Combinations containing TDF plus a nonnucleoside reverse transcriptase inhibitor (NNRTI) were associated with less frequent somatic symptoms of depression. Specifically, this pattern was observed for EFV, TDF, FTC; and RPV, TDF, FTC (Fig. 1).

Subsequent analyses were conducted to examine the specific CES-D items that were linked to those combinations (see Fig. 2). The combinations DRV, COBI, FTC, TAF and EVG, COBI, DRV, FTC,

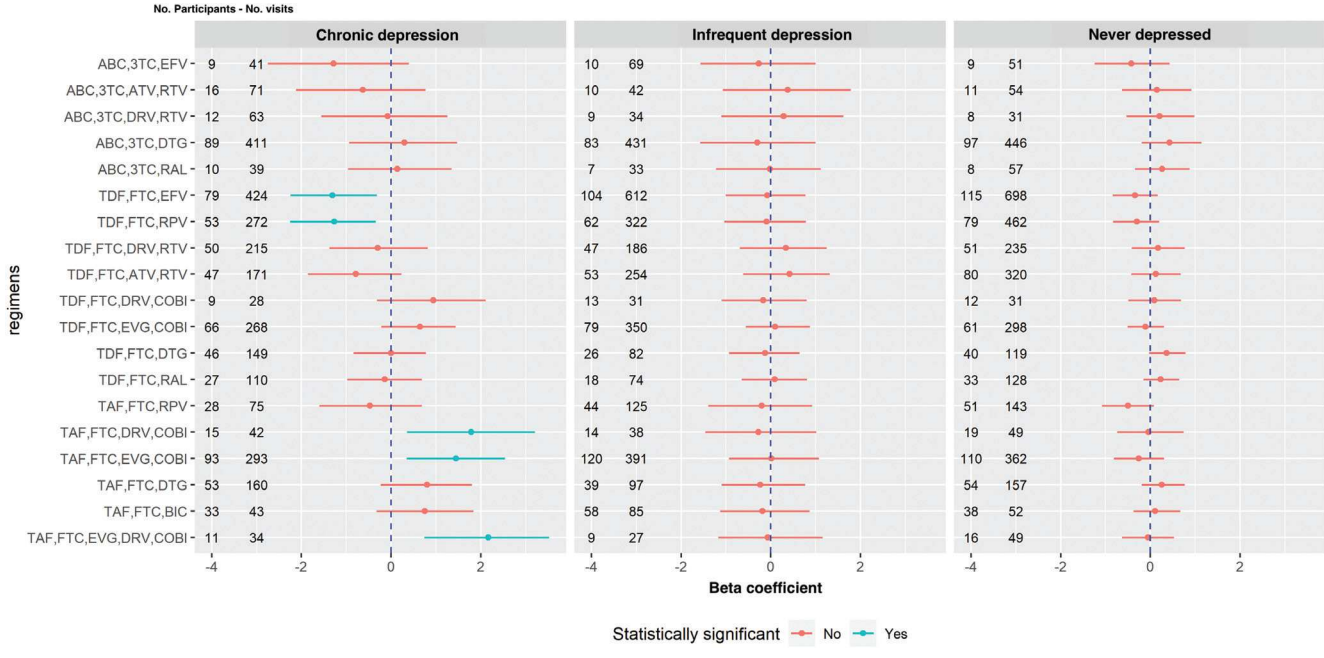

Fig. 1. Combined effects of different ART regimens according to frequency on somatic depressive symptoms by depression group. 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BIC, bictegravir; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. All models controlled for: study enrollment site; age; race/ethnicity; years of education; exposure time of ART drugs used prior to 2014 (drugs used less than 100 times in the database are not included); average household income; $CD4^+$ cell count; body mass index; substance use (crack, cocaine, and/or heroin use; cannabis; tobacco; alcohol); menopausal status; diabetes; and undetectable viral load.

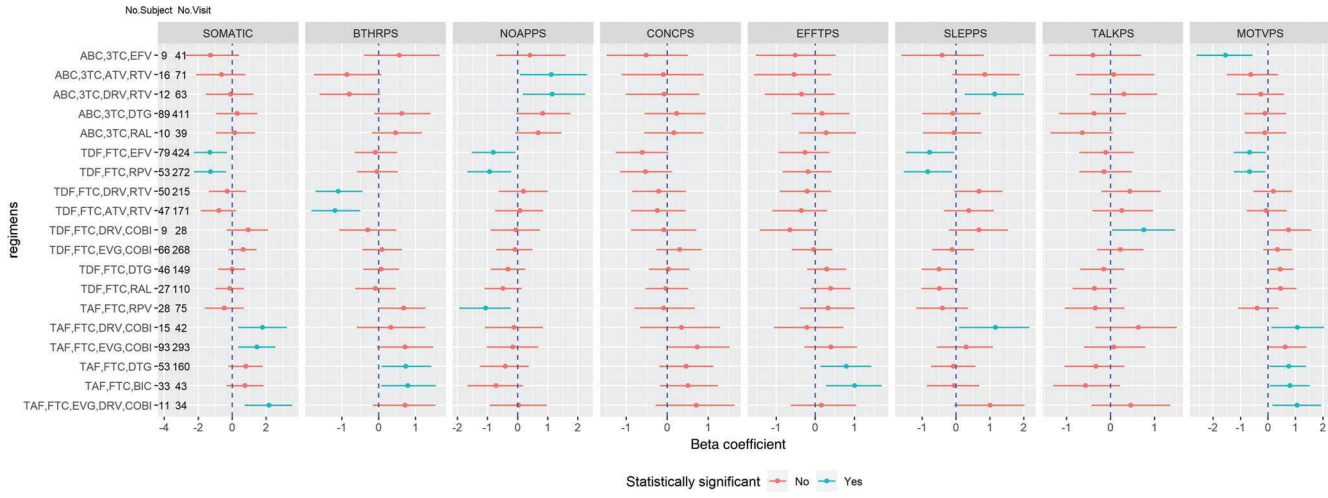

Fig. 2. Item-level analysis of the effects of different ART regimens on somatic depressive symptoms in the chronic-depression group. 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BIC, bictegravir; BTHRPS, I was bothered by things that usually don't bother me; COBI, cobicistat; CONCPS, I had trouble keeping my mind on what I was doing; DRV, darunavir; DTG, dolutegravir; EFFTPS, I felt that everything I did was an effort; EFV, efavirenz; EVG, elvitegravir; MOTVPS, I could not get going; NoAPPS, I did not feel like eating; my appetite was poor; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SLEPPS, My sleep was restless; TAF, tenofovir alafenamide; TALKPS, I talked less than usual; TDF, tenofovir disoproxil fumarate. All models controlled for: study enrollment site; age; race/ethnicity; years of education; exposure time of ART drugs used prior to 2014 (drugs used less than 100 times in the database are not included); average household income; $CD4^+$ cell count; body mass index; substance use (crack, cocaine, and/or heroin use; cannabis; tobacco; alcohol); menopausal status; diabetes; and undetectable viral load.

TAF were associated with higher scores on CES-D item 20 ('I could not get going') while DRV, COBI, FTC, TAF was also associated higher scores on item 11 ('my sleep was restless'). In addition, combinations containing TDF plus an NNRTI, including both EFV- and RPV-based regimens, were associated with lower scores on item 2 ('I did not feel like eating; my appetite was poor'), CES-D item 11, and CES-D 20.

Discussion

There is a growing body of literature describing the association of some ART drugs and drug classes with depression and depressive symptomatology, including the INSTIs. Given its superior efficacy and otherwise good tolerance, INSTIs are the currently recommended first-line therapy in most parts of the world. Here we analyzed data from the WIHS, a cohort of WWH, to evaluate the relationship of the commonly used ART regimens in clinical practice with symptoms of depression. We found that specific ART combinations are associated with somatic symptoms of depression. This association is complex, and the magnitude and directionality vary depending on baseline characteristics and drug combination. This could be due to a number of factors including a modulation of the toxicity risk posed when certain drugs are combined, as well as interactions with concomitant medications, or other off-target effects.

Among participants in the chronic depression group, certain drug combinations were associated with more somatic symptoms of depression, while nonsomatic symptoms showed no significant relationship. For instance, in this group, we observed that combinations including TAF with either COBI-boosted EVG and/or DRV were linked to greater somatic symptoms, whereas there was no difference when TDF was used instead of TAF in similar regimens. Moreover, no association was found with RTV-boosted regimens, un-boosted regimens, or those not containing TAF. We found no association between regimens containing DTG or BIC and symptoms of depression.

Considering these observations, certain scenarios are possible. Like RTV, COBI is a strong inhibitor of cytochrome P450 (CYP) 3A4, the intestinal transporters P-glycoprotein (P-gp), and the breast cancer resistance protein (BCRP), which can lead to increased exposure to any drug metabolized through these pathways. There have been no reports of neurotoxicity of COBI itself although it has not been extensively studied. COBI could play an enhancing effect on the neurotoxicity of other concomitant medications. For example, TAF is a substrate of P-gp and co-administration with a P-gp inhibitor such as COBI has been reported to result in 6–183% increases in TAF exposures. Therefore the TAF dose is typically decreased from 25 to 10 mg when combined with a boosting agent [47,48]. However, TAF achieves greater intracellular concentrations than TDF which could potentially lead to increased risk of toxicity in some

people [49,50]. While some studies have not found biomarker evidence of neuronal injury in people switching TDF to TAF [51], a recent study suggest that compared to TDF, TAF is associated with reduced cellular respiration and reduced mitochondrial ATP production rate, among other bioenergetic measurements, in peripheral blood mononuclear cells (PBMCs) of PWH both *in vitro* and *in vivo* [52]. Mitochondrial dysfunction has a key role in HIV pathogenesis and may be a common denominator driving the pathophysiology of HIV-associated comorbidities. Mitochondrial dysfunction has also been implicated in the pathophysiology of depression [53,54]. On the other hand, COBI is a more selective inhibitor of other CYP enzymes but it can still increase the exposure of multiple other non-ART medications [55] which can contribute to the risk of depressive symptoms.

Additionally, we found that combinations containing TDF plus an NNRTI were associated with fewer somatic symptoms of depression. However, this effect was not observed when NNRTIs were combined with TAF or ABC. These findings, together with the lack of association of TDF plus either an INSTI or a PI with depressive symptoms, suggest that TDF may not have a detrimental effect on the risk of somatic symptoms of depression.

For those drug combinations associating with somatic symptoms of depression, we performed item-level analyses and found that the combinations DRV, COBI, FTC, TAF and EVG, COBI, DRV, FTC,TAF were associated with higher scores on item 20 ('I could not get going'). This item can be related to both somatic (lack of energy) and nonsomatic (lack of motivation, helplessness, problems with concentration) symptoms. Additionally, DRV, COBI, FTC, TAF was also associated with restless sleep. A recent randomized trial suggested favorable results on sleep quality and mood in people with insomnia switching from DTG, ABC, 3TC to DRV, COBI, FTC, TAF [56], however, this was an open-label study with a small, predominantly male population without depression. Moreover, PIs including DRV have been shown to interfere with oligodendrocyte maturation *in vitro* [57], and there is evidence to suggest an implication of these cells in the pathogenesis of depression [58]. Nevertheless, the number of people using DRV, COBI, FTC, TAF in our study was relatively low and conclusions regarding this regimen should be drawn with caution.

The evidence linking the INSTI class, and its individual agents, and depression is conflicting [23,59–63]. However, in a prospective cohort analysis of young male PWH, switching to DTG-based regimens did not have a clear association with worsening of clinically relevant mood symptoms and those with higher depression preswitch had a decrease in depression score after switch [63]. Additionally, an analysis including clinical trials of PWH receiving DTG-based combinations, and a large pharmaco-epidemiology cohort found that depressive symptoms occurred at a low rate, mild to moderate in intensity, typically in the first 6 months, and in those who continued treatment, resolved or improved [62]. This may explain the lack of association between DTG-based combinations and depression in our study. In addition, a potential link between DTG drug levels and central nervous system side effects has been inconsistently described [64,65] and there is some evidence to suggest an influence of genetic polymorphisms on DTG-related NPAEs [66]. Moreover, an analysis of a large prospective cohort of PWH found that, in people with preexisting depression, the risk of depression was higher for EVG compared to DTG [67].

Lastly, EFV, TDF, FTC and RPV, TDF, FTC were associated with lower scores (better function) in items relating to poor appetite, restless sleep, and fatigue/lack of motivation. While this appears paradoxical considering the abundant literature on EFV neurotoxicity, it is now known that the association between EFV and NPAEs is complex and dependent on pharmacokinetic and genetic factors. For example, a correlation between CNS side effects and EFV plasma concentration has been inconsistently described [68]. A pooled analysis of two prospective studies in Uganda found that genetic polymorphisms associated with poor EFV metabolism were associated with a fourfold increase in the odds of depression in those without pre-ART depression but not in the cohort as a whole [69]. Moreover, a 2022 study of 15 people with late-onset EFV neurotoxicity syndrome found that all participants had a slow EFV metabolizer genotype and supra-therapeutic EFV plasma levels [70]. Our findings of a possible protective association of EFV in those in the chronic-depression group may be related to fundamental differences in the population studied (ethnically-diverse women) and does not allow us to draw conclusions regarding a beneficial effect. On the other hand, prescription bias is still possible due to factors unaccounted for in our model. Regarding RPV, TDF, FTC combination, our findings suggest that it has no detrimental association with depressive symptoms and rather a possible improvement which has been previously described [71,72].

It is known that depression in PWH is conditioned by multiple factors including viral-related, HIV-associated inflammation, psychosocial factors, and ART-related neurotoxicity, among others; hence ascertaining the 'net' contribution of ART to this problem has proven difficult. The fact that ART has traditionally been comprised of three-drug combinations adds an additional layer to the problem given the modulatory effect that some drugs may have on others. Here we found that ART can have a different relationship with the risk of symptoms of depression in WWH that depends on the specific drug combination used and the frequency of depressive

symptoms, with a predominant association in those with more symptoms at baseline.

Our study has limitations due to its observational nature, which may introduce channeling bias and overlook unaccounted factors contributing to symptoms of depression. To address prescribing bias, we incorporated in our model a broad range of covariates previously linked to depression, and variables related to depression itself including the frequency of depressive symptoms (overall CES-D score), and the presence of a positive depression screening (CES-D $\geq$16). This was not a prespecified analysis of the WIHS cohort, and data regarding concomitant medications or prior psychiatric diagnoses was not available which can be a significant confounder. Although our analysis is restricted to females, women have been found to have a higher risk of depression than men. Additionally, our dataset lacked direct medication adherence information, but we excluded participants that had discordant ART use 'at study visit' and 'since last study visit' to ensure ART stability for around six months. The CES-D score evaluates the frequency of depressive symptoms in the prior week with higher scores indicating greater symptomatology, and we observed significant associations with ART in the chronic depression group only. Whether these changes represent pathologic, clinically significant events, or rather natural fluctuation of depressive symptoms cannot be ascertained from our study. Finally, direct causality cannot be concluded based on our results. Monitoring the trajectory of depressive symptoms in PWH on ART and depression is advised with attention to those receiving the highlighted drug combinations.

In summary, we found the association between ART and symptoms of depression depends on the baseline frequency of depressive symptoms and the specific combination of drugs used. Some ART combinations may increase the risk of somatic symptoms of depression in WWH. This study provides evidence comparing different specific regimens rather than individual drugs. The goal was to provide data that is readily relevant to clinicians as it compares the regimens more commonly used in clinical practice. These findings also add to a growing body of literature to provide evidence regarding the complex relationship between ART and depression and has potential utility for clinicians when managing the longitudinal care of PWH who may experience depression. Lastly, prospective randomized, double-blind studies are necessary to better understand the relationship between ART and depression in PWH.

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Conflicts of interest

There are no conflicts of interest.

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