Comparative effectiveness of dual vs single-action antidepressants on HIV clinical outcomes in HIV-infected people with depression

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Abstract

Objective—Depression is highly prevalent among people living with HIV/AIDS (PLWHA) and has deleterious effects on HIV clinical outcomes. We examined changes in depression symptoms, viral suppression and CD4 T-cells/mm^3 among PLWHA diagnosed with depression who initiated antidepressant treatment during routine care, and compared the effectiveness of dual-action and single-action antidepressants for improving those outcomes.

Design—Comparative effectiveness study of new user dual-action or single-action antidepressant treatment episodes occurring from 2004–2014 obtained from the Center for AIDS Research Network of Integrated Clinical Systems.

Methods—We identified new user treatment episodes with no antidepressant use in the preceding 90 days. We completed intent-to-treat and per-protocol evaluations for the main analysis. Primary outcomes, were viral suppression (HIV viral load <200 copies/mL) and CD4 T-cells/mm^3. In a secondary analysis, we used the Patient Health Questionnaire-9 (PHQ-9) to evaluate changes in depression symptoms and remission (PHQ<5). Generalized estimating equations with inverse probability of treatment weights were fitted to estimate treatment effects.

Results—In weighted intent-to-treat analyses, the probability of viral suppression increased 16% after initiating antidepressants [95% Confidence Interval (CI) = (1.12,1.20)]. We observed an increase of 39 CD4 T-cells/mm^3 after initiating antidepressants (30,48). Both the frequency of remission from depression and PHQ-9 scores improved after antidepressant initiation. Comparative effectiveness estimates were null in all models.

Conclusions—Initiating antidepressant treatment was associated with improvements in depression, viral suppression and CD4 T-cells/mm^3, highlighting the health benefits of treating depression in PLWHA. Dual- and single-action antidepressants had comparable effectiveness.

Keywords

Introduction

Depression is the most common psychiatric comorbidity among people living with HIV/AIDS (PLWHA) [1] with prevalence estimates ranging from 20%-42% [1–7]. Depression has a detrimental impact on antiretroviral treatment (ART) adherence, viral load and CD4 T-cell count [1]. Therefore, timely delivery of effective depression treatment is important for PLWHA.

Several antidepressants with various pharmacokinetic properties are used to treat PLWHA for depression. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine

reuptake inhibitors (SNRIs), bupropion and mirtazapine are commonly used antidepressants for treating depression in this population [8]. SSRIs (e.g. citalopram) are single–action antidepressants given their selective impact on one neurotransmitter, specifically serotonin [9]. SNRIs (e.g. venlafaxine), bupropion, and mirtazapine are considered dual-action antidepressants because they impact two neurotransmitter systems (e.g. serotonin, norepinephrine or dopamine) in various combinations at the same time [9].

Both single-action and dual-action antidepressants are efficacious for improving depressive symptoms in PLWHA [5, 6, 10, 11]. Researchers have sought to expand this line of work to include outcomes such as viral load and CD4 T-cell count. The rationale driving these studies is based on the proposition that alleviating depression symptoms should lead to better HIV clinical outcomes through improved ART adherence or direct biological effects on the immune system [12, 13]. To date, these studies have produced mixed results. Several randomized controlled trials (RCTs) have not revealed a link between antidepressants and improvements in HIV clinical outcomes, even in the presence of reduced depression symptoms. [12, 14–16]. However, in a recent pilot study conducted in sub-Saharan Africa, 55 HIV positive patients with depression who received an evidence-based antidepressant management intervention experienced improvements in depression symptoms, ART adherence and HIV clinical outcomes [17]. Supportive evidence is also found in observational studies, which have demonstrated antidepressants have a positive association with ART adherence, viral load and CD4 T-cell count [13, 18].

Logically, variations in HIV clinical outcomes might be observed between antidepressants if there are differential effects on depression symptoms and subsequent ART adherence. Sparse comparative evidence exists among PLWHA. However, evidence from the general population indicates dual-action antidepressants may have advantages in certain circumstances relevant to PLWHA. Mirtazapine (dual-action) has been shown to have a faster onset of action compared to single-action antidepressants [19], which is important to PLWHA given the detrimental effects of depression in this population. Bupropion (dual-action) has demonstrated fewer sexual side effects[19], which is relevant to PLWHA because this population is at risk for sexual dysfunction independent of antidepressant exposure [20]. Finally, SNRIs have demonstrated superior efficacy in more severe cases of depression [21], which is important given PLWHA are prone to worse depression [22].

Unfortunately, the few comparative studies of antidepressants on depression symptoms among PLWHA are inconclusive [23, 24]. Moreover, the investigations that were identified did not include HIV clinical outcomes. Furthering the knowledge regarding this relationship through a comparative effectiveness study is important because choosing an antidepressant requires physician consideration of complex factors, including side effect profile, cost, and past response [8]. A comparative study is well suited to address whether or not differential effectiveness should be included as an additional factor in the choice of an antidepressant.

Accordingly, we examined the change in HIV clinical outcomes among PLWHA with depression initiating antidepressants, and compared the effectiveness of dual-action and single-action antidepressants on improving viral load suppression and CD4 T-cell count. We hypothesized that initiation of antidepressant treatment would be associated with

improvements in HIV clinical outcomes for both types of antidepressants. We also hypothesized that dual-action antidepressants would be more effective than single-action antidepressants for improving viral suppression and CD4 T-cell count. Additionally, we performed a secondary analysis using depression measures as outcomes among a sub-sample of observations to examine whether improvements in depression symptoms parallel improvements in HIV clinical outcomes.

Methods

Data and participants

This study used data between 2004 to 2014 from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) [25] CNICS is a network of clinics located across the United States that provide care to PLWHA. CNICS integrates demographic information, medical records diagnoses, medication utilization, lab results, health service appointment history and patient-reported outcomes (PROs). Data verification and standardization procedures are described elsewhere [26].

We employed a new user approach [27] to identify the first occuring antidepressant treatment episode for a participant, consisting of a pre-index date washout period (baseline), index date and a twelve-month post-index period (follow-up). We required a washout period of at least 90 days where the patient did not receive an antidepressant under investigation. The day immediately following the end of the washout period was considered to be the index date, or date of treatment initiation. Antidepressant treatment episodes were divided into two groups based on the number of neurotransmitters affected by the medication. Dual-action antidepressants included mirtazapine, bupropion, venlafaxine, desvenlafaxine, and duloxetine [9]. Single-action antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline [9]

The main approach was intent-to-treat, meaning that episodes were analyzed based on the initial antidepressant prescription regardless of whether the treatment was maintained, discontinued, augmented or switched during follow-up. Since intent-to-treat estimates can be biased due to these therapeutic changes, we also conducted a per protocol sensitivity analysis [28]. We defined per protocol as continuous receipt of the original antidepressant for the entire follow-up period, with no switching or augmentation.

A total of 4,985 participants received an antidepressant medication under investigation in this study (Figure 1). We excluded 950 participants diagnosed with a serious mental illness other than depression (e.g. schizophrenia, bipolar disorder, personality disorders) that could potentially alter the prognosis of antidepressant treatment. Another 50 participants were excluded due to missing date information in their medication utilization records. This left 3,985 participants eligible to contribute a treatment episode. Among these participants, 1,771 had a diagnosis of depression, with a treatment episode meeting the ninety-day washout period that occurred on or after August 1, 2004. Of these 1,771 treatment episodes, 361 were excluded due to missing data. This left 1,410 intent-to-treat episodes for analysis including 418 (30%) for dual-action and 992 (70%) for single-action antidepressants.

Main analysis outcomes

The primary outcomes included viral suppression and CD4 T-cell count which were obtained from lab history files. We defined viral suppression as a binary measure (yes/no) using a threshold of < 200 HIV-1 RNA copies/mL [29]. CD4 T—cell count was defined as the mean difference in the absolute number of CD4 T lymphocytes/mm^3. We used observations closest to the index date as baseline measures and the last observed lab in the post-index period for the follow-up measure.

Baseline covariates

Several baseline covariates were identified to control for differences in the treatment groups at baseline. Covariates included exposure to single-action or dual-action antidepressants prior to the current treatment episode; a history of other diagnoses (anxiety, an AIDS-defining illness, history of smoking, at risk drinking or drug use) identified with medical records, and whether or not the patient was receiving ART on the index date obtained from medication utilization data. Demographic variables included age at index date, race/ ethnicity, gender and CNICS clinic. We also identified appointments with a psychiatrist using health service appointment data.

Other covariates

For descriptive purposes, several other covariates reflecting events occurring during the post-index period were identified. These covariates included augmentation (the addition of a new psychotropic medication with concurrent receipt of the original antidepressant lasting more than thirty days); switching (the addition of a new psychotropic medication with concurrent receipt of the original antidepressant lasting fewer than thirty days); treatment exposure days (number of days of continuous receipt of original antidepressant beginning on the index date during the follow-up period); and a binary variable (yes/no) indicating whether or not the participant received ART continuously throughout the treatment episode follow-up period. We also identified if the patient had attended an appointment with a psychiatrist.

Statistical analysis

All statistical analyses were conducted using SAS® version 9.4 [30]. We first ran tests for association on each outcome. For viral suppression, we used SAS® PROC FREQ with the McNemar's option and Cochran-Mantel-Haenszel test for paired binary data to test for: 1) a statistical difference in frequencies between the baseline and follow-up period; 2) a statistically significant interaction between time period and treatment group. We used SAS® PROC GLM for repeated measures to test for differences in CD4 T- cells/mm^3 between baseline and follow-up to and to assess the statistical significance of the interaction between treatment group and time period. We generated average treatment effect estimates with generalized estimating equations (GEE) [31]. GEEs address within-patient correlation for repeated measures and clustering by CNICS site. GEEs were created using the SAS® PROC GENMOD procedure with an exchangeable working correlation matrix and the "repeated" option for patient identifier, clustered by CNICS site. In the GEE model for viral load suppression, we used a binomial distribution with a log link to estimate risk ratios. For CD4

T- cell count, we used a normal distribution with an identity link to estimate mean differences.

We generated estimates for three treatment effects. First, we estimated the expected difference in the outcomes at baseline between dual-action and single-action antidepressants. Additionally, we estimated the expected change in the outcome between baseline and follow-up associated with initiating antidepressants independent of the treatment group. Finally, comparative effectiveness was estimated with a difference-in-difference approach by adding an interaction term for treatment group (dual- vs single-action) and study period (baseline vs follow-up). This estimate is the difference in the expected change in the outcome from follow-up between study periods for dual-action antidepressants and the same change for single-action antidepressants.

We used inverse probability of treatment (IPT) weights to address confounding due to absence of randomization. Covariates were selected to create IPT weights based on previous literature and the potential for confounding. IPT weight extreme values were stabilized using a method developed by Harder and colleagues [32]. We assessed balance on baseline covariates using standardized differences in means and frequencies [33]. We considered a covariate to have good balance if the weighted standardized difference was less than 0.25 [32]. Per protocol results did not significantly deviate from the intent-to-treat evaluation, therefore we only reported the latter. Per protocol models are contained in the Online Supplemental Appendix.

Secondary Analysis

We conducted a secondary analysis to examine the role depression symptoms play in the relationship between antidepressants and HIV clinical outcomes. The impact of depression was assessed using a self-reported Patient Health Questionnaire – 9 (PHQ-9), a previously validated instrument for assessing depression symptoms [34]. CNICS began collecting PROs such as the PHQ-9 between 2005 and 2013, however implementation varied by CNICS clinic and patients only complete PROs at appointments during routine care visits. Lack of control over collection of PROs resulted in the loss of 78% of the main sample (n=1,410) to missing a PHQ-9 at baseline. This left 306 treatment episodes for the secondary analysis. We added two outcome measures in the secondary analysis including remission from depression and symptom severity. Remission from depression (yes/no), was defined as a PHQ-9 score of <5 [34]. Symptom severity was the raw score of the PHQ-9 ranging between 0–27[34].

Due to the limited sample size, these secondary analyses included only intent-to-treat evaluations. The same statistical methods used in the main analysis were employed for depression outcomes, however we used inverse probability of observation (IPO) weights [35] in conjunction with IPT weights to address potential bias from missing data, as 22% (n=72) of the 306 treatment episodes did not have an observed PHQ-9 in the follow-up period. The method for combining IPO and IPT weights is described elsewhere [36]. IPO and IPT weight models details are contained in the Supplemental Appendix.

Ethical Reviews

The CNICS Research Review Committee approved this study on December 12, 2014. The University of Florida Institutional Review Board approved this study on March 5, 2015.

Results

Characteristics

In the unweighted sample (n=1,410), a majority of the participants were male (81%), white (59%) and virally suppressed (67%) with a mean CD4 T-cell count of 472 in the washout period (Table 1). The frequency of receiving ART on the index date and continuously during following up was 83% and 70%, respectively. Only 31% of the treatment episodes met the per-protocol criteria and the mean number of continuous days with the antidepressant initiated on the index date was 217. Compared single-action participants, dual-action participants were more likely to switch or augment treatment during follow up. Additionally, dual-action participants were more likely to have an appointment with a psychiatrist in either the washout or follow-up period. Also, dual-action participants had a greater frequency of receiving dual-action antidepressants prior to the current treatment episode washout period. The most commonly prescribed single-action antidepressant was citalopram, while bupropion represented the majority of dual-action treatment episodes (Supplemental Appendix). The IPT weighted sample was well-balanced on baseline confounders.

Weighted intent-to-treat analysis: viral suppression

The frequency of viral suppression at baseline 67% vs 78% at follow-up ($P = <0.001$) (Figure 2a). Additionally the within treatment group differences from baseline were statistically significant ($P = <0.001$). In GEE models, initiating antidepressants was associated with a 16% increase in the probability of viral suppression [(Risk Ratio (RR) = 1.16 (1.12,1.20)] (Table 2). For the difference-in-difference estimate, we did not observe a statistically significant interaction between treatment group and study period.

Weighted intent-to-treat analysis: CD4 T – cells/mm^3

There was a statistically significant difference in mean CD4 T- cell count between study periods (baseline = 472 vs follow-up = 511) ($P = <0.001$) (Figure 2b). The within treatment group differences from baseline were also statistically significant ($P = <0.001$). Results for the GEE models show that initiating antidepressants was associated with a mean increase of 39 CD4 T- cells/mm^3 [MD = 39 (30,48)] (Table 3). The difference-in-difference estimate was not statistically significant.

Secondary Analysis

Characteristics—Of the 306 treatment episodes in the secondary analysis, 220 (72%) were for single-action and 86 (28%) were for dual-action antidepressants (Supplemental Appendix Table 13). Viral suppression (76%), mean CD4 T-cell count (526) and receipt of ART (90%) in the pre-index period were somewhat higher in this sub-sample, but otherwise the treatment episodes characteristics were similar to the main sample. After applying stabilized IPT weights, pre-index period covariates were well balanced between treatment

groups except for at-risk drinking, smoking, race (other/unknown) and CNICS site, therefore we included these unbalance covariates into the regression equations. The HIV clinical outcome analyses, when repeated in this sub-sample, yielded substantively similar results to those reported from the main sample above (Supplemental Appendix).

Weighted Intent-to-treat analysis: Depression remission and PHQ-9 score—
The frequency of remission (PHQ-9 <5) at baseline was 26% vs 35% at follow-up (P=0.01) (Supplemental Appendix Table 13). Within treatment group differences from baseline were statistically significant (P=0.01). In GEE models (Table 3), there was a 36% increase in the probability of remission associated with initiating antidepressants, [RR=1.36 (1.08,1.71). The interaction between treatment group and study period (difference-in-difference) was not statistically significant.

Baseline mean PHQ-9 was 10.2 compared to 7.8 at follow-up (P<0.001) (Supplemental Appendix Table 13). Within treatment group differences were statistically significant for both single- and dual-action antidepressants (P<0.001). In GEE models (Table 3) there was a 2.5 point decrease in the mean PHQ-9 score associated with initiating antidepressants [MD=−2.5(−3.5,−1.6)]. The difference-in-difference estimate was not statistically significant.

Discussion

Our results demonstrated that initiating antidepressant treatment in the course of routine HIV care is associated with improvements in viral suppression and CD4 T-cell count. Additionally, we found that initiation of antidepressant treatment was associated with reductions in depression symptoms. Such findings suggest improvements in depression correspond to improvements in HIV clinical outcomes following the initiation of antidepressant treatment. It is therefore possible the relationship between initiating antidepressant treatment and HIV clinical outcomes is mediated by reductions in depression symptoms and subsequent improvements ART adherence. However, we cannot speak definitively to this mediation pathway because data restrictions (lack of treatment episodes with ART adherence PROs) prevented us from conducting a mediation analysis. Despite the inability to conduct a mediation analysis, our results strengthen evidence supporting the mediation pathway generated from past studies [13, 17, 18].

Contrary to our second hypothesis, single-action and dual-action antidepressants appear to have comparable effectiveness on the outcomes in this study. Out results for depression are consistent to a related study we previously reported using a different sample from the same cohort which showed comparable effectiveness between single- and dual-action antidepressants[23]. However, this previous analysis was not able to control for baseline depression severity as done here. Our depression results are also consistent with a prior randomized controlled trial comparing mirtazapine (dual-action) to escitalopram (single-action) [24]. While consistency with past study results may explain our findings, another potential explanation exists. Specifically, post-index period therapeutic changes in the present study may be driving the depression results. Specifically, we observed a greater frequency of switching and augmentation in the dual-action group. These occurrences may

be due inadequate treatment response, however, data restrictions prevented identifying what drove these changes.

Given that we observed similar changes in depression symptoms, it is plausible that participants experienced comparable improvements in ART adherence. As such, the observed comparable improvements in HIV clinical outcomes are not surprising. Nevertheless, we cannot definitely speak to the impact of ART adherence due to data restrictions as noted above.

It is important to note that participants experienced a relatively small therapeutic response in depression symptoms. We observed a 2.5 point decrease PHQ-9 scores (Supplemental Appendix Table 13), which is below the defined level of a clinically meaningful change (5 points) [35]. Additionally, the mean PHQ-9 at follow-up was 7.8 which is still indicative of unresolved depression [34]. Moreover, only 35% of participants met the criteria for remission at follow-up which represents a relatively small increase (11% points) in remission rates. These findings indicate more research is needed to improve the overall effectiveness of depression treatment for PLWHA.

Our results should be interpreted with caution given the limitations encountered in this study. We were unable to control for baseline depression severity in the main analysis. However, we were able to control for baseline depression severity in the secondary analysis which produced similar results for HIV clinical outcomes as those observed in the main analysis. Consistency in the findings for HIV clinical outcomes between the main and secondary analyses indicates depression severity was most likely not a significant confounder. We were also unable to account for ART adherence due to data restrictions. As such we cannot determine if differences in baseline ART adherence biased our estimates for HIV clinical outcomes. However, ART adherence is theoretically a mediator rather than a confounder, therefore this omission does not raise significant concerns about uncontrolled confounding. Another limitation comes from combining multiple medications into our treatment groups. This approach assumes comparable effectiveness across individual medications within each group; however, our grouping is theoretically justified based on the "dual-action" hypothesis which suggests that medications with dual-action may have systematic differences in effectiveness compared to SSRIs [9, 36]. Data restrictions also prevented us from fully accounting for important aspects of treatment beyond antidepressants. Specifically we could not determine the impact of variations in non-pharmacological interventions, prescribing physician type and medication dosage. However, we were able to balance treatment groups on a rich set of covariates, which likely mitigated some bias from these confounders (e.g. past treatment experiences, psychiatric appointments).

Despite these limitations, this study makes several contributions to the field of HIV research. First, to our knowledge this is the only study that has compared the impact of dual-action and single-action antidepressants on depression symptoms and HIV clinical outcomes. Second, the results from this study strengthen findings from prior work that have demonstrated support for the connection between antidepressants and HIV clinical outcomes. Such evidence highlights the potential for circumventing the deleterious impact

depression has on HIV disease progression with antidepressants. Third, our evidence adds support for current guidelines that suggest available antidepressants have roughly comparable effectiveness, and antidepressant selection can therefore be guided by patient preferences, side effect profiles, previous responses and potential drug interactions [8]. Finally, we used observational data collected in the course routine HIV care; therefore, our results are generalizable to the complex circumstances physicians face when treating depression among PLWHA.

Conclusion

We found that dual-action and single-action antidepressants have a comparable positive impact on depression symptoms and HIV clinical outcomes for PLWHA diagnosed with depression. Additional studies should build upon this investigation by comparing specific medications, therapeutic classes and existing collaborative care interventions. Future studies should also model ART adherence and depression symptom severity as mediators. Uncovering the nature of this complex relationship should prove useful in advancing the treatment of psychiatric comorbidities in PLWHA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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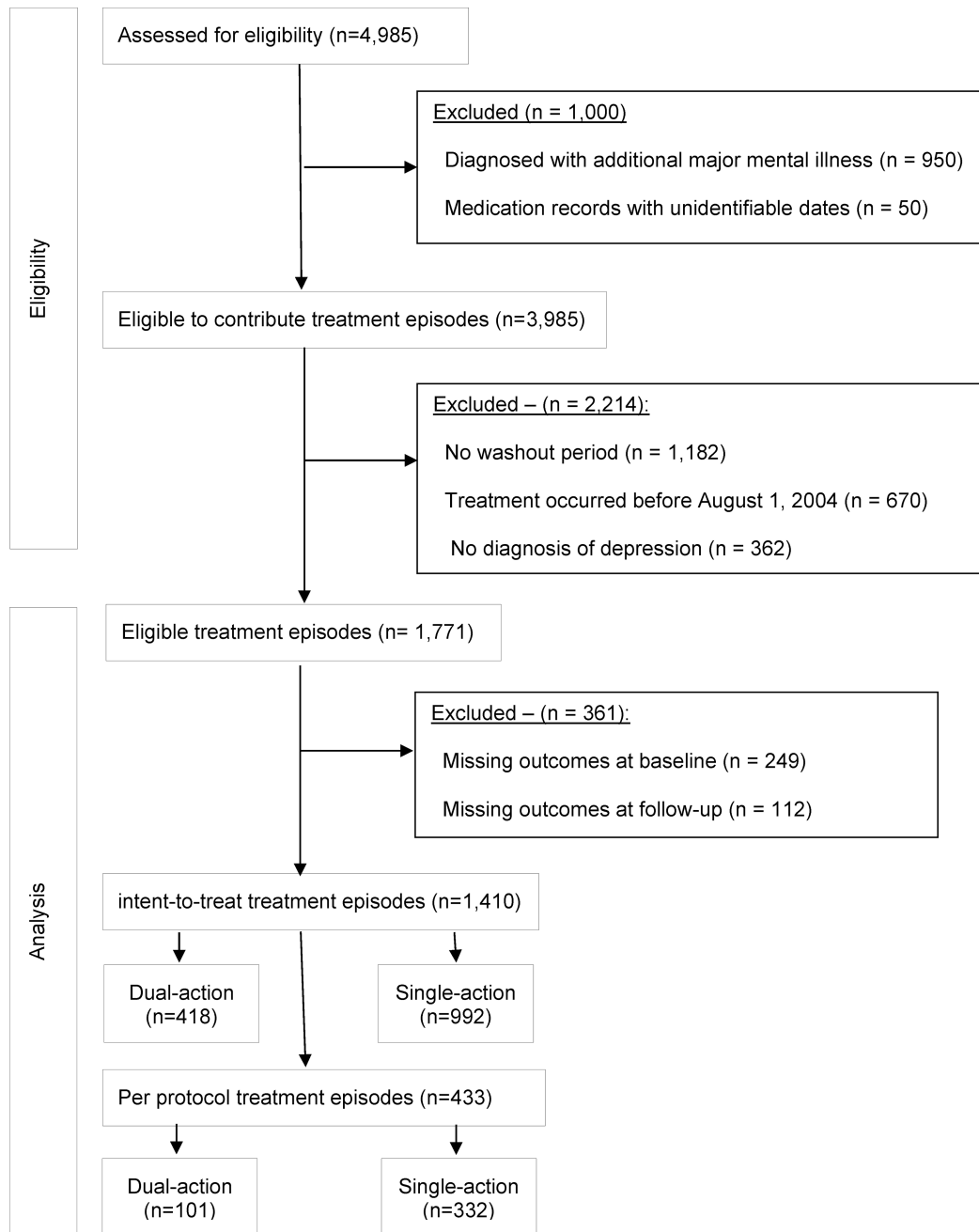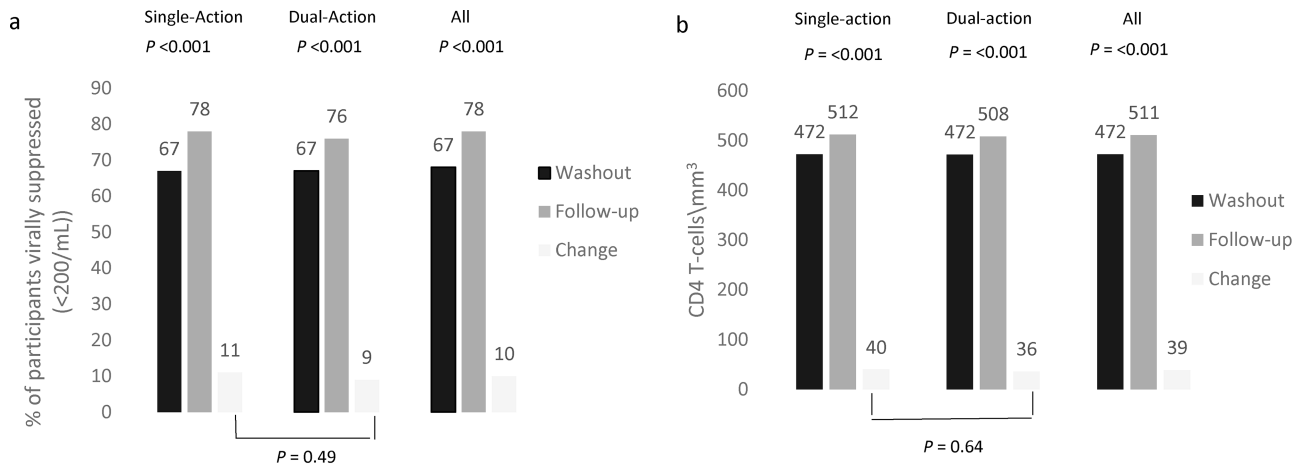**Fig. 1.**
Consort diagram

Fig. 2.
(a) Results of McNemar's and Cochran-Mantel-Haenszel tests for differences in viral suppression. (b) Results of ANOVA for repeated measures test for differences in CD4 T-cells/mm^3.

Table 1

Intent-to-treat treatment episode characteristics (n=1,410)

	Total	Unweighted			IPT Weighted		
		Dual-action (n=418)	Single-action (n=992)	STD	Dual-action (n=418)	Single-action (n=992)	STD
	%	%	%		%	%	
Prior single-action [*]	16	16	16	0.008	17	16	0.032
Prior dual-action [*]	10	17	7	0.358	10	10	0.003
Psychiatrist appointment in washout period [ℱ]	23	31	20	0.276	23	23	0.004
Demographics							
Age, mean (SD)	39 (9)	40 (9)	38 (9)	0.214	39	39	0.018
Male	81	84	80	0.099	82	81	0.019
White	59	63	58	0.102	59	59	0.004
Black	30	28	31	0.067	30	30	0.002
Other/unknown	11	9	11	0.063	11	11	0.011
Hispanic	17	13	18	0.151	14	17	0.073
Health status – conditions identified any time prior to the index date unless otherwise specified							
Viral suppression(<200 copies/mL) [ℱ]	67	72	65	0.166	67	67	0.004
CD4 T-cell count, mean [ℱ] (SD)	472 (276)	479 (284)	469 (273)	0.036	472 (285)	472 (277)	0.002
Anxiety	26	25	26	0.015	25	25	0.002
ADI	30	33	28	0.118	32	30	0.037
At risk drinking	17	20	15	0.128	17	16	0.006
Drug use	33	38	31	0.130	33	33	0.010
Smoker ever	39	42	37	0.094	39	39	0.005
On ART at index	83	86	82	0.103	82	83	0.016
Clinic							
A	13	13	14	0.038	14	13	0.013
B	11	15	10	0.146	11	11	0.016
C	23	23	23	0.008	24	23	0.025
D	21	15	24	0.213	20	21	0.019

	Total	Unweighted			IPT Weighted		
		Dual-action (n=418)	Single-action (n=992)	STD	Dual-action (n=418)	Single-action (n=992)	STD
	%	%	%		%	%	
E	16	16	16	0.004	16	16	0.001
F	16	18	15	0.089	15	15	0.011
Psychiatrist appointment during follow-up	35	43	32	0.231	38	35	0.059
# days received treatment during follow-up continuously, mean (SD)	217 (137)	202 (141)	224 (135)	0.160	209 (141)	223 (135)	0.103
Per protocol£	31	24	33	0.202	25	33	0.178
Switch out€	17	21	16	0.129	21	16	0.128
Augmented±	8	14	6	0.320	15	6	0.351
On ART continuously during follow-up	70	74	66	0.132	71	69	0.048

IPT, inverse probability of treatment; STD, standardized difference; SD, standard deviation, ART; antiretroviral therapy; ADI, AIDS defining illness.

*
Antidepressant treatment received prior to the current treatment episode; includes periods of treatment that did not have at least a 90-day washout period

Ŧ
Measure taken or event occurred in the washout period but not more than 6 months prior to the treatment episode index date

£
Treatment episode with no switch out, augmentation or discontinuation of antidepressant initiated on the index date during follow-up

€
Addition of a new psychotropic medication with concurrent receipt of the original antidepressant lasting fewer than thirty days

±
Addition of a new psychotropic medication with concurrent receipt of the original antidepressant lasting more than thirty days

Table 2

Weighted GEE intent-to-treat analysis: HIV clinical outcomes

	Probability of viral suppression (<200 copies/mL)		CD4 T – cell count	
	RR	95% CI	Mean difference	95% CI
Baseline difference: dual *vs* single-action antidepressants	1.00	(0.91,1.09)	−1	(−36,35)
Initiation of antidepressants [*]	1.16	(1.12,1.20)[¥]	39	(30,48)[¥]
Difference-in-difference: dual *vs* single-action antidepressants [**]	0.97	(0.90,1.06)	−4	(−24,16)

GEE, generalizing estimating equations; RR, risk ratio; CI, confidence interval.

[*]
Estimated change from baseline in GEE model without interaction term

[**]
Interaction between treatment group and study period. This is the comparative effectiveness difference-in-difference estimate which represents the change in the outcome from baseline for dual-action antidepressants minus the same difference for single-action antidepressants.

[¥]
P value <0.001

Table 3

Secondary analysis - weighted GEE intent-to-treat analysis: depression outcomes [*]

	Probability of remission (PHQ < 5)		PHQ-9 score	
	RR	95% CI	Mean difference	95% CI
Baseline difference: dual action vs single-action	1.0	(0.62,1.60)	0.7	(−1.4,2.9)
Initiation of antidepressants [**]	1.36[¥]	(1.08,1.71)	−2.5	(−3.5, −1.6) [€]
Difference-in-difference: dual vs single-action antidepressants [***]	1.06	(0.65,1.72)	−0.6	(−2.7,1.5)

GEE, generalized estimating equations; RR, risk ratio; CI, confidence interval; PHQ-9, patient health questionnaire.

[*] n = 306, both models included at-risk drinking as a covariate in regression equation because the standard difference for at-risk drinking, smoking, race other or unknown and CNICS site after inverse probability of treatment weighting was > 0.25 threshold indicating potential for confounding not addressed with the inverse weighting method.

[**] Estimated change from baseline in GEE model without interaction term

[***] Interaction between treatment group and study period. This is the comparative effectiveness difference-in-difference estimate which represents the change in the outcome from baseline for dual-action antidepressants minus the same difference for single-action antidepressants.

[¥]P value <0.01

[€]P value <0.001