Comparative Effectiveness of Dual-Action versus Single-Action Antidepressants for the Treatment of Depression in People Living with HIV/AIDS

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Abstract:

Background:

Depression is the most common psychiatric comorbidity among people living with HIV/AIDS (PLWHA). Little is known about the comparative effectiveness between different types of antidepressants used to treat depression in this population. We compared the effectiveness of dual-action and single-action antidepressants in PLWHA for achieving remission from depression.

Methods:

We used data from the Centers for AIDS Research Network of Integrated Clinic Systems to identify 1,175 new user dual-action or single-action antidepressant treatment episodes occurring from 2005-2014 for PLWHA diagnosed with depression. The primary outcome was remission from depression defined as a Patient Health

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This is the author's manuscript of the article published in final edited form as:
Mills, J. C., Harman, J. S., Cook, R. L., Marlow, N. M., Harle, C. A., Duncan, R. P., … Pence, B. W. (2017). Comparative Effectiveness of Dual-Action versus Single-Action Antidepressants for the Treatment of Depression in People Living with HIV/AIDS. Journal of Affective Disorders. https://doi.org/10.1016/j.jad.2017.03.042

Questionnaire-9 (PHQ-9) score <5. Mean difference in PHQ-9 depressive symptom severity was a secondary outcome. The main approach was an intent-to-treat (ITT) evaluation complemented with a per protocol (PP) sensitivity analysis. Generalized linear models were fitted to estimate treatment effects.

Results:

In ITT analysis, 32% of the episodes ended in remission for both dual-action and single-action antidepressants. The odds ratio (OR) of remission was 1.02 (95%CI=0.63,1.67). In PP analysis, 40% of dual-action episodes ended in remission compared to 32% in single-action episodes. Dual-action episodes had 1.33 times the odds of remission (95%CI=0.55,3.21), however the result was not statistically significant. Non-significant differences were also observed for depressive symptom severity.

Limitations:

Missing data was common but was addressed with inverse probability weights.

Conclusions:

Results suggest that single-action and dual-action antidepressants are equally effective in PLWHA. Remission was uncommon highlighting the need to identify health service delivery strategies that aid HIV providers in achieving full remission of their patients' depression.

Keywords: HIV/AIDS; depression; antidepressants; comparative effectiveness; new user treatment episode; inverse probability weights

1. Introduction[2]

Depression is the most common psychiatric disorder among people living with HIV/AIDS (Nanni et al., 2015). People living with HIV/AIDS (PLWHA) are two to four times as likely to suffer from depression compared to the general population (Kaaya et al., 2013; Nanni et al., 2015; Wendorf and Mosack, 2013). Depression is associated with suboptimal antiretroviral treatment (ART) adherence, accelerated HIV disease progression, decreased quality of life, increased morbidity and premature mortality (Nanni et al., 2015).

Given the consequences of depression for PLWHA, depression treatment is extremely important. One common treatment approach is antidepressant medication. Several antidepressants with different pharmacological properties are considered appropriate for 1st line treatment in PLWHA. Currently selective-serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of antidepressants to PLWHA (Freudenreich et al., 2010). SSRIs (e.g. citalopram) are considered to be single–action antidepressants because they impact only one neurotransmitter known as serotonin (Delgado, 2009; Rakesh, 2004). Dual-action antidepressants are another category of medications used as treatment for depression in PLWHA. Dual-action antidepressants differ from those with single-action in that they impact two neurotransmitters thought to be associated with depression (i.e. serotonin, norepinephrine, or dopamine) at the same time (Rakesh, 2004). Examples of dual-action antidepressants considered appropriate for PLWHA include serotonin-

[2] People living with HIV/AIDS (PLWHA); Intent-to-treat (ITT), Per protocol (PP); Selective-serotonin reuptake inhibitors (SSRIs); Antiretroviral treatment (ART); Center for AIDS Research Network of Integrated Clinic Systems CNICS; Patient Healthcare Questionnaire-9 (PHQ-9); Inverse probability of treatment (IPT); Inverse probability of treatment weights (IPTW); Inverse probability of observation (IPO); Inverse probability of treatment and observation (IPTO); Standardized Difference (STD)

norepinephrine reuptake inhibitors (e.g. venlafaxine), bupropion and mirtazapine (Adams et al., 2012).

Randomized controlled trials have demonstrated that antidepressants have high levels of efficacy in PLWHA (Hill and Lee, 2013; Himelhoch and Medoff, 2005; Pence et al., 2012). However, there is limited literature that has compared the effectiveness of the different antidepressants currently used to treat PLWHA for depression. In fact we found only one study that compared a single-action and dual-action antidepressant commonly used today among PLWHA (Patel, 2013). This randomized open label eight-week trial compared mirtazapine (dual-action) to escitalopram (single-action) in a sample of seventy HIV positive patients. While remission and response rates did not differ statistically, the median Hamilton Rating Scale for Depression (HAM-D) score at eight weeks was significantly lower for mirtazapine (median=4) compared to escitalopram (median=12) with a p-value of <0.001.

In contrast, substantial effort has been given to comparing effectiveness between antidepressants among populations without HIV infection (Bauer et al., 2009; Bradley and Lenox-Smith, 2013; Delgado, 2009; Gartlehner et al., 2011; Grunebaum et al., 2013; Rakesh, 2004; Richelson, 2013). These studies are based on the hypothesis that broader spectrum antidepressants with dual action may be more effective than those with single action because depression can arise out of dysfunction along multiple neurotransmitters pathways (Delgado, 2009; Rakesh, 2004). While earlier studies revealed potential advantages for dual-action antidepressants (Bauer et al., 2009; Delgado, 2009; Rakesh, 2004), results from a more recent meta-analysis analysis concluded that there were no significant differences according to type of medication

(Gartlehner et al., 2011). However, there was a paucity of evidence specific to PLWHA contained in the meta-analysis, therefore caution is warranted when generalizing the conclusion to those with HIV-infection.

In fact, more nuanced findings from general population studies suggests that further investigation of the comparative effectiveness of dual-vs. single-action antidepressants is warranted in PLWHA. First, mirtazapine is known to have a faster onset of action compared to single-action SSRIs (Gartlehner et al., 2011). While timely alleviation of depressive symptoms is important for all people with depression, it is especially salient to PLWHA given the negative HIV/AIDS related health consequences associated with this psychiatric condition. Secondly, bupropion has a lower risk of sexual side effects compared to single-action SSRIs which may lead to better antidepressant treatment adherence (Gartlehner et al., 2011) and therefore better response. PLWHA have been shown to be at higher risk of sexual dysfunction, independent of antidepressant exposure (Bouhnik et al., 2008), therefore in order to avoid additional exascerbation of this problem, bupropion may be more advantageous in the context of HIV infection. Finally, in a systematic review conducted in 2013, authors found sufficient evidence to conclude that SNRIs may have greater efficacy than SSRIs for more severe cases of depression. (Bradley and Lenox-Smith, 2013) These findings are relevant to PLWHA given depression in HIV/AIDS is typically chronic and often accompanied by additional psychiatric diagnoses (e.g. anxiety, substance use disorder), which in turn lends itself to greater severity in depressive symptomology.

Despite the potential advantages from dual-action antidepressants for PLWHA highlighted above, a significant gap remains in research comparing antidepressants in

PLWHA. To address this gap, we compared the effectiveness of dual-action and single-action antidepressants for achieving remission from depression among PLWHA. We also assessed comparative effectiveness for depression symptom severity. Results from this study have the potential to generate much needed comparative evidence that can reduce uncertainty for a physician when choosing an antidepressant to treat depression in PLWHA. We hypothesized that dual-action antidepressants would be more effective than single-action antidepressants for achieving remission and reducing depression symptoms.

2. Methods

2.1. Data and study population

This comparative effectiveness study used data from the Center for AIDS Research Network of Integrated Clinic Systems (CNICS, 2014a). CNICS is a network of eight clinics located across the United States that collects, standardizes and stores point of care electronic data obtained during the delivery of routine HIV primary care. CNICS collects patient demographic information, documented diagnoses from medical records, medication utilization history (pharmacy fill and medical records), HIV biomarker lab results (HIV viral load and CD4 T-cell count) and health care appointment history. As of 2005, CNICS began collecting several self-administered patient-reported outcome (PRO) surveys assessing symptom severity (e.g. depression, anxiety), quality of life and health related behaviors (e.g. alcohol use). PROs are completed during clinical appointments at a CNICS site typically occurring every four to six months. Given that the outcome of interest described below is derived from a PRO, our study period was 2005-2014.

We employed a new-user approach (Ray, 2003) to identify antidepressant treatment episodes with a minimum washout period of 90-days; meaning participants received no treatment with any antidepressant considered in this analysis during a period of at least 90 days prior to the treatment episode initial prescription date (index date). Additionally, a treatment episode consisted of a twelve-month follow-up period. We limited our analysis to the patient's first occurring treatment episode with the earliest index date, therefore a patient could contribute only one observation. Treatment episodes were separated into two comparison groups based on the number of neurotransmitters impacted by the antidepressant. Dual-action antidepressants were defined as the intervention group and included mirtazapine, bupropion, desvenlafaxine, duloxetine or venlafaxine (Delgado, 2009; Rakesh, 2004). Single-action (SSRIs) antidepressants were used as the active comparator group. Single-action antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline (Delgado, 2009; Rakesh, 2004).

The primary analysis used an intent-to-treat approach, in which participants were analyzed according to the initial antidepressant prescribed, regardless of whether the participant remained on that antidepressant, discontinued, augmented or switched medications during the twelve-month follow-up period. Since discontinuation, switching and augmenting can introduce bias to the estimates of treatment effects, we conducted a sensitivity analysis limiting the sample to per protocol treatment episodes (Brookhart et al., 2013). Per protocol treatment episodes were defined as continuous receipt of the original medication without switching or augmenting for the entire twelve-month follow-up period.

At the time of the query for this study, the CNICS cohort included 5,777 participants that had received any type of antidepressant medication (Figure 1). A total of 1,642 participants were excluded due to the following: (1) Antidepressants received where not medications under investigation in this study; (2) had a diagnosis of a major mental illness other than depression with the potential to impact treatment prognosis (e.g. bipolar disorder, psychosis); (3) contained unidentifiable dates in their antidepressant treatment history which would preclude the identification of valid washout periods. After applying the above exclusion criteria, 4,135 participants remained. Among these participants, we identified 1,579 treatment episodes that began after January 1, 2005 with a washout period ≥ 90-days. We excluded an additional 211 treatment episodes because the participant did not have a recorded diagnosis of depression. A depression diagnosis was identified based on CNICS's verification methods for medical diagnoses described elsewhere (CNICS, 2014b). Finally, 193 treatment episodes were removed due to missing a baseline HIV viral load or CD4 T-cell count lab result. This final exclusion was made because we considered these lab results to be potential confounders. The final sample included 1,175 new user intent-to-treat episodes, of which 347 (30%) were for dual-action antidepressants and 828 (70%) were for single-action antidepressants. Of the 1,175 intent-to-treat episodes, 342 (29%) met our definition of a per protocol treatment episode. The per protocol sample included 82 (24%) dual-action and 260 (76%) single-action treatment episodes.

2.2. Measures

The primary outcome, remission from depression (yes/no), was measured using the Patient Healthcare Questionnaire-9 (PHQ-9), a previously validated instrument for

assessing depression severity on a scale from 0-27 (Kroenke et al., 2001). A score of <5 was considered to be remission based on the defined severity levels of the PHQ-9 (Kroenke et al., 2001). The mean difference in depression symptom severity, a secondary outcome, was defined as the difference in the raw PHQ-9 score between treatment groups. Only the last observation that occurred during the twelve-month follow-up period was used in the analysis in order to allow for the maximum amount of therapeutic exposure.

Several categories of pre-index date covariates were used to help control for any baseline differences in the two comparison groups. Medication utilization data was used to identify history of single-action or dual-action antidepressant treatments (yes/no) prior to the 90-day minimum washout period. Anxiety, any diagnosed history of smoking, alcohol use and drug use were obtained from recorded diagnoses in medical records. Additional variables included the most recent HIV viral load and CD4 T-cell count and any mental health appointments occurring within six months prior to the index date. HIV viral load was dichotomized into a binary variable indicating viral suppression (yes/no), defined as less than 200 copies/mL (DHHS, 2014). Other baseline covariates included CNICS site, health insurance type, gender, race/ethnicity, age at treatment initiation, and receipt of ART on the index date (yes/no).

Additional variables were identified to aid in the interpretation of our results reflecting events during the follow-up period. These variables included augmentation (the addition of a new antidepressant medication during the treatment episode where receipt of both medications concurrently lasted more than thirty days); switching (the addition of a new antidepressant medication during the treatment episode where receipt

of both medications concurrently lasted less than thirty days); treatment exposure days (the number of continuous days in the treatment episode that the patient received the antidepressant identified as the exposure); and continuous receipt of ART during follow-up. We also identified if the patient had attended an appointment with a psychiatrist or non-prescribing mental health specialist. These variables are reported in the Supplemental Online Appendix.

2.3. Confounding and treatment episodes with missing outcomes

We used inverse probability of treatment (IPT) weights (Austin and Stuart, 2015) to balance comparison groups on baseline (pre-index date) covariates that had the potential for confounding. IPT weights were computed with a two-step process. First we used logistic regression to model the predicted probability of receiving the intervention (dual-action antidepressants). Second, we took the inverse of the predicted probabilities from the logistic regression model to derive the IPT weights. Balance between treatment groups on baseline covariates was assessed using standardized differences in mean and frequencies (Austin and Stuart, 2015). We considered a standard difference of ≤0.25 to be indicative of good balance on the covariate (Harder et al., 2010).

While 1,175 intent-to-treat treatment episodes were identified, only 494 (42%) had an observed PHQ-9 during the 12-month follow-up period. If PHQ-9 “missingness” is related to the treatment group and the value of the outcome, then estimates limited to complete cases (treatment episodes with a PHQ-9 at follow-up) will be biased. We chose to address this potential bias by using inverse probability of observation weights (Seaman and White, 2013). Inverse probability of observation (IPO) weights were calculated with the same process as IPT weights, the only difference being weights

were modeled as the predicted probability of having an observed PHQ-9 during the follow-up period.

We then multiplied the IPT and IPO weights to create a unified inverse probability of treatment and observation (IPTO) weight (Cole et al., 2010). By applying the IPTO weights to our sample, we created a theoretical pseudo-population that approximates what we would have observed if: (1) All 1,175 treatment episodes had an observed PHQ-9 at follow-up and; 2) treatment selection was independent of the observed baseline covariates included in the IPT model. All weights (IPT, IPO and IPTO) were stabilized per Harder et al. (2010) and met distributional recommendations (Harder et al. 2010). Details regarding the IPT, IPO and IPTO models are provided in the Supplemental Online Appendix.

2.4. Statistical analysis

Statistical analyses were conducted using Statistical Analysis Software (SAS®) version 9.4 (SAS®, 2012). We estimated the relative odds of achieving remission with SAS® PROC GENMOD, whereby a generalized linear model was fitted with a binomial distribution and logit link. Additionally, we fitted a generalized linear model with a normal distribution and identity link to estimate the mean difference in depression symptom severity. Robust standard errors were used to account for potential bias in standard error estimates that can arise when using inverse probability weighting methods.

2.5. Ethics Approval

This study was reviewed and approved by the CNICS Research Review Committee on December 12, 2014. The University of Florida Institutional Review Board approved this study on February 26, 2015.

3. Results

3.1. Intent-to-treat treatment episode characteristics

Citalopram (single-action) and bupropion (dual-action) were the most commonly prescribed antidepressants (see Supplemental Online Appendix). Approximately 19% of all patients had a history of being treated with single-action antidepressants prior to the current treatment episode, while 11% had prior exposure to dual-action antidepressants (Table 1). The mean age at the index date was 38 (standard deviation [SD] = 10 years) with the majority of subjects being white non-Hispanic males. Most subjects (87%) were receiving ART on the index date and based on the last lab result in the washout period, the mean CD4 T-cell count was 484 (SD = 281) and 69% of the patients were virally suppressed. About one third of the patients had a diagnosis of anxiety and a documented history of drug use. In the dual-action group, patients were more likely to have received dual-action antidepressant therapy prior to the current treatment episode, to have seen a psychiatrist during the washout period, to be white non-Hispanic, to be virally suppressed during the washout period and to have a history of drug use compared to patients in the single-action group. IPTO weighting had little influence on our results, and were similar to unweighted analyses. For simplicity we only report the estimates from IPTO models.

3.2. Intent-to-treat analysis

After applying IPT weights, the standardized differences for all baseline covariates were below the 0.25 threshold, ranging from 0.002 to 0.066 (Table 1). The IPTO weighted frequency of remission (32% vs 32%) and mean depression severity (9.2 vs 8.1) at follow-up were not statistically different between dual-action and single-

action treatment episodes, respectively (Table 1). Results of the IPTO weighted generalized linear models for both outcomes were not statistically significant (Table 2). The odds ratio for achieving remission was 1.02 (95% CI 0.63-1.67). The mean difference in depression symptom severity between groups was 1.1 units on the PHQ-9's 0-27 scale (95% CI -0.4-2.6).

3.3. Per-protocol sensitivity analysis

Per protocol baseline covariates and outcome values at follow-up are reported in Table 3. In the IPT weighted sample, all baseline covariates had standardized differences less than 0.25. After applying IPTO weights, the frequency of remission at follow-up for dual-action treatment episodes was 40% compared to 32% for single-action treatment episodes, however the difference was not statistically significant. The IPTO weighted mean depression severity was lower, but not statistically different, for dual-action treatment episodes compared to single-action treatment episodes (6.9 vs 8.0). Table 4 contains the results of the IPTO weighted generalized linear models. Dual-action treatment episodes had 1.33 times the odds of ending in remission compared to single-action treatment episodes (OR=1.33, 95% CI 0.55-3.21), but this result was not statistically significant. The finding for the mean difference in depression symptom severity between treatment groups was also not statistically significant (β=-0.7, 95% CI -3.2-1.7).

4. Discussion

This is the first comparative effectiveness study we are aware of that compared dual-action to single-action antidepressants for the treatment of depression in PLWHA using data outside clinically controlled environments. We found no evidence to support

our hypothesis that dual-action antidepressants were more effective than single-action antidepressants in this population. This finding was the same in both intent-to-treat and per protocol analyses.

Our data suggest that therapeutic changes may have underestimated the effectiveness of dual-action relative to single-action antidepressants in intent-to-treat analyses. Specifically, post-index measures reveal that patients in dual-action treatment episodes tended to discontinue earlier and switch or augment more frequently (see Supplemental Online Appendix). More frequent changes could be due to lack of treatment response or intolerance of side effect profiles. Unfortunately, we did not have measures to indicate what precipitated these changes. However, comparative effectiveness is intended to incorporate factors such as treatment alterations, therefore based on our data, overall effectiveness appears comparable between dual-action and single-action antidepressants.

Our results are consistent in part with the only study in the field of HIV/AIDS that we identified which compared antidepressants included in our investigation (Patel, 2013). Similar to Patel et al. (2013), no differences were observed in remission from depression between dual-action and single-action antidepressants. However, contrary to our findings, Patel et al. (2013) did detect a difference in depression symptom level at follow-up. The discrepancy in findings for depression symptom level could be due to differences in the survey instruments used for assessing depression (HAM-D vs PHQ-9). Additionally, the differences observed by Patel et al. (2013) occurred at week 8, whereas our follow-up observation occurred on average 184 days (26 weeks) from the index date.

In terms of research outside the field of HIV/AIDS, our results are in line with the findings from an Agency for Healthcare Research and Quality systematic review which concluded there were no advantages between different classes of antidepressants (Gartlehner et al., 2011). However, our findings differed with Bradley and Lenox-Smith (2013) which concluded that dual-action serotonin-norepinephrine reuptake inhibitors (e.g. duloxetine) demonstrated greater efficacy compared to single-action SSRIs in more severe cases of depression (Bradley and Lenox-Smith, 2013). Had we limited dual-action treatment episodes to include only serotonin-norepinephrine reuptake inhibitors, we could make a more definitive comparison with Bradley and Lenox-Smith (2013). However, we were unable to identify an adequate number of serotonin-norepinephrine reuptake inhibitor treatment episodes to define our intervention in this manner (see Supplemental Online Appendix for the specific medications identified in this study).

It is also important to note the low frequency of remission we observed for all patients in this study. Only 32% and 34% in total achieved remission at follow-up in the intent-to-treat and per protocol analysis, respectively (See Tables 1 and 3). Our results are similar to prior estimates of remission rates (28%) in real world conditions (Pence et al., 2012). However, 32% is well below commonly observed remission rates in randomized controlled trials (median of 72%) (Pence et al., 2012). The differences in outcomes between research and standard practice environments suggests that there is potential for improvement when treating depression outside controlled settings. An additional implication is that remission may not always be possible and less aggressive treatment goals may be more realistic. Specifically, patients in our study may have

experienced substantial reductions in symptom severity but still not fall below the PHQ-9 definition of remission. A mean PHQ-9 score of 8 was observed at follow-up in our analysis. A score of 8 is still indicative of mild depression, however, the patient may have experienced a significant improvement in depression severity after initiating treatment compared to baseline levels. Yet due to inconsistent availability of a pre-treatment PHQ-9 measure in our dataset, we were unable to examine change in PHQ-9 score as an outcome.

Missing or unavailable data was the most significant limitation we faced. We were unable to control for baseline depression severity because, as noted above, so few patients had a recorded PHQ-9 within the washout period. Given this data limitation, we chose not to require a baseline PHQ-9 as an inclusion criterion. This decision increased the probability of unknown bias in the estimation of treatment effects due to potential differences in depression severity at baseline. One possible reason baseline depression severity would differ by treatment group is because several medications included in our analysis can be used for conditions other than depression. Bupropion (dual-action) is known to be used for smoking cessation (PDR, 2015b). Likewise, paroxetine (single-action) can be used for social anxiety disorder (PDR, 2015a). Unfortunately, treatment indication was not available in the data, therefore we cannot be certain that depression was the primary concern driving the initiation of antidepressant treatment. However, all included medications have a primary indication for depression treatment and are commonly used to treat depression in this population. Additionally, we sought to address this indication bias by limiting the sample to patients with a recorded diagnosis of depression in their medical record. Nevertheless, even though

CNICS has a rigorous method for verifying diagnosis data (CNICS, 2014b), using such data raises the potential for miss-classification bias stemming from coding and reporting errors as well as missed diagnoses.

In addition to unobserved depression severity at baseline, we also encountered a significant number (58% of the treatment episodes) of missing PHQ-9s during the follow-up period. Given we could not rule out the possibility that depression severity was related to missing a PHQ-9 at follow-up, we chose to employ sophisticated statistical methods, specifically IPO weights to address this limitation. While IPO weighting would not necessarily eliminate all the bias stemming from missing outcomes, it is a stronger approach than a complete case analysis which assumes that the missing data introduce no bias.

Several other important treatment selection factors exist that could have confounded our findings. For example, given literature suggests that single-action medications are the most commonly prescribed antidepressants for depression in PLWHA (Freudenreich et al., 2010), clinicians may be more experienced in managing this group of medications. Greater familiarity with these medications could improve the effectiveness of single-action antidepressants thereby biasing the results towards the null, assuming dual-action antidepressants are indeed more effective. Physician specialty (e.g. psychiatrists) could also influence treatment selection as this factor could be indicative of experience with a greater variety of antidepressants. Indeed, we did observe that participants initiating dual-action antidepressants were somewhat more likely to have seen a psychiatrist during the follow-up period compared to participants in single-action treatment episodes (39% vs 31%) (Online Supplemental Appendix).

However, appointment data also suggests that approximately 59% of the dual-action treatment episodes were administered by a prescribing physician other than a psychiatrist. These data indicate that non-specialists (e.g. HIV primary care physicians) also possess a level of comfort utilizing a variety of antidepressants including both dual-action and single-action medications. Ultimately, the potential impact of clinician experience and specialty described above is unobserved, therefore we used IPT weights to balance treatment groups on an observed appointment with a psychiatrist in the washout period. This measure may be a crude indicator of whether or not the prescribing physician specialized in the treatment of psychiatric disorders. However, our approach only partially addressed this issue as data was not available that confirmed the actual physician prescribing the medication.

An additional unobserved factor that could have biased our results is the selection of one type of antidepressant over another based on potential drug interactions between ART and antidepressants. While research indicates the pharmacokinetics of citalopram, escitalopram, duloxetine and mirtazapine is not known to be significantly altered by ART (Adams et al., 2012; Hill and Lee, 2013), interactions have been identified between the remaining antidepressants and certain protease inhibitors and non-nucleoside reverse transcriptase inhibitors (Hill and Lee, 2013). However, the potential impact of the drug interactions (potentiation or inhibition) varied by antidepressant and ART combination across both treatment groups, therefore we were unable to assess the effect of this factor in the present study.

A further limitation arose from the fact we were not able to measure adherence to antidepressant treatment. Overestimation and underestimation is possible with this

factor depending on which group had the higher likelihood of non-adherence. We found no literature that specifically addressed differential rates of adherence based on how we classified antidepressants. However, the absence of literature does not indicate there is no difference. Therefore, we cannot speak thoroughly to the impact of this unobserved factor.

Finally, we were limited by how we operationalized the intervention. First we were unable to adequately define receipt of non-pharmacological treatment. The approach we took was to create a weight on a variable indicating the presence of an appointment with a mental health specialist at the CNICS clinic. However, we do not know the type and quality of therapy provided. Moreover, this approach only identifies a sub-set of patients receiving non-pharmacological treatment because the cohort can seek this type of treatment elsewhere. Secondly, data limitations prevented us from determining the consistency of adequate dosing across treatment groups.

Despite these limitations, this study makes several significant contributions to the field of psychiatric HIV/AIDS research. First, while our data did not support the hypotheses for differential effectiveness, the purpose of a comparative effectiveness study is to enhance certainty in treatment decisions. Our study provides evidence that suggests differential effectiveness is not a reason to prefer dual-action antidepressants over single-action antidepressants, and medication choice can be driven by other factors such as patient preference, side effects, costs and provider familiarity. Second, this is the first study to address the question of antidepressant comparative effectiveness in a sample limited to PLWHA using data collected outside of controlled clinical trials. Given our results show achieving remission from depression in real world

settings is difficult for PLWHA, this study highlights the importance for continued comparative effectiveness research in this field. Third, this study draws attention to the data challenges faced when conducting comparative effectiveness research. Our approach to dealing with data limitations should prove useful to other investigators.

There are several future research projects that would logically flow from our present study. Given prior literature has identified citalopram as one of the most commonly used antidepressants in PLWHA (Freudenreich et al., 2010), future studies could compare the effectiveness of individual antidepressants against this medication. This would help inform the validity of the current practice. Additionally, future investigations are warranted that aim to increase the probability that patients start regimens requiring minimal adjustments (switching, augmenting) and achieve remission in the shortest time frame. Such research could circumvent the negative interaction between depression and HIV/AIDS. Finally, the low rates of remission observed in this study highlight the need for on-going closely managed antidepressant therapy in PLWHA. In light of this fact, research that compares the long-term effectiveness of dual-action and single-action antidepressants is necessary to identify potential variations in treatment outcomes that may arise over an extended period of time.

In conclusion, we observed no difference in effectiveness between dual-action and single-action antidepressants for treatment of depression in PLWHA. This finding suggests both single-action and dual-action antidepressants are appropriate choices for first line treatment. However, we also found remission rates substantially lower compared to results achieved in randomized controlled trials. Therefore, research is

needed to identify health service delivery strategies that can aid HIV providers in achieving full remission of their patients' depression.

Footnotes

[1] People living with HIV/AIDS (PLWHA); Intent-to-treat (ITT), Per protocol (PP); Selective-serotonin reuptake inhibitors (SSRIs); Antiretroviral treatment (ART); Center for AIDS Research Network of Integrated Clinic Systems CNICS; Patient Healthcare Questionnaire-9 (PHQ-9); Inverse probability of treatment (IPT); Inverse probability of treatment weights (IPTW); Inverse probability of observation (IPO); Inverse probability of treatment and observation (IPTO); Standardized Difference (STD)

Acknowledgements

This work was supported by National Institute of Allergy and Infectious Diseases of the National Institutes of Health (T32AI007001). Additional support was provided by CFAR-Network of Integrated Clinical Systems, a NIH funded program (R24 AI067039) made possible by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Heart, Lung, and Blood Institute (NHLBI). The CFAR sites involved in CNICS include Univ of Alabama at Birmingham (P30 AI027767), Univ of Washington (P30 AI027757), Univ of California San Diego (P30 AI036214), Univ of California San Francisco (P30 AI027763), Case Western Reserve Univ (P30 AI036219), John Hopkins Univ (P30 AI094189, U01 DA036935), Fenway Health/Harvard (P30 AI060354), and Univ of North Carolina Chapel Hill (P30 AI50410). We thank the patients, providers and research staff from the CFAR-Network of Integrated Clinical Systems for providing access to the required data to complete this study.

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Table 1 Characteristics of intent-to-treat treatment episodes

	Unweighted				Weighted			
	Total (N=1,175)	Dual-action (N=347)	Single-action (N=828)		Total (N=1,175)	Dual-action (N=347)	Single-action (N=828)	
	%	%	%	STD	%	%	%	STD
Outcomes at follow-up					**Outcomes at follow-up***			
Remission: PHQ-9 < 5	32	30	32	0.042	32	32	32	0.001
Mean depression symptom severity PHQ-9 (SD)	8.3 (6.4)	9.1 (6.6)	8.0 (6.3)	0.164	8.4 (6.5)	9.2 (7.2)	8.1(6.1)	0.166
Covariates at baseline					**Covariates at baseline****			
Receipt of prior ADT (single-action) €	19	20	18	0.070	19	19	19	0.002
Receipt of prior ADT (dual-action)€	11	21	7	0.444	11	11	11	0.002
Psychiatrist appt in washout period₮	21	28	18	0.243	21	21	21	0.007
Mental health specialist appt in washout period₮	14	15	13	0.041	14	14	14	0.004
Demographics								
Age, mean (SD)	38 (10)	40 (9)	38 (10)	0.144	38 (10)	38 (9)	38 (10)	0.020
Male	83	87	82	0.130	84	85	83	0.066
White	62	69	59	0.198	61	60	62	0.027
Black	26	21	29	0.184	27	28	27	0.021
Other/unknown	11	10	12	0.046	12	12	12	0.012
Hispanic	17	15	19	0.099	17	16	18	0.050

Health Insurance[Ω]								
Private	5	3	6	0.115	5	5	5	0.002
Public	27	25	29	0.077	27	26	27	0.024
Unknown	66	71	64	0.139	66	67	66	0.020
Uninsured	1	0	1	0.052	1	1	1	0.006
Health status								
Viral load <200 mL[¥]	69	73	67	0.121	69	68	69	0.006
CD4 count, mean (SD) [¥]	484 (281)	496 (285)	480 (280)	0.056	486 (284)	489 (289)	485 (281)	0.014
Alcohol use[×]	16	18	15	0.105	16	16	16	0.004
Drug use[×]	34	38	32	0.134	33	33	34	0.023
Smoker ever[×]	40	42	39	0.048	40	39	40	0.006
Anxiety[×]	29	29	28	0.019	28	27	28	0.025
On ART at index date	87	89	86	0.089	86	86	86	0.028
Clinic								
A	13	15	12	0.067	13	13	13	0.005
B	28	28	28	0.013	29	29	28	0.014
C	22	16	25	0.233	22	21	22	0.023
D	15	17	14	0.096	15	16	15	0.014
E	22	25	20	0.112	21	21	21	0.007

STD: Standardized difference
ADT: Antidepressant treatment
APPT: Appointment
No statistically significant comparisons at $p < 0.05$
*Weighted with inverse probability of treatment and observation (IPTO) weights
**Weighted with inverse probability of treatment (IPT) weights
[€] ADT received prior to the current treatment episode but the prior period of treatment did not have a 90-day washout period
[₮] Appointments in the washout period but the appointment did not occur more than 6 months prior to the index date if the washout period was more than 90 days
[Ω] Last insurance status reported in the past year from the index date
[¥] Labs taken closest to the index date but not occurring more than 6 months prior to the index date if the washout period was more than 90 days
[×] Lifetime occurrence

Table 2 IPTO weighted generalized linear models for intent-to-treat analysis

	Remission		**Depression symptom severity**	
	Odds ratio	**95% C.I.**	**Mean difference (PHQ-9)**	**95% C.I.**
Dual-action (Ref: Single-action)	1.02	0.63,1.67	1.1	-0.4,2.6

IPTO – Inverse probability of treatment and observation
No statistically significant comparisons at $p < 0.05$

Table 3 Characteristics of per protocol treatment episodes

Characteristic	**Unweighted**			**Weighted**		
	Total	**Dual-action**	**Single-action**	**Total**	**Dual-actio**	**Single-**

						n	action	
	(N=342)	(N=82)	(N=260)		(N=342)	(N=82)	(N=260)	
	%	%	%	STD	%	%	%	STD
Outcomes at follow-up					**Outcomes at follow-up***			
Remission: PHQ-9 < 5	39	47	37	0.202	34	40	32	0.169
Mean depression symptom severity PHQ-9 (SD)	7.1 (6.2)	6.4 (6.0)	7.3 (6.3)	0.147	7.8 (6.2)	6.9 (6.4)	8.0 (6.2)	0.176
Covariates at baseline					**Covariates at baseline****			
Receipt of prior ADT (single-action) €	19	23	18	0.139	18	16	19	0.063
Receipt of prior ADT (dual-action)€	11	22	7	0.499	10	10	10	0.016
Psychiatrist appt in washout period₮	15	18	14	0.113	16	16	16	0.011
Mental health specialist appt in washout period₮	18	21	17	0.110	16	15	17	0.059
Demographics								
Age, mean (SD)	39 (9)	41 (9)	39 (9)	0.234	39 (9)	39 (9)	39 (9)	0.033
Male	82	90	80	0.279	83	89	81	0.228
White	63	71	60	0.222	62	63	62	0.004
Black	27	18	30	0.264	28	29	28	0.029
Other/unknown	10	11	10	0.032	10	8	10	0.051
Hispanic	21	22	21	0.019	20	16	21	0.141
Health Insurance$^{\Omega}$								
Private	6	6	7	0.018	7	7	7	0.022
Public	27	29	27	0.052	26	24	27	0.055
Unknown	66	65	67	0.040	67	69	66	0.063
Uninsured	0	0	0	0.000	0	0	0	0.000
Health status								
Viral load <200 mL¥	70	74	68	0.129	69	69	70	0.019
CD4 count, mean (SD) ¥	495 (279)	504 (274)	492 (282)	0.043	501 (293)	513 (317)	498 (286)	0.057
Alcohol use×	12	11	13	0.052	14	16	13	0.099
Drug use×	31	38	29	0.203	30	29	31	0.047
Smoker ever×	33	30	34	0.071	37	43	34	0.182
Anxiety×	25	22	26	0.088	25	26	24	0.024
On ART at index date	86	88	86	0.059	85	84	86	0.050
Clinic								
A	16	18	15	0.090	15	14	16	0.037
B	35	29	37	0.153	37	41	36	0.097

C	28	29	28	0.035	27	27	27	0.018
D	13	13	13	0.010	12	11	13	0.047
E	8	10	8	0.075	8	7	8	0.037

STD: Standardized difference
ADT: Antidepressant treatment
APPT: Appointment
No statistically significant comparisons at $p < 0.05$
*Weighted with inverse probability of treatment and observation (IPTO) weights
**Weighted with inverse probability of treatment (IPT) weights
€ ADT received prior to the current treatment episode but the prior period of treatment did not have a 90-day washout period
ǂ Appointments in the washout period but the appointment did not occur more than 6 months prior to the index date if the washout period was more than 90 days
Ω Last insurance status reported in the past year from the index date
¥ Labs taken closest to the index date but not occurring more than 6 months prior to the index date if the washout period was more than 90 days
ˣ Lifetime occurrence

Table 4 IPTO weighted generalized linear models for per protocol analysis

	Remission		**Depression symptom severity**	
	Odds ratio	**95% C.I.**	**Mean difference (PHQ-9)**	**95% C.I.**
Dual-action (Ref: Single-action)	1.33	0.55,3.21	-0.7	-3.2,1.7

IPTO – Inverse probability of treatment and observation
No statistically significant comparisons at $p < 0.05$

Highlights:

- Dual-action and single-action antidepressants were compared in people with HIV
- Both types of antidepressants are effective for depression in people with HIV
- Both types of antidepressants are suitable 1st line treatments for people with HIV
- Depression remission rates were lower than results observed in controlled trials
- Comparisons of other health services for depression are needed in people with HIV

Figure 1: Consort Diagram