AIDS PATIENT CARE and STDs
Volume 26, Number 7, 2012

DOI: 10.1089/apc.2011.0447

Approaches to Identifying Appropriate Medication Adherence Assessments for HIV Infected Individuals with Comorbid Bipolar Disorder

Jayraan Badiee, M.P.H.,[1] Patricia K. Riggs, B.S.,[1] Alexandra S. Rooney, B.A.,[1]
Florin Vaida, Ph.D.,[2] Igor Grant, M.D.,[1] J. Hampton Atkinson, M.D.,[1]
David J. Moore, Ph.D.,[1] and the HIV Neurobehavioral Research Program (HNRP) Group

Abstract

Assessing medication adherence in already difficult-to-treat HIV-infected subpopulations presents a unique challenge. The objective of this study was to compare different approaches to assessing medication adherence: (1) electronic medication monitoring, (2) standardized self-report questionnaire, and (3) self-report visual analogue scale, and to determine whether antiretroviral therapy (ART) adherence measures differed for HIV-infected persons with bipolar disorder (HIV+ /BD+) as compared to HIV-infected persons without bipolar disorder (HIV+ /BD−). ART adherence was assessed for 74 HIV-positive participants using the Medication Event Monitoring System (MEMS), AIDS Clinical Trials Group (ACTG) adherence questionnaire, and visual analogue scale (VAS). Participants were classified as adherent or nonadherent on each measure by previously validated cutscores. Correlations and logistic regressions were used to examine associations between adherence measures and demographic and clinical variables. In the HIV+ /BD− group, significant correlations existed between each self-report measure and the MEMS. Males comprised 81% of the study population. Participants averaged 44 years of age and 13 years of education. No significant correlations were found among adherence measures in the HIV+ /BD+ group. Among participants reporting adherence on either self-report measure but classified as nonadherent based on MEMS, 94% had a diagnosis of bipolar disorder. Bipolar disorder was a significant predictor of adherence classification discordance among self-report measures. Our findings suggest that it remains difficult to assess ART adherence among HIV-positive individuals with bipolar disorder. Combined approaches of self-report and objective measures may be the best way to estimate adherence, and may provide the best basis for interventions designed to improve adherence in difficult-to-treat populations.

Introduction

Among HIV-infected individuals, survival and quality of life have improved markedly as a result of improved antiretroviral treatment (ART).[1–4] Despite these improvements in outcomes as a result of ART treatment, medications still need to be taken, and taken consistently, to work effectively.[5,6] Although poor ART adherence does not mean a complete lack of therapeutic benefit,[7] it is clear that benefits increase as adherence improves,[8,9] and the best outcomes are associated with better adherence.[10,11] Limited ART adherence may create treatment-resistant HIV-strains, and poorer clinical outcomes including virologic failure and death.[9,12,13] Less complicated ART regimens are now available and decrease adherence demands, yet, once-daily dosing may only generate a modest improvement in adherence.[14]

There are several threats to effective medication adherence among HIV infected persons including lack of access to treatment, social support, and significant side effects.[15] One often overlooked factor that appears to negatively impact adherence to HIV medications is the co-occurrence of serious mental illness (SMI) and HIV infection.[16,17] Of note, HIV infection appears to be significantly more prevalent among individuals with SMI compared to the general population,[18–22] and individuals with SMI represent a growing subset of persons living with HIV.[23–25] Patients with bipolar

Departments of [1]Psychiatry, [2]Family and Preventive Medicine, University of California, San Diego, School of Medicine, La Jolla, California.

disorder (BD), especially those with co-occurring substance use disorders, appear much more likely to be HIV infected than the general population and represent a rarely recognized, and infrequently studied, subgroup of HIV-infected patients.[26–29]

A small number of studies have focused on medication adherence and the lack of data on medication adherence difficulties among HIV-positive persons with BD.[10,30–32] Treating both disorders (HIV infection and BD) is expensive, and becomes even more costly when patients are nonadherent to prescribed medication regimens. There are numerous factors that may be important for medication adherence among HIV-positive individuals with comorbid bipolar disorder including psychiatric fluctuations, greater pill burden, and stability of living situation.[30] In studies of HIV-uninfected persons with BD, nonadherence to psychotropic medication can have significant consequences as well; individuals who fail to adhere to their psychiatric medications are at greater risk for both manic and depressive episodes.[33] Mood instability can increase risk for dangerous behaviors such as suicide, substance use, and unprotected sexual activity.[34–36] Poor adherence is common among individuals with BD.[33] Outcomes for patients with BD who are nonadherent are at higher risk of relapse, recurrence, and hospitalization.[37,38] Moreover, there is the possibility that nonadherence to psychiatric medications may in turn lead to nonadherence to antiretroviral medications.[39]

Multiple methods have been utilized to assess medication adherence in HIV-infected persons. Some of the most commonly used adherence assessment methodologies include the Medication Event Monitoring System (MEMS), the AIDS Clinical Trials Group (ACTG) adherence questionnaire,[40] and the visual analogue scale (VAS).[41] The MEMS methodology provides detailed, objective, and comprehensive adherence data. MEMS devices are thought to provide a more accurate estimate of adherence than self-report or pill counts.[42–44] MEMS generates data on the date and time of cap openings and serves as a proxy for medication taking at those times. The latter two methods (ACTG and VAS) rely on participant self-report. The ACTG 4-day questionnaire has been widely used to gauge adherence in HIV-positive individuals[40] and asks participants to recall the number of pills they have missed over the past 4 days. Although the ACTG questionnaire is commonly used and easy to administer, it only provides a partial picture of an individual's overall adherence. On the other hand, the VAS is a more abstract method of assessing medication adherence and also requires persons to inherently understand the idea of percentages.

Each of these methods have advantages and disadvantages, and the accuracy of these measures to true ART adherence may be further complicated by mental illness. Although the MEMS can provide objective adherence data, it may be unreliable in populations such as HIV-positive persons with bipolar disorder because of the cumbersome nature of MEMS caps, the difficulty of concurrently using other adherence assistive devices (e.g., pill organizers, blister packs), and the nomadic nature of some patients who might keep supplies of medications at multiple locations rather than taking medications from a consistent place at a consistent time. In addition, the cost of MEMS can be prohibitive and is not well-suited for use in clinical settings. The self-report measures, on the other hand, may be difficult for mental health populations because of problems with insight and response bias (e.g., persons wanting to present themselves in a favorable light).

Few studies have compared these adherence measures in HIV-positive populations. In a low-income HIV-positive population, the VAS and ACTG correlated comparably well to a gold standard of unannounced pill counts.[45] Findings from a resource-limited setting also indicate strong correlations between self-report adherence measures (i.e., VAS and ACTG) and objective measures of adherence (i.e., MEMS and pill counts).[46] However, in a community-based sample of HIV-positive individuals, rates of MEMS adherence were consistently lower than rates of ACTG adherence.[47] In an extensive review, Simoni and colleagues[48] identified numerous studies comparing various adherence measures and the methodological difficulties associated with assessing medication adherence accurately in HIV-positive populations; however, this review did not address the potential impact of mental illness on adherence measurement. Investigators have also further emphasized the usefulness of assessing adherence both subjectively and objectively,[49] as well as combining multiple assessments of adherence in clinical practice.[50]

Assessing medication adherence in difficult-to-treat subpopulations presents a unique challenge and a true gold standard for assessing medication adherence in these populations has not been identified. To that end, the objective of this study was to compare electronic monitoring of medication adherence (MEMS) to two different self-report measures of adherence (ACTG and VAS) and to determine whether adherence reports differ for HIV+/BD+ individuals as compared to HIV+/BD− individuals.

Methods

Participants

Forty-three HIV-infected individuals with comorbid bipolar disorder (HIV+/BD+) and 31 HIV-infected individuals without bipolar disorder (HIV+/BD−) underwent a comprehensive adherence assessment. All participants recruited into the bipolar group were required to be taking medications to treat both HIV infection and bipolar disorder. HIV+/BD− comparison participants were required to be taking medication to treat their HIV illness.

Participants were excluded from the study if they met DSM-IV criteria for a psychotic spectrum disorder (e.g., schizophrenia), mood disorder due to a general medical condition, or if they had a neurologic condition known to impact cognitive functioning such as stroke, traumatic brain injury, or a closed head injury with loss of consciousness for more than 30 min. After meeting all the above prerequisites, the participants provided written informed consent to participate. All participants received monetary compensation for both the initial and follow-up assessments.

Procedure

Participants were recruited from ongoing studies at the HIV Neurobehavioral Research Center at the University of California, San Diego. The present study was designed to recruit HIV+/BD+ participants as well as a demographically comparable group of HIV+/BD− participants. Participants were administered a multimodal series of assessments that included adherence measures, a medical examination

and interview, psychiatric evaluation, and blood work. The present study was approved by the local Institutional Review Board.

A master's- or Ph.D.-level clinician assigned diagnoses of bipolar disorder I or II based on the Structured Clinical Interview for DSM-IV (SCID). The SCID was used for BD diagnosis as it is considered the gold standard in determining psychiatric diagnoses. Participants in the HIV+ /BD+ group must have met diagnostic criteria for bipolar disorder (I or II). Participants in the HIV+ /BD− group were not excluded if they met diagnostic criteria for major depressive disorder (MDD) because of the high occurrence of MDD in HIV infection and the desire to have a comparison group that was representative of the overall HIV-infected population in the United States.

We used three different approaches to assessing medication adherence in this study.

1. Medication Event Monitoring System (AARDEX, Switzerland): An objective measure of medication adherence was calculated using the MEMS over the last 30 days. At the initial assessment we selected a "sentinel" ART medication to be tracked for the MEMS. The sentinel drug was the participant's protease inhibitor (PI), since this is the agent most critically sensitive to nonadherence. If the participant was not prescribed a PI, we selected the most frequently dosed non-nucleoside reverse transcriptase inhibitor (NNRTI) or nucleoside reverse transcriptase inhibitor (NRTI) as the sentinel drug to complete our sample. The primary outcome variable for analysis was MEMS-derived percent adherence over the last 30 days (number of bottle openings divided by number of prescribed doses multiplied by 100) dichotomized into adherent (≥90%) or nonadherent (<90%). This 90% cut score has shown sensitivity to adverse events in previous studies of HIV infection,[51] as well as studies of HIV infection in SMI.[31] We adjusted adherence to a maximum of 100% in order to control for overestimating adherence and assured that the number of recorded events does not exceed the number of prescribed doses.
2. ACTG 4-day adherence to antiretrovirals questionnaire[40]: For the present study we used the ACTG 4-day questionnaire as one measure of self-reported adherence. The ACTG adherence questionnaire was completed at the follow-up visit when MEMS caps were returned. Data from the ACTG were dichotomized into adherent (≥95%) or nonadherent (<95%). This 95% cut score was shown to be predictive of virologic response.[52] The ACTG questionnaire records the 4-day adherence for all prescribed antiretrovirals. In order to be consistent with the MEMS and VAS data, only the ACTG 4-day adherence data for the sentinel medication was used in this comparative study. The adherence percentage for this assessment = 1 − (number of missed dosage units ÷ number of dosage units prescribed) × 100.
3. VAS[41]: Participants were presented with a 100-mm line anchored at 0% and 100%. They were then asked to mark a line on the scale indicating their adherence over the past 30 days to the sentinel ART medication.[41] The data from the VAS were gathered at the follow-up visit when MEMS caps were returned. Data from the VAS were dichotomized into adherent (≥95%) or nonadherent (<95%). This 95% cut score was used in order to be consistent with both the other self-report measure used in this study (ACTG questionnaire) and what has been reported in relevant literature.[53] The adherence percentage was determined by measuring the length (in millimeters) between the 0% anchor and the participant's pencil mark (e.g., 85 mm = 85% adherent).

Statistical analyses

Data were analyzed using JMP version 8.0. Frequencies and descriptive statistics were computed for clinical and demographic variables. χ^2 tests were used to assess group differences for categorical variables. *t* tests were used to assess group differences for continuous variables. Nonparametric tests were used for non-normally distributed variables. Nonparametric correlations and multivariate regression models were used to compare the three measures of medication adherence.

Because of known biases of the electronic monitoring methodology (i.e., underestimating adherence) compared to self-report methodologies (i.e., overestimating adherence), we chose to use a single previously established cut point for each adherence measure (VAS: ≥95%; MEMS: ≥90%; ACTG: ≥95%). These cut points are consistent with those frequently used in the literature.[31,51–53] In order to capture potential bias from these established cut points, we also analyzed continuous adherence measures.

All medication adherence measures were analyzed both continuously and dichotomously. Correlations between continuous adherence measures were assessed using Spearman's ρ, due to the non-normal distribution of these measures. Separate regression models were used to analyze the relationship between each individual adherence measure and MEMS adherence. In each multivariate regression model, MEMS adherence was evaluated as a dichotomous outcome measure. Covariates included in each model were the individual adherence measure (either continuous or dichotomized), BD status, and the interaction between these two terms.

Logistic regression was used for models in which MEMS adherence was evaluated as a dichotomous outcome. As a continuous outcome, the MEMS adherence measure was transformed by subtracting the MEMS adherence value from 100 and evaluated using overdispersed Poisson (quasi-Poisson) generalized linear models.[54] On this transformed scale, perfect MEMS adherence counts as a zero. The quasi-Poisson model is invariant to rescaling the outcome by a multiplicative factor. This model was used due to the pronounced skew of the distribution of MEMS toward 100% adherence.

Discrepancies between the self-report adherence measures (ACTG and VAS) and MEMS (an objective measure) were examined by creating a nominal discrepancy variable with four levels: (1) adherent by either self-report measure and MEMS; (2) adherent by MEMS and nonadherent by either self-report measure; (3) nonadherent by MEMS and adherent by either self-report measure; and (4) nonadherent by MEMS and either self-report measure. This variable was used to examine potential correlates of discordant adherence classifications. Discrepancy variables were also created to examine discordance between MEMS and each individual self-report

adherence measure. Multinomial logistic regressions were used to evaluate predictors of adherence classification discordance.

Results

Characteristics of the entire sample are provided in Table 1. The HIV+ /BD+ and HIV+ /BD− groups were comparable on all descriptive and HIV disease characteristics. There were no significant differences in mean number of prescription medications and mean total doses of prescription medications per day between HIV+ /BD+ and HIV+ /BD− participants. Rates of current substance abuse or dependence were low in the study population (i.e., less than 8% for alcohol, cocaine, marijuana, and methamphetamine). Overall, 66% of the study population ($n=49$) was classified as adherent to their antiretroviral medications based on the MEMS. Using the VAS adherence measure, 59% of participants were adherent, and 87% were adherent based on the ACTG measure. Proportion adherent using standard cutscores by bipolar status are provided in Fig. 1. As shown in Fig. 2, mean percentages of MEMS and VAS adherence were significantly higher in HIV+ /BD− individuals than in HIV+ /BD+ individuals (MEMS: 94% versus 76%, $p=0.001$; VAS: 91% versus 87%, $p=0.04$). There was no significant difference in mean percentage of ACTG adherence between the two groups. Detailed analysis of the MEMS data has been previously published.[16]

Among HIV+ /BD− participants, there was a significant correlation between continuous values of adherence on each of the self-report measures of ART adherence (ACTG and VAS) and ART adherence measured by MEMS (ACTG/MEMS, Spearman's $\rho=0.48$, $p=0.008$; VAS/MEMS, Spearman's $\rho=0.56$, $p=0.001$). Interestingly, there was not a significant correlation between the two self-report ART adherence measures (i.e., ACTG and VAS) in this group (Spearman's $\rho=0.29$, $p=0.13$). Among HIV+ /BD+ participants, there were no significant correlations among any of the ART adherence measures (ACTG/MEMS, Spearman's $\rho=0.20$, $p=0.22$; VAS/MEMS, Spearman's $\rho=0.08$, $p=0.66$; ACTG/VAS, Spearman's $\rho=0.17$, $p=0.30$).

To further examine the association between the self-report measures and MEMS by group, we conducted logistic regression analyses using MEMS adherent/nonadherent as the outcome. A regression analysis examining VAS (continuous) and group (HIV+ /BD− versus HIV+ /BD+) predicting dichotomous MEMS ART adherence was significant and showed that continuous VAS adherence ($p<0.0001$) and group ($p<0.0001$) were each significantly predictive of MEMS adherence (overall model: $\chi^2=33.9$; $df=3$; $p<0.0001$; $R^2=0.39$). The interaction between VAS and BD status was also significant ($p<0.001$). Results were comparable when the VAS was analyzed as a dichotomous predictor. In a parallel logistic regression analysis evaluating ACTG adherence and BD status as predictors of MEMS adherence, the overall model was significant ($\chi^2=21.0$; $df=2$; $p<0.0001$; $R^2=0.25$); however, only BD status was significantly associated with MEMS ART adherence ($p=0.001$). Neither the continuous nor the dichotomous ACTG adherence measures were significantly associated with MEMS adherence (continuous $p=0.11$, dichotomous $p=0.08$); the interaction between BD status and ACTG adherence was not significant in either ACTG analysis (dichotomous ACTG $p=0.77$, continuous ACTG $p=0.67$).

Adherence classifications based on adherent/nonadherent classification between self-report measures and MEMS were in agreement for the majority of the study group ($n=51$, 72%). Bipolar diagnosis was a significant predictor of adherence classification discordance among the adherence measures ($\chi^2=16.5$, $p<0.001$). Among those who were adherent by self-report measures but nonadherent by MEMS ($n=18$), 94% ($n=17$) had a diagnosis of bipolar disorder. Bipolar diagnosis was also a significant predictor of ACTG/MEMS adherence discrepancy ($p<0.001$) and of VAS/MEMS adherence discrepancy ($p<0.001$). Demographic (age, gender, education) and clinical characteristics (plasma HIV RNA, current CD4 count, CD4 nadir, HCV status, and BDI-II total score) were not associated with adherence classification discordance.

Table 1. Demographic and Clinical Characteristics of Study Population ($N=74$)

Age (yrs; mean, SD)	44.8 (8.3)
Gender (*n*, % male)	60 (81%)
Education (yrs; mean, SD)	13.2 (2.3)
Bipolar (*n*, %)	43 (58%)
Current CD4 (cells/mm^3; median, IQR)	541 (334-847)
Nadir CD4 (cells/mm^3; median, IQR)	128 (20-263)
Plasma HIV RNA <50 c/mL	56 (76%)
HCV+	10 (14%)
BDI-II Total (median, IQR)	10 (3-19)
YMRS Total (median, IQR)	4.5 (1.8-8.3)
# Rx Meds (mean, SD)	8.3 (4.1)
# Rx med doses/day (mean, SD)	14.2 (9.0)

SD, standard deviation; IQR, interquartile range; HCV, hepatitis C virus; BDI-II, Beck Depression Inventory–II; YMRS, Young Mania Rating Scale.

Discussion

Findings from our study show that estimated adherence rates can vary greatly when assessing HIV-positive individuals with co-occurring bipolar disorder. That is, among HIV-positive persons without bipolar disorder, both self-report ART adherence measures (ACTG and VAS) correlated significantly with the objective assessments of medication adherence (i.e., MEMS), whereas correlations among self-report and objective measures were not significant in the dually affected (HIV+ /BD+) group. This suggests that HIV-positive individuals without a co-occurring bipolar diagnosis may be able to accurately assess their medication adherence abilities utilizing self-report measures. However, HIV-positive persons with bipolar disorder did not show these associations suggesting difficulties with insight into adherence abilities. Alternatively, the broader range of MEMS values among HIV-positive persons with bipolar disorder may increase difficulty of providing an accurate self-report compared to HIV-positive persons without bipolar disorder who were more likely to be adherent.[16]

In the HIV+ /BD− group, the correlation between VAS and MEMS (Spearman's $\rho=0.56$) was slightly stronger than the correlation between ACTG and MEMS (Spearman's $\rho=0.48$), suggesting that the VAS may slightly better reflect objective MEMS adherence than the ACTG 4-day questionnaire in those without bipolar disorder, which is consistent

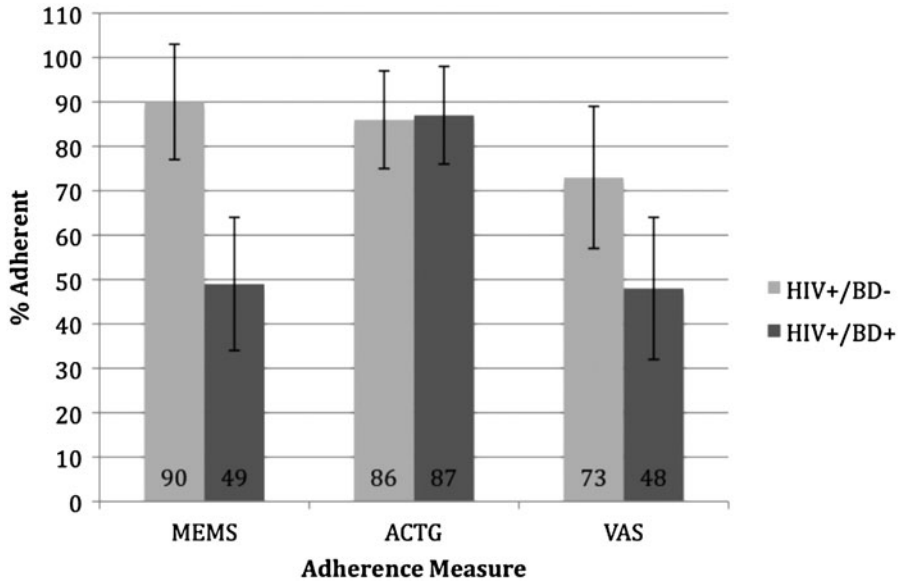

FIG. 1. Proportion deemed adherent based on common cutscores for given measurement tools between HIV+/BD− and HIV+/BD+ individuals (MEMS $p<0.0001$; ACTG $p=0.90$; VAS $p=0.04$); error bars denote 95% confidence intervals. BD, bipolar disorder; MEMS, Medication Event Monitoring System; ACTG, AIDS Clinical Trials Group (ACTG) adherence questionnaire; VAS, visual analogue scale.

with other reports.[45,46] Greater overlap in the time periods assessed by these measures (i.e., both the MEMS and VAS are 30-day instruments whereas the ACTG is a 4-day assessment) may have also contributed to the stronger correlation. The significant interaction between VAS and BD status reinforced the finding that VAS was associated with MEMS in HIV+/BD− individuals, but not in HIV+/BD+ individuals. The ACTG adherence data were not significantly associated with MEMS adherence when using the regression approach, and again seems to suggest that the VAS may more strongly approximate the values generated by an objective approach as compared to the ACTG 4-day questionnaire among individuals without bipolar disorder.

The lack of significant associations between any of the adherence indicators among HIV-positive individuals with bipolar disorder speaks to the considerable difficulties in finding a reliable methodology for adherence assessment in this population. The objective MEMS data has been shown to be significantly associated with clinical outcomes in our cohort, and this method does appear to provide the most reliable data[16]; however, utilizing MEMS may not be pragmatic in most clinical situations. Composite approaches[42] have been proposed, but again, likely require more effort than is available in all but the most comprehensive clinical assessments. Directly observed therapy may be another possible approach to adherence improvement, but this approach can be burdensome.[55] At this point in time, the most practical solution may be to assume that there is no optimal assessment of adherence for persons with HIV and bipolar disorder and to recognize that each approach has its own limitations. As such, a multipronged approach may be the most accurate way to assess ART adherence in this population, a suggestion that has been echoed in prior reports.[49]

Interestingly, no significant correlation was found between the ACTG and the VAS in either study group suggesting differences in outcomes based on the utilized self-report methodology; this may be as a result of minimal overlap time in the periods questioned in these assessments. Interchangeably using the most common self-report adherence assessments may not be appropriate as has been previously shown.[46]

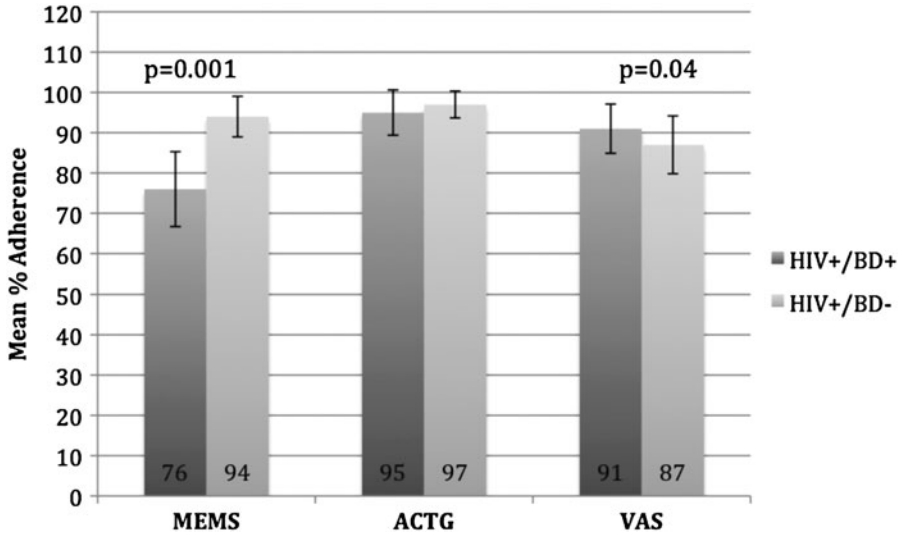

FIG. 2. Mean adherence percentages by bipolar status.

Administration of inappropriate adherence measures may result in an incomplete picture of ART adherence in populations that are most in need of effective interventions to improve medication adherence and health outcomes.

Limitations

Several potentially confounding factors may have limited the results of the present study. Study limitations included the relatively small sample size, although this represents a large sample of participants who are difficult to track and assess. Non-normal distributions of the adherence data limited the scope of the statistical analyses. Other methods of adherence assessment could have been taken into account, such as pill counts and pharmacy refill records. Since participants in this study tended to refill their medications often, and were prone to frequent pharmacy changes, evaluation of these methods was not ideal.

Future directions

Results from this study could be used to inform future investigations to improve, refine and develop a standardized ART adherence assessment for use in clinical settings. Adoption of a standardized adherence measure in HIV clinical care as well as education about the limitations of self-report measures in certain subsets of the HIV-infected population (i.e., individuals with serious mental illness) may be recommended and may be superior to other approaches. Intervention studies for improving adherence to psychiatric and HIV medications are crucial in order to find methods for effectively improving adherence in difficult-to-evaluate subpopulations. However, results from this study show that careful consideration of adherence assessment methodology is warranted for future studies.

Author Disclosure Statement

No competing financial interests exist.

References

1. Brettle RP, Wilson A, Povey S, et al. Combination therapy for HIV: The effect on inpatient activity, morbidity and mortality of a cohort of patients. Int J STD AIDS 1998;9:80–87.
2. Heaton RK, Clifford DB, Franklin DR, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy CHARTER Study. Neurology 2010;75: 2087–2096.
3. Morineau G, Vun MC, Barennes H, et al. Survival and quality of life among HIV-positive people on antiretroviral therapy in Cambodia. AIDS Patient Care STDs 2009;23:669–677.
4. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853–860.
5. Kelly JA, Kalichman SC. Behavioral research in HIV/AIDS primary and secondary prevention: Recent advances and future directions. J Consult Clin Psychol 2002;70:626–639.
6. Nachega JB, Hislop M, Dowdy DW, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. J Acquir Immune Defic Syndr 2006;43:78–84.
7. Bangsberg DR, Deeks SG. Is average adherence to HIV antiretroviral therapy enough? J Gen Intern Med 2002;17:812–813.
8. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 2001;15:1181–1183.
9. Gross R, Yip B, Lo Re V, 3rd, et al. A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. J Infect Dis 2006;194:1108–1114.
10. Carrico AW, Bangsberg DR, Weiser SD, Chartier M, Dilworth SE, Riley ED. Psychiatric correlates of HAART utilization and viral load among HIV-positive impoverished persons. AIDS 2011;25:1113–1118.
11. Deeks SG, Hecht FM, Swanson M, et al. HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: Response to both initial and salvage therapy. AIDS 1999;13:F35–43.
12. Hinkin CH, Castellon SA, Durvasula RS, et al. Medication adherence among HIV+ adults: Effects of cognitive dysfunction and regimen complexity. Neurology 2002;59:1944–1950.
13. Kalichman SC. Co-occurrence of treatment nonadherence and continued HIV transmission risk behaviors: Implications for positive prevention interventions. Psychosom Med 2008;70:593–597.
14. Parienti JJ, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: A meta-analysis. Clin Infect Dis 2009;48:484–488.
15. Malta M, Magnanini MM, Strathdee SA, Bastos FI. Adherence to antiretroviral therapy among HIV-infected drug users: A meta-analysis. AIDS Behav 2010;14:731–747.
16. Moore DJ, Posada C, Parikh M, et al. HIV-infected individuals with co-occurring bipolar disorder evidence poor antiretroviral and psychiatric medication adherence. AIDS Behav (in press).
17. Walkup J, Akincigil A, Bilder S, Rosato NS, Crystal S. Psychiatric diagnosis and antiretroviral adherence among adolescent Medicaid beneficiaries diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome. J Nerv Ment Dis 2009;197:354–361.
18. Cournos F, McKinnon K. HIV seroprevalence among people with severe mental illness in the United States: A critical review. Clin Psychol Rev 1997;17:259–269.
19. Essock SM, Dowden S, Constantine NT, et al. Risk factors for HIV, hepatitis B, and hepatitis C among persons with severe mental illness. Psychiatr Serv 2003;54:836–841.
20. Goldberg RW. Supported medical care: A multi-faceted approach to helping HIV/hepatitis C virus co-infected adults with serious mental illness. AIDS 2005;19(Suppl 3):S215–220.
21. Rosenberg SD, Goodman LA, Osher FC, et al. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness. Am J Public Health 2001;91:31–37.
22. Rosenberg SD, Swanson JW, Wolford GL, et al. The five-site health and risk study of blood-borne infections among persons with severe mental illness. Psychiatr Serv 2003;54:827–835.
23. Klinkenberg WD, Sacks S. Mental disorders and drug abuse in persons living with HIV/AIDS. AIDS Care 2004;16(Suppl 1):S22–42.
24. Weiser SD, Wolfe WR, Bangsberg DR. The HIV epidemic among individuals with mental illness in the United States. Curr Infect Dis Rep 2004;6:404–410.

25. Gaynes BN, Pence BW, Eron JJ, Jr., Miller WC. Prevalence and comorbidity of psychiatric diagnoses based on reference standard in an HIV+ patient population. Psychosom Med 2008;70:505–511.
26. Beyer JL, Taylor L, Gersing KR, Krishnan KR. Prevalence of HIV infection in a general psychiatric outpatient population. Psychosomatics 2007;48:31–37.
27. Otto-Salaj LL, Stevenson LY. Influence of psychiatric diagnoses and symptoms on HIV risk behavior in adults with serious mental illness. AIDS Read 2001;11:197–204, 206–198.
28. Sacks MH, Silberstein C, Weiler P, Perry S. HIV-related risk factors in acute psychiatric inpatients. Hosp Community Psychiatry 1990;41:449–451.
29. Walkup J, Crystal S, Sambamoorthi U. Schizophrenia and major affective disorder among Medicaid recipients with HIV/AIDS in New Jersey. Am J Public Health 1999;89:1101–1103.
30. Kemppainen JK, Levine R, Buffum M, Holzemer W, Finley P, Jensen P. Antiretroviral adherence in persons with HIV/AIDS and severe mental illness. J Nerv Ment Dis 2004;192:395–404.
31. Wagner GJ, Kanouse DE, Koegel P, Sullivan G. Adherence to HIV antiretrovirals among persons with serious mental illness. AIDS Patient Care STDs 2003;17:179–186.
32. Wagner GJ, Kanouse DE, Koegel P, Sullivan G. Correlates of HIV antiretroviral adherence in persons with serious mental illness. AIDS Care 2004;16:501–506.
33. Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. Am J Psychiatry 2002;159:1927–1929.
34. Hanson M, Kramer TH, Gross W, Quintana J, Li PW, Asher R. AIDS awareness and risk behaviors among dually disordered adults. AIDS Educ Prev. Spring 1992;4:41–51.
35. Kapetanovic S, Wiegand RE, Dominguez K, et al. Associations of medically documented psychiatric diagnoses and risky health behaviors in highly active antiretroviral therapy-experienced perinatally HIV-infected youth. AIDS Patient Care STDs 2011;25:493–501.
36. Sacks M, Dermatis H, Looser-Ott S, Perry S. Seroprevalence of HIV and risk factors for AIDS in psychiatric inpatients. Hosp Community Psychiatry 1992;43:736–737.
37. Li J, McCombs JS, Stimmel GL. Costs of treating bipolar disorder in the California Medicaid (Medi-Cal) program. J Affect Disord 2002;71:131–139.
38. Scott J, Pope M. Non-adherence with mood-stabilizers: Prevalence and predictors. J Clin Psychiatry 2002;63:384–389.
39. Lee S, Rothbard AB, Noll E, Blank MB. Use of HIV and psychotropic medications among persons with serious mental illness and HIV/AIDS. Adm Policy Ment Health 2011;38:335–344.
40. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: Tthe AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committe of the Adult AIDS Clinical Trials Group (AACTG). AIDS Care 2000;12:255–266.
41. Amico KR, Fisher WA, Cornman DH, et al. Visual analog scale of ART adherence: Association with 3-day self-report and adherence barriers. J Acquir Immune Defic Syndr 2006;42:455–459.
42. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med 2001;134:968–977.
43. Twagirumukiza M, Kayumba PC, Kips JG, et al. Evaluation of medication adherence methods in the treatment of malaria in Rwandan infants. Malar J 2010;9:206.
44. Vriesendorp R, Cohen A, Kristanto P, et al. Adherence to HAART therapy measured by electronic monitoring in newly diagnosed HIV patients in Botswana. Eur J Clin Pharmacol 2007;63:1115–1121.
45. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. HIV Clin Trials 2004;5:74–79.
46. Oyugi JH, Byakika-Tusiime J, Charlebois ED, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. J Acquir Immune Defic Syndr 2004;36:1100–1102.
47. Levine AJ, Hinkin CH, Marion S, et al. Adherence to antiretroviral medications in HIV: Differences in data collected via self-report and electronic monitoring. Health Psychol 2006;25:329–335.
48. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. AIDS Behav 2006;10:227–245.
49. Pearson CR, Simoni JM, Hoff P, Kurth AE, Martin DP. Assessing antiretroviral adherence via electronic drug monitoring and self-report: An examination of key methodological issues. AIDS Behav 2007;11:161–173.
50. Deschamps AE, De Geest S, Vandamme AM, Bobbaers H, Peetermans WE, Van Wijngaerden E. Diagnostic value of different adherence measures using electronic monitoring and virologic failure as reference standards. AIDS Patient Care STDs 2008;22:735–743.
51. Singh N, Berman SM, Swindells S, et al. Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. Clin Infect Dis 1999;29:824–830.
52. Fletcher CV, Testa MA, Brundage RC, et al. Four measures of antiretroviral medication adherence and virologic response in AIDS clinical trials group study 359. J Acquir Immune Defic Syndr 2005;40:301–306.
53. Harris J, Pillinger M, Fromstein D, et al. Risk factors for medication non-adherence in an HIV infected population in the Dominican Republic. AIDS Behav 2011;15:1410–1415.
54. McCullagh P, Nelder JA. Generalized Linear Models. New York: Chapman and Hall, 1989.
55. Ford N, Nachega JB, Engel ME, Mills EJ. Directly observed antiretroviral therapy: A systematic review and meta-analysis of randomised clinical trials. Lancet 2009;374:2064–2071.

Address correspondence to:
David J. Moore, Ph.D.
220 Dickinson Street, Suite B
Mail Code 8231
San Diego, CA 92103-8231

E-mail: djmoore@ucsd.edu