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Authors

Kamat, Rujvi

Cattie, Jordan E

Marcotte, Thomas D

et al.

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Incident Major Depressive Episodes increase the severity and risk of apathy in HIV infection

Rujvi Kamat[a,b], **Jordan E. Cattie**[a], **Thomas D. Marcotte**[b], **Steven Paul Woods**[b], **Donald R. Franklin**[b], **Stephanie H. Corkran**[b], **Ronald J. Ellis**[c], **Igor Grant**[b], **Robert K. Heaton**[b], and **the HIV Neurobehavioral Research Program (HNRP) Group**

[a]San Diego University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California 92120, USA

[b]Department of Psychiatry, University of California, San Diego, La Jolla, California, 92093, USA

[c]Department of Neurosciences, University of California, San Diego, School of Medicine, La Jolla, California, 92093, USA

Abstract

Apathy and depression are inter-related yet separable and prevalent neuropsychiatric disturbances in persons infected with HIV. In the present study of 225 HIV+ persons, we investigated the role of an incident depressive episode in changes in apathy. Participants completed the apathy subscale of the Frontal Systems Behavior Scale during a detailed neuropsychiatric and neuromedical evaluation at visit 1 and again at approximately a 14 month follow-up. The Composite International Diagnostic Interview was used to obtain diagnoses of a new major depressive disorder. At their follow-up visit, participants were classified into four groups depending on their visit 1 elevation in apathy and new major depressive episode (MDE) status. Apathetic participants at baseline with a new MDE (n=23) were at risk for continued, clinically elevated apathy at follow-up, although severity of symptoms did not increase. Of the 144 participants without clinically elevated apathy at visit 1, those who developed a new MDE (n=16) had greater apathy symptomatology at follow-up than those without MDE. These findings suggest that HIV+ individuals, who do not as yet present with elevated apathy, may be at greater risk of elevated

Corresponding author: Rujvi Kamat, Ph.D. rkamat@ucsd.edu.

Conflict of interest

The authors have nothing to disclose regarding relationships that could be interpreted as a conflict of interest.

Contributors

Drs. Grant, Heaton, and Ellis serve as PIs of the parent study. Ms. Kamat completed the literature search, statistical analyses, and wrote the drafts of the manuscript. Dr. Wood and Marcotte assisted with study design and reviewed manuscript drafts. Mr. Franklin, Ms. Corkran, and Ms. Cattie assisted with data analyses and manuscript preparation. All authors contributed to and have approved the final manuscript.

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psychiatric distress should they experience a new/recurrent depressive episode. Thus, in the context of previous findings, it appears that although apathy and depression are separable constructs, they interact such that a new depressive episode is a risk factor for incident apathy.

Keywords

HIV/AIDS; Neuropsychiatry; motivation; longitudinal study

In the past decade, research has identified the apathy syndrome as a distinct and clinically significant neuropsychiatric disturbance, which, alongside depressive disorders, increases risk of disability across many patient populations (e.g., Freds et al., 1992; Posada et al., 2010), including persons living with HIV infection (e.g., Barclay et al., 2007; Tate et al., 2003). Apathy refers to a cluster of symptoms representing a lack of motoric, emotional, and cognitive motivation (e.g., reduced drive, poor initiation and control of self-directed purposeful behavior; Marin et al., 1991; Stuss, van Reekum, & Murphy, 2000; Levy & Dubois, 2006). Approximately 30 – 50% of HIV+ individuals present with clinically elevated signs of apathy (Castellon et al., 1998, 2000; Rabkin et al., 2000; Kamat et al., 2012). In HIV-infected persons, apathy symptomatology is associated with poor performance on many instrumental activities of daily living, such as medication adherence and health-related quality of life (e.g., Barclay et al., 2007, Tate et al., 2003; Kamat et al., 2012).

Growing evidence from cross-sectional studies suggests that apathy may arise via direct involvement of the central nervous system in HIV; specifically, from HIV-related injury to frontostriatal circuits including the nucleus accumbens (Paul, Brickman, et al., 2005) and frontal white matter tracts (e.g., corona radiata and corpus callosum; Hoare et al., 2010; Kamat et al., 2014). Although the presence and severity of apathy do not simply reflect HIV disease severity (Castellon et al., 1998; Paul, Flanigan, et al., 2005; Rabkin et al., 2000), a recent study from our group showed stronger relationships between white matter abnormalities and apathy among HIV+ persons with lower CD4 cell counts (Kamat et al., 2014). Apathy severity may also be associated with HIV plasma level (Shapiro et al., 2013). Despite common neurobiological substrates, apathy does not appear to correspond strongly with HIV-associated neurocognitive deficits (Rabkin et al., 2000; Robinson-Papp et al., 2008), although a handful of studies suggest that apathy may be modestly related to impairments in specific aspects of executive functions (Castellon et al., 1998; Paul, Flanigan et al., 2005) and episodic memory (Paul, Flanigan et al., 2005). Thus, the current body of literature suggests that apathy is a discrete neuropsychiatric aspect of HIV disease.

Apathy and depression, often characterized by symptoms of dysphoria and anhedonia, commonly co-occur in HIV infection (e.g., Castellon et al., 2000), but cross-sectional results regarding their association are mixed. At least two studies reported moderately strong, positive correlations between self-reported apathy and depression scores (Castellon et al., 1998; Rabkin et al., 2000), but there is ample evidence of the separability of these related constructs. For example, one study found that elevated levels of apathy are present in non-depressed HIV-infected persons as compared to seronegatives (Hoare et al., 2010). Also,

three studies reported that apathy ratings of HIV+ individuals do not correlate with depressed mood (Paul, Brickman et al., 2005; Paul, Flanigan et al., 2005; Tate et al., 2003), while another study showed that apathy was predictive of problems in everyday functioning independent of depression (Kamat et al., 2012). These findings are consistent with the neurophysiological dissociation between the two syndromes demonstrated by empirical studies in Parkinson's disease (PD) and Alzheimer's disease (AD; e.g., Ott, Noto, Fogel, 1996; Starkstein et al., 1992).

The longitudinal relationship between apathy and depression is of particular interest as each may modify the trajectory of the other. Longitudinal studies allow the characterization of stability and change in individuals over time, help to establish the directionality of hypothesized causal relationships, and identify relationships between variables of interest (Singer & Willett, 2002). A rigorous longitudinal design also may help to further characterize the separability of apathy and depression. For example, in a study of participants with AD, Starkstein and colleagues (2006) found that a depressive episode was neither necessary nor sufficient to produce apathy over time, although apathy at baseline was predictive of a longitudinal increase in depressive symptomatology. In the stroke literature, a longitudinal increase in neuropathology is thought to result in greater comorbidity in apathy and depression over time (Withall et al., 2011), raising the possibility of an additive effect through which the neural mechanisms underlying each syndrome may contribute to the longitudinal exacerbation in neuropsychiatric distress. These longitudinal studies provide early evidence regarding the behavioral and neurologic interplay between apathy and depression, such that, while separable, apathy may serve as a risk factor for the exacerbation of major depressive disorder, and vice versa.

Within HIV+ cohorts, the extant literature has focused solely on the cross-sectional relationship between apathy and current mood symptoms. While it is known that these two syndromes are common in HIV infection, their trajectory over time and the extent to which they interact with each other to modify the risk of exacerbated psychiatric distress is yet to be studied. In the context of neuroAIDS, these important questions have implications for improved interventions for psychiatric outcomes as well as associated declines in daily functioning. Accordingly we aimed to examine, for the first time, the role of an episode of clinical depression in the longitudinal change in apathy. Based on data from non-HIV populations (e.g., Starkstein et al., 2006; Withall et al., 2011), a longitudinal correlation between apathy and depression was expected. We hypothesized that baseline levels of apathy would affect the impact of a new MDD episode on the trajectory of apathy symptomatology in HIV+ persons.

Methods

Participants

Study participants included 225 HIV+ individuals recruited from HIV clinics and community organizations, each of whom underwent detailed neuropsychiatric evaluations at two visits, which were a mean of 14.1 (3.3) months apart (range 10 to 24 months) (see Table 1). These data were derived retrospectively from the HIV Neurobehavioral Research Center, an NIMH-funded cohort study of the features, course, etiology, and pathogenesis of HIV

involvement of the CNS, which was approved by the institutional review board of the University of California, San Diego. Individuals with histories of neurological diseases (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 30 minutes, central nervous systems neoplasms, opportunistic infections) or severe psychiatric illnesses (e.g., schizophrenia) that might affect cognitive functioning were excluded from the study, as were participants who met criteria for current psychoactive drug dependence (i.e., within the past 30 days) at either study visit. Individuals with current major depressive disorder diagnosis at visit 1 were also excluded. This allowed us to specifically examine the effect of a new MDE in the absence of on-going depression. Participants provided written, informed consent, and were only included in this study if they had completed apathy and psychiatric assessments at both visits. HIV status was determined by enzyme-linked immunosorbent assays and confirmed by a western blot test.

Procedure

Apathy Assessment—The 14-item apathy subscale of the self-report version of the Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001) was administered to obtain current ratings of apathy symptomatology. Ratings are on a Likert-type scale that ranges from 1 (“almost never”) to 5 (“almost always”) for each question. The scale does not contain items related to mood disturbance (e.g., sadness). Following the manual guidelines, the raw scores were converted into demographically (i.e., age, education, and gender) adjusted T-scores. The standard FrSBe cut-point of $T \geq 65$ (Grace & Malloy, 2001) was used to classify participants as ‘apathetic’ at each visit. In addition to this categorical classification as ‘apathetic’ or ‘not apathetic’, the difference in apathy T-scores at visit 1 and 2 was calculated to provide a continuous index of change in self-reported apathy symptomatology.

Psychiatric Assessment—Diagnoses of current, new (i.e., occurring during the interval between visits 1 and 2/concurrent with visit 2), and past major depressive disorder and psychoactive substance abuse and dependence were determined via the Composite International Diagnostic Interview (CIDI). The CIDI is a computer-assisted interview that provides a cross-cultural assessment of alcohol, drug, and mental disorders using DSM-IV criteria (Wittchen et al., 1991).

To obtain ratings of current mood symptoms, participants completed the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). The BDI-II is a 21-item instrument assessing mood symptoms. Each item has four graded statements ordered to show increasing symptomatology. Based on previous studies (e.g., Marin et al., 1994; Castellon et al., 2006; Rabkin et al., 2000; Kamat et al., 2012), severity of depressive symptoms was obtained from an adjusted BDI-II score that excluded three apathy-associated items (i.e., #4: loss of pleasure; #12: loss of interest; and #13: ability to make decisions). Excluding these apathy items provided an internally reliable scale of depression (Cronbach’s $\alpha = .75$) that allowed us to minimize the influence of apathy in our assessment of change in mood symptoms.

Neurocognitive Assessment—All participants were administered a standardized neuropsychological battery that included tests of executive functions, learning, memory (delayed recall), speed of information processing, verbal fluency, motor skills, and working

memory (See Woods et al., 2004, Weber et al., 2012 for a list of tests within each cognitive domain). Raw scores were converted to demographically-adjusted, practice-corrected T-scores (e.g., Heaton et al., 2003), which were converted to deficit scores (range = 0 [T > 39] to 5 [T < 20]), and then averaged to generate the Global Deficit Score (GDS; Carey et al., 2004). A GDS of ≥ .5 is the standard cut-point indicative of global neurocognitive impairment in HIV. Neurocognitive impairment status was utilized as a covariate in the analyses described below.

Data Analysis—In order to accommodate departures from normality in individual variable distributions, nonparametric statistical tests were employed, including the Wilcoxon signed-rank test for between-group comparisons and Spearman's ρ for correlations. Cohen's *d* statistic and odds ratio calculations were used to measure the effect sizes of group comparisons. Variables that significantly differed between the groups were included in a least squares regression analysis to examine the relative influence of an incident MDD episode on change in apathy symptomatology at varying levels of baseline apathy elevations. Visit 1 variables (i.e., lifetime diagnosis of MDD, age, neurocognitive impairment (GDS impaired vs. unimpaired), and current CD4 count were included as covariates. A critical alpha level of .05 was set for all analyses.

Results

Neuropsychiatric findings

Of the 225 participants, 81 (36%) reported clinically significant elevations in their apathy symptomatology at visit 1. In this apathetic group, 28% (n=23) of the individuals developed an incident MDE prior to/concurrent with visit 2. The occurrence of a new MDE in this group did not have a significant effect on the rate of clinically elevated apathy at the second visit (OR = 1.73, 95% CI = .59, 5.05). Within the group that was non-apathetic at visit 1 (n = 144), 16 (11%) individuals developed a new MDE. In this group, a new MDE was associated with a 6.5 fold risk of being apathetic at visit 2 (95% CI 2.16, 19.71). In the total sample, 14% of participants developed a new MDE prior to/concurrent with visit 2.

Apathy/MDE group classification

Based on visit 1 apathy elevations and occurrence of a new MDE prior to/concurrent with visit 2, participants were classified into four groups: I) Non-apathetic at visit 1, no new MDE (A−D−; n=128); II) Non-apathetic at visit 1, with new MDE (A−D+; n=16); III) Apathetic at visit 1, with no new MDE (A+D−; n=58); IV) Apathetic at visit 1, with new MDE (A+D+; n=23). The baseline demographic and clinical characteristics of the participants in the four groups are presented in Table 1.

The four groups were comparable in ethnicity, age, and education, but not gender. The four groups were also comparable in terms of the follow-up interval and proportion of participants with lifetime substance use disorders. The four study groups did not differ in their duration of known HIV infection, plasma viral load, proportion of individuals prescribed ART, or proportion of participants co-infected with Hepatitis C Virus (HCV; Table 1). The A+D+ group had lower visit 1 CD4 count relative to the A+D− and A−D−

groups (p's < .05). The overall four group comparison was non-significant (p=.21). Lower nadir CD4 count was also noted for the A+D+ group, relative to the A−D+ group (p <.01).

As seen in Table 1, the rate of lifetime MDD at visit 1 was highest in the A+D+ group and lowest in the A−D− group, with the A−D+ and A+D− groups having intermediate rates of MDD, the lowest rate of MDD was in the A−D− group. Proportionately fewer participants in the A−D− group were prescribed antidepressant medication at their first visit compared to the other three groups, although the group differences did not reach statistical significance (ps>.10). The four groups were comparable in terms of lifetime substance use disorders. Overall, the groups differed in the rates of neurocognitive impairment at the trend level (p=. 06), driven by lower rates of impairment in A−D− than A+D− group (p<.05).

Is a new MDE associated with change in apathy?

In order to examine the unique influence of a new MDE prior to/concurrent with visit 2 on apathy change across the two visits, we conducted a regression analysis predicting the apathy change score in the context of visit 1 variables that significantly differed among the four apathy-MDE groups. In addition to apathy-MDE status, visit 1 neuropsychological status (impaired vs. unimpaired), lifetime diagnosis of MDD, and CD4 count were entered as covariates. The overall model accounted for a significant amount of variance (Adjusted R^2=.13, p<.0001), and revealed that there was a significant effect of apathy-MDE status on apathy change after controlling for covariates, F(3, 215) = 10.75, p < .0001. Planned contrasts revealed that apathy decreased in both the apathetic groups (A+D−, A+D+) compared to the A−D− group (p<.0001, p=.02 respectively). The two apathetic groups (A +D+, A+D−) did not differ in their apathy change score (p=.58). Non-apathetic individuals with a new MDE (A−D+) reported worsened apathy compared to those without an MDE (A −D−) (p< .01). Of the covariates entered, none was significantly associated with change in apathy scores (p's >.10).

Is a new MDE associated with clinical change in apathy?

We examined whether the group differences noted in univariate and multivariate analyses reflected a change in the risk of clinically elevated apathy. As seen in Figure 1, across apathy groups, a new MDE resulted in a higher risk for onset and persistence of clinically elevated apathy over time. The risk of developing elevated apathy at visit 2 was highest in the non-apathetic individuals who had a new MDE (OR = 6.5, 95% CI = 2.16, 19.71). Fifty percent of initially non-apathetic participants with a new MDE were apathetic at their second visit; substantially higher than those who did not develop a new MDE (13%). In the visit 1 apathetic group, the odds of staying apathetic at the second visit were 1.7 (95% CI = . 59, 5.05). Of those individuals who were apathetic at baseline, but did not develop a new MDE, 62% remained apathetic at the second visit, while 74% of baseline apathetic participants were classified as apathetic following a new MDE.

Longitudinal change in affective distress

To further characterize the role of affective symptoms in the longitudinal changes in apathy, we examined group differences in mood change across the two visits. Apathy-adjusted BDI-II scores (i.e., with the apathy items removed) were used in these analyses. A step-wise

pattern of change in mood scores was observed within the two apathy groups, as shown in Figure 2. Regardless of apathy status, the participants with a new MDE had significantly higher mood ratings at visit 2 than those without an MDE ($p < .001$; see Table 2). Apathetic and non-apathetic individuals who developed an MDE reported increased mood symptoms, with a larger change in the A−D+ group relative to the A+D+ group that was significant at the trend level ($p = .07$). Mood symptoms declined in those who did not develop a new MDE prior to/concurrent with visit 2, with the A+D− group reporting a significantly greater decline than the A−D− group ($p = .03$).

Discussion

This is the first study to investigate the longitudinal relationship between apathy and depression in HIV-infected individuals. The key finding was that although apathy and major depressive disorder appear to be dissociable syndromes cross-sectionally, they are related longitudinally such that the occurrence of a new depressive episode significantly increases the risk of developing apathy in persons who were previously not apathetic. These data suggest that neuropsychiatric syndromes, and/or the underlying neural circuits may interact over time to increase the psychiatric burden in HIV+ persons.

Consistent with prior reports (e.g., Atkinson et al., 2008; Castellon et al., 1998; Cysique et al., 2007; Hoare et al., 2010; Kamat et al., 2012) we observed a high rate of psychiatric distress, with 36% of our HIV+ participants reporting clinically significant levels of apathy and 14% of all individuals developing an episode of major depressive disorder prior to/ concurrent with visit 2. We found that after adjusting for visit 1 variables such as lifetime depression status, CD4 count, gender, and neurocognitive impairment, the occurrence of a new MDD episode was associated with a significant increase in apathy symptomatology only in participants who were not apathetic at their first visit. In contrast, apathetic HIV-infected participants at visit 1 who experienced an MDE after their first visit did not demonstrate worsened apathy ratings. In fact contrary to expectations, a very modest drop in apathy was observed. It is likely that the slight drop in this group's apathy score at visit 2 reflects regression to the mean. Overall, these findings highlight that depressive symptoms may be more salient in those with a lower prior neuropsychiatric burden. Future studies are needed to replicate this finding and extend it to consider the relative contribution of other factors (e.g., length and severity of MDE) to the relationship between depression and apathy. Also worthy of consideration is the duration of clinically elevated apathy. It is possible that patients with prolonged apathy may develop some coping skills over time, which reduce their apathetic symptoms, thereby explaining the reduction in apathy ratings and elevation observed here. A closer examination of this neuropsychiatric syndrome and accompanying behavioral changes would be needed to test this theory. Although cognitive impairment was not a significant predictor of longitudinal change in apathy in this study, the longitudinal interplay between cognitive impairment and apathy may be worthy of future investigation.

To explore the underpinnings of change in psychiatric distress, we examined changes in mood symptomatology in the context of apathy and depressive episodes. This was particularly of interest in the visit 1 apathetic group, as these participants demonstrated a decline in apathy ratings over the interval. Accordingly, we sought to examine whether

mood symptoms were increasing despite the decrease in apathy scores. Contrasting with the reduction in apathy ratings, mood symptoms increased slightly over time in the A+D+ group. Non-apathetic participants who developed an MDE (A−D−) reported an even greater increase in mood symptoms, whereas individuals (apathetic or otherwise) who did not develop an MDE reported a decline in mood symptoms over time. These findings raise the possibility that HIV+ persons who have a greater psychiatric burden may experience some alleviation in their symptoms (rather than maintenance) over time, provided they do not suffer incident new psychopathology. Exacerbation in mood ratings is expected to correspond to a new depressive episode; however, the divergence noted in the pattern of change for apathy and BDI-II scores is notable for its implications for future studies to tease apart the mechanisms of psychiatric distress in HIV infection. From the neuroanatomical perspective, it remains to be seen if the contrasting patterns of mood and apathy changes reflect divergent neural mechanisms of each and the varying susceptibility of the respective pathways to HIV-associated CNS pathology. Neuroimaging studies to characterize the relative HIV-associated change in white matter integrity in key regions of the circuits underlying each psychiatric syndrome may shed light on these theories.

Consistent with findings reported previously in the literature (e.g., Castellon et al., 1998; Paul, Flanigan et al., 2005; Rabkin et al., 2000; Cysique et al., 2007), HIV disease characteristics (e.g., AIDS status, HIV RNA viral load) were largely unrelated to apathy at the first visit as well as development of a depressive episode. In contrast to the association noted by Paul, Flanigan et al. (2005), we did not observe a correspondence between apathy and duration of illness. In general, our participants had been infected with HIV for considerably longer than the individuals in the Paul, Flanigan et al (2005) study (i.e., an average of 156 months vs. 95.5 months). Future studies should examine whether length of infection is more strongly correlated with apathy early in the course of the disease rather than during later stages. In the visit 1 apathetic group, lower nadir and current CD4 count were associated with the development of a new MDE. These findings suggest that neuromedical mechanisms might underlie or contribute to psychiatric dysfunction in HIV infection and warrant closer examination in future studies.

This study is not without limitations. First, a self-report measure of apathy (i.e., FrSBe) was used as opposed to a clinical interview (e.g., Neuropsychiatric Inventory, Cummings et al., 1994). Compared to clinical assessment, the accuracy of self-report measures may be affected by bias, poor insight, and/or mild anosognosia. Second, the sample consisted of well-educated, predominantly male and Caucasian individuals with relatively well-managed HIV characteristics (e.g., more than 70% were virally suppressed on their ART medications and only 28% had current CD4 counts below 350). This may limit the extrapolation of our findings to more diverse and symptomatic HIV+ groups. Finally, the duration of follow up was not homogeneous, ranging from 10 to 24 months. However, the interval duration was statistically comparable across all the study groups.

In the context of prior studies, these findings suggest that HIV+ individuals who are not currently apathetic are likely to be at a greater risk of developing clinically significant levels of apathy if they experience a depressive episode. In persons who are apathetic, a new depressive episode may serve to maintain their clinical level of psychiatric distress. Apathy

is associated with a number of adverse functional outcomes, and consequently it is important to identify factors that may be precursors of apathy or may exacerbate its symptoms. The present findings support efforts for the early detection of depression in non-apathetic HIV+ individuals so as to limit the impact this syndrome has on the development of apathy. This may be accomplished by conducting routine assessments of depressive symptomatology and providing psychotropic or behavioral intervention at the earliest opportunity to minimize the risk of developing a depressive episode. Better management of known risk factors of depression, such as decreased social support, stressful life events, substance use, and medication non-adherence may also help avert onset of depression and subsequent apathy symptomatology. Assessing apathy symptoms in clinical settings also appears to be warranted in order to track a patient's psychiatric burden. Preliminary studies examining behavioral interventions for apathy in patients with dementia suggest that mentally stimulating activities and interactive social settings may be effective (reviewed in Roth, Flashman, & McAllister, 2007). These interventions may have the added benefit of reducing depressive symptoms as well. Further investigation of pharmacological and behavioral interventions for HIV-infected persons is warranted as such therapies may have a positive impact on functional outcomes and quality of life.

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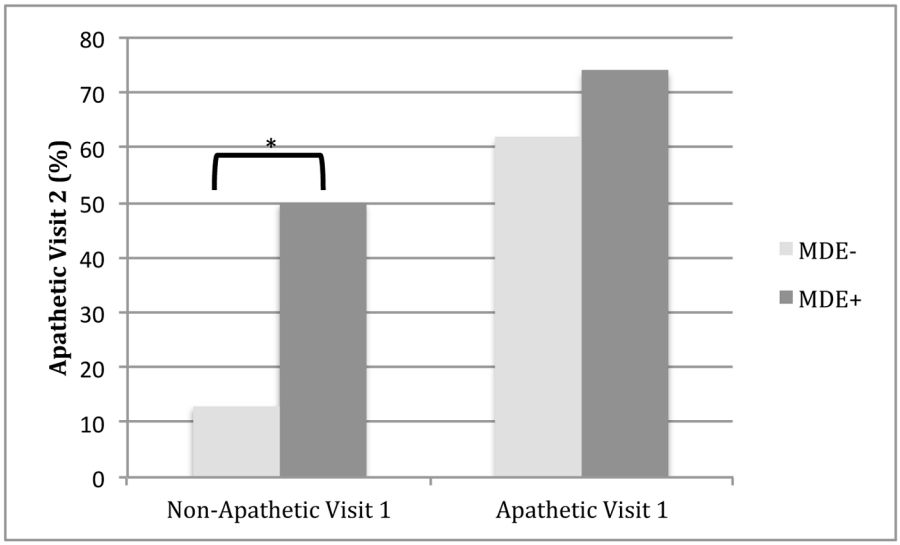

Figure 1.

A new MDE increases risk of clinically elevated apathy at follow up.

Note: * indicates significant difference in proportion across groups

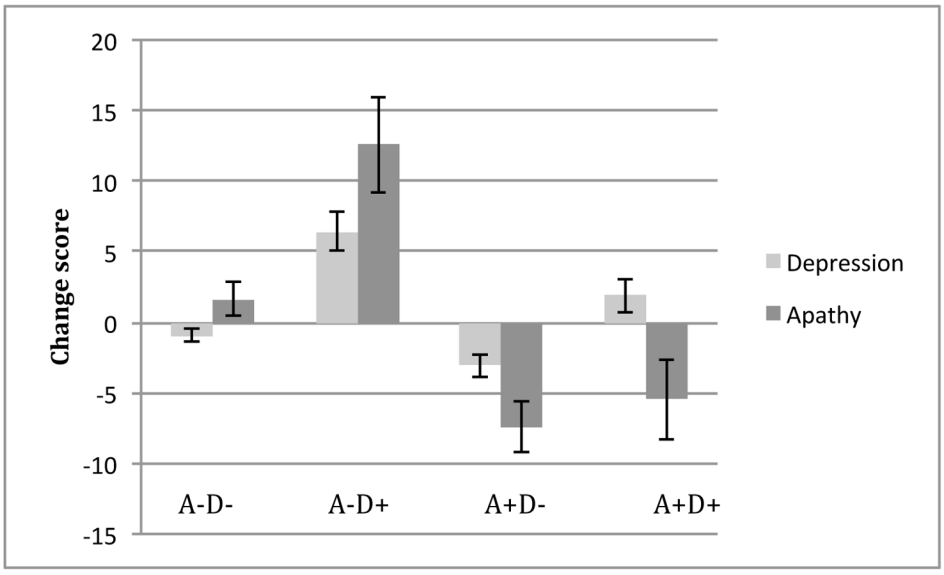

Figure 2.

Pattern of change across two visits in Apathy ratings and apathy-adjusted BDI-II ratings. Standard errors are represented in the figure by the error bars on each column.

Note: Change scores were calculated using the self-reported apathy and apathy-adjusted BDI-II ratings

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Table 1

Baseline demographic, neuropsychiatric and clinical findings for the sample of HIV+ persons (n=225)

	Non-Apathetic		Apathetic		Group comparisons
	Without new MDE (n=128) (a)	**With new MDE (n=16) (b)**	**Without new MDE (n=58) (c)**	**With new MDE (n=23) (d)**	**p[+]**
Age (years)	46.2 (10.5)	46.12 (12.6)	50.2 (9.7)	46.6 (6.8)	.10
Gender (%female)	21.1	25.0	10.3	39.1	.03
Education (years)	13.3 (2.9)	13.6 (3.7)	12.7 (3.5)	12.6 (3.3)	.53
Ethnicity (%Caucasian)	57.0	56.3	60.3	60.9	.88
Apathy T-score	47.5 (11.1)	48.2 (14.3)	75.4 (8.8)	79.3 (12.3)	<.001
Apathy-adjusted BDI-II score	5.9 (5.0)	5.8 (4.9)	12.6 (7.8)	13.9 (7.2)	<.001
Proportion with Lifetime (past) MDD at visit 1 (%)	47.8	56.3	58.6	78.3	.01
Proportion on antidepressant medication at visit 1 (%)	26.6	50.0	37.9	43.5	.11
Proportion NP impaired (%)	25.0	31.3	44.8	39.1	.05
Proportion with lifetime substance use disorders at visit 1 (%)	61.7	62.5	68.9	69.6	.74
Duration of illness (years)	13.2 (6.7)	13.0 (7.5)	13.7 (6.5)	13.2 (5.6)	.97
Proportion with AIDS (%)	63.0	43.8	68.9	78.3	.13
Current CD4 count (median, IQR)	539 (300, 775.8)	543.5 (387.3, 790.5)	503 (344.3, 778.3)	354.5 (174.3, 619.8)	.21
Nadir CD4 (median, IQR)	150 (32, 235)	205 (117.8, 295.8)	131.5 (25.8, 250)	50 (19, 180)	.10
Log_{10} Plasma Viral Load	1.7 (1.7, 1.7)	1.7 (1.7, 2.4)	1.7 (1.7, 2.0)	1.7 (1.7, 2.2)	.80
Plasma viral load (% undetectable)	76.8	71.4	74.1	66.7	.79
ART prescribed (%Yes)	94.8	85.7	97.9	100	.20
Proportion with HCV coinfection (%)	11.8	11.1	10.2	11.8	.86
Interval between visits (months)	14.0 (3.2)	15.0 (3.7)	13.8 (3.2)	14.9 (3.8)	.38

Note. Values represent *Mean (standard deviation)* unless otherwise noted

[+]Results from Wilcoxon Rank Sums, Chi-Square, or Fisher's Exact tests

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Table 2

Changes in clinical variables for the four Apathy/MDE groups.

	Non-Apathetic		Apathetic		Group comparisons	
	Without new MDE (a)	**With new MDE (b)**	**Without new MDE (c)**	**With new MDE (d)**	***p*+**	**Pairwise++**
Change in apathy T-score	1.6 (13.3)	12.7 (20.2)	−7.4 (12.6)	−5.6 (13.2)	<.001	b > a b> c, d+++ a > c
Change in apathy-adjusted BDI-II score	−.91 (4.5)	6.4 (7.8)	−3.1 (6.2)	1.9 (9.3)	<.001	b> a+++ a, b> c d> c
Change in current CD4	7.05	23.50	38.68	75.05	.18	

Note. Values represent *Mean (standard deviation)* unless otherwise noted

+Results from Wilcoxon Rank Sums, Chi-Square, or Fisher's Exact tests

++Indicates significant group differences from pairwise comparisons (p<.05, unless otherwise noted)

+++p<.001