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ORIGINAL ARTICLE

Retrospective Study

Poor CD4 count is a predictor of untreated depression in human immunodeficiency virus-positive African-Americans

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Abstract

AIM: To determine if efforts to improve antiretroviral

therapy (ART) adherence minimizes the negative impact of depression on human immunodeficiency virus (HIV) outcomes.

METHODS: A cross-sectional study of a clinic-based cohort of 158 HIV seropositive (HIV+) African Americans screened for major depressive disorder (MDD) in 2012. CD4 T lymphocyte (CD4+) counts were obtained from these individuals. Self-report on adherence to ART was determined from questionnaire administered during clinic visits. The primary outcome measure was conditional odds of having a poorer CD4+ count (< 350 cells/mm^3). Association between CD4+ count and antidepressant-treated or untreated MDD subjects was examined controlling for self-reported adherence and other potential confounders.

RESULTS: Out of 147 individuals with available CD4+ T lymphocyte data, 31% hadCD4+ count < 350 cells/mm^3 and 28% reported poor ART adherence. As expected the group with > 350 cells/mm^3 CD4+ T lymphocyte endorsed significantly greater ART adherence compared to the group with < 350 cells/mm^3 CD4+ T lymphocyte count (P < 0.004). Prevalence of MDD was 39.5% and 66% of individuals with MDD took antidepressants. Poor CD4+ T lymphocyte count was associated with poor ART adherence and MDD. Adjusting for ART adherence, age, sex and education, which were potential confounders, the association between MDD and poor CD4+ T lymphocyte remained significant only in the untreated MDD group.

CONCLUSION: Therefore, CD4+ count could be a clinical marker of untreated depression in HIV+. Also, mental health care may be relevant to primary care of HIV+ patients.

Key words: Human immunodeficiency virus positive; Depression; CD4 T lymphocyte count; Antiretroviral Therapy; African Americans

Core tip: A retrospective data review was done on human immunodeficiency virus+ patients of a primary care clinic. We examined data on depression diagnosis of patients over a two-year period. Antiretroviral therapy (ART) adherence and major depressive disorder were associated with CD4+ lymphocyte counts. Non-treatment of depression was associated with poor CD4+ lymphocyte count independent of ART adherence.

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INTRODUCTION

Human immunodeficiency virus (HIV) epidemic is a major public health concern, with significant clinical, social and economic impacts, disproportionately affecting minority populations who have less access to care. Approximately 1.2 million people are living with HIV in the United States[1] with 50000 new infections yearly and 1 out of 5 infected people unaware of their status[2]. Since its discovery, HIV/AIDS (acquired immunodeficiency syndrome) has been studied and researched widely and there have been significant improvements in our knowledge of HIV disease and its treatment. The advent of highly active antiretroviral therapy (HAART) has made it possible to suppress the infection, thus prolonging life and putting HIV in the class of chronic long-term infections for many individuals.

Evidence strongly suggests significant association between HIV infection and depression[3]. Prevalence rates of depression are significantly higher in HIV-infected (HIV+) individuals than in the general population[4-7]. The prevalence of depressive symptoms or mood disorders in HIV+ individuals may be about 30% in the United States[4,8]. These prevalence rates vary across specific population groups in HIV+ individuals, with studies reporting higher prevalence rates in HIV+ women than in HIV+ men[3,9,10] and increased depression risk among HIV+ individuals with substance abuse disorders[4,11,12] and among those who have same-sex sexual partners[13,14]. While the prevalence rate of depression decreases with increasing age for the general adult population, this may not be the case for HIV+ adults as evidenced in some studies[15]. Although earlier studies failed to depict this relationship, recent longitudinal studies, especially since the advent of HAART, have observed significant associations between depression and markers of poorer HIV disease outcomes including lower CD4 counts and higher viral loads[16]. The reported associations between depression and HIV disease severity might be mediated by risky behaviors, such as substance abuse, unsafe sexual practices or ART non-adherence, which may further increase transmission risk or exacerbate infection in HIV+ individuals - especially with new drug-resistant viral strains. Indeed, majority of current studies on the subject suggest that co-morbid depression may negatively impact adherence to ART, while non-adherence to HAART, depression and lack of antidepressant use have been associated with accelerated progression of HIV[16-18] and increased mortality[19-21]. On the other hand, given the growing body of scientific evidence implicating important role of immunologic mechanisms in the pathophysiology of major depressive disorder (MDD)[22-24], especially in people with chronic illnesses, it is plausible that the association between MDD and CD4+ outcome could be driven by immunologic mechanisms that are independent from ART adherence and other relevant health behaviors.

This study was conducted with a clinical cohort

of African-American HIV+ individuals with or without MDD comorbidity, who reside in a community that has received intense focus and concerted efforts to improve HIV screening, treatment and ART adherence. In an effort to determine if integrating specialized depression management is needed in addition to intense ART adherence promotion, we collected clinical and immunologic data to examine the indirect and direct associations between MDD and CD4+ counts, adjusting for ART adherence. We hypothesized that non-adherence to ART and non-treatment of co-morbid depression would be independently associated with poor CD4+ levels on admission.

MATERIALS AND METHODS

Study site and sample

The study sample consisted of adult HIV+ African Americans who received care at the Family and Medical Counseling Service (FMCS), Inc. during years 2011 and 2012, and who were formally screened for depression during their intake registration. The FMCS, Inc. is a primary care center that provides health services for the largely African American communities living in the South-East zone district of Washington, DC. A blood specimen was collected for each patient at entry, for measurement of viral load, immunologic profiles and other routine tests. All participants completed a detailed biopsychosocial form, comprised of sociodemographic, behavioral, and medical information. All collected data were stored in an encrypted and password-protected electronic medical record (EMR). To search for additional information missing in the EMR, such as names of ART prescribed prior to intake admission and names of abused substances, we reviewed patient paper documents and charts with handwritten notes. This retrospective study was approved by the Howard University Institutional Review Board.

Assessment of depression

As part of their intake registration into the clinic between 2011 and 2012, patients were interviewed with the Substance Abuse and Mental Illness Symptoms Screener (SAMISS), a well-validated 16-item clinician-administered questionnaire that screens for patterns of substance abuse and key psychiatric syndromes, including manic and major depressive episodes, generalized anxiety disorder, panic disorder, post-traumatic stress disorder and adjustment disorder[25]. Additionally, the SAMISS inquires about use of antidepressants in the past year. It is usually administered in 10 min, and has exhibited good psychometric properties[26]. All intake clinical personnel at FMCS were trained to administer the SAMISS in a reliable manner. Patients interviewed with the SAMISS were asked if they had experienced a period lasting two weeks or more in the past year when they felt depressed, and then subsequently asked if they received a diagnosis or treatment(s) for depression. An affirmative response to a two-week period of depression was used for classification of MDD in this study. All patients who screened positive for MDD in the past year either received antidepressants or a physician's diagnosis of MDD, thereby providing some support to the validity of self-report of MDD in this questionnaire.

Other assessments

CD4+ T lymphocyte counts were measured from blood specimen collected from each patient on the day of clinic intake and during follow-up visits. These results were abstracted from the EMR, were all clinical and laboratory data were stored. We used the most recent CD4+ count for the purpose of this study.

ART adherence and other potential correlates of CD4+ outcome, including age, gender, education, monthly income, housing, and insurance status were derived from the biopsychosocial section of the EMR. As part of their intake interview and during subsequent primary care visits, all patients regardless of their HIV status were asked if they knew about their HIV status, and if they were receiving HIV treatments. Patients who acknowledged being HIV positive were subsequently asked what percentage of time they took their HIV treatments as prescribed by their physicians. For the purpose of this study, we used 80% adherence as threshold for classification of adequacy of ART adherence: $\geqslant$ 80% adherence was classified as good or adequate adherence and < 80% was classified as poor or inadequate adherence. Adherence status for subjects who recently became seropositive for HIV was classified as unknown. Substance abuse and pattern of alcohol use were determined from responses to questions in the SAMISS. Problem drinking was defined as heavy drinking (*i.e.*, > 4 drinks per drinking episode) in addition to having experienced difficulty cutting down on drinking or social problems as a consequence of drinking. Additionally, two questions in the SAMISS specifically assessed abuse of prescription and nonprescription drugs in the past year. Presence or absence of substance abuse history was determined from questions in SAMISS inquiring about problem drinking, illicit drug use, and abuse of prescription drugs.

Statistical analysis

The STATA statistical package, version 12 was used to carry out this analysis. The CD4 count data was incomplete with 11 missing values. Since our outcome of interest is CD4 count differences across groups, we excluded subjects with missing information on CD4 count from the regression analyses. We could efficiently do so because the individuals with missing CD4 count values had similar distribution as non-missing across other variables in the data set.

Age, monthly income, and CD4 T lymphocyte count were grouped into categories because of their highly skewed distributions. Age was thus categorized into < 35 years, 35-55 years and > 55 years. Monthly income was grouped into categories according to quartiles. CD4 count was categorized into < 350 cell/mm^3

Table 1 Demographic and behavioral characteristics of study participants with and without a CD4 count of < 350 cells/mm^3

Characteristics	CD4 count > 350 (n = 102) %	CD4 count < 350 (n = 45) %	P
Gender			
Male	62.75	51.11	0.19
Female	37.25	48.89	
Age groups (yr)			
< 35	12.75	17.78	0.16
35-55	65.69	73.33	
> 55	21.57	8.89	
Monthly income ($)			
0-200	35.11	27.27	0.72
204-670	15.96	22.73	
672-739	25.53	25	
743-2650	23.4	25	
Educational status[1]			
College	22.22	42.31	0.049
No college	77.78	57.69	
HIV treatment adherence			
No	20.59	44.44	0.004
Yes	50	44.44	
Unknown	29.41	11.11	
Substance abuse			
No	38.24	44.44	0.48
Yes	61.76	55.56	
Problem drinking			
No	63.73	61.36	0.79
Yes	36.27	38.64	
Depression			
No	66.67	46.67	0.02
Yes (treated)	24.51	28.89	
Yes (untreated)	8.82	24.44	

[1]Data on education was missing in 49 patients. HIV: Human immunodeficiency virus.

("poor CD4+ count") and > 350 cells/mm^3 based on earlier findings in studies, that observed that deferring treatment until CD4 count was < 350 cells/mm^3 was associated with worse prognosis and mortality[27-29].

χ^2 and Fisher's exact test were used to compare social, demographic and behavioral factors by CD4+ status. For all bivariate analyses, a P value of < 0.05 was regarded as threshold for significance. With the exception of education status and insurance status, missing response rates were less than 8%. Educational status was missing in 33% of individuals and insurance status was missing in 55% of individuals; hence, these latter variables were not included in our multivariate analysis.

We used multiple logistic regression analysis to determine the independent association of MDD with HIV immunological status, adjusting for MDD treatment, ART adherence, age and gender. Several epidemiologic studies have implicated age and gender as key determinants of MDD and HIV outcomes; hence our decision to include these two variables in our multivariate model[30,31]. Ethnicity, another key determinant was not included because our study base consisted of 99% African Americans. The primary outcome measure of interest was the adjusted OR of poor CD4+ outcome comparing MDD treatment groups to nonMDD controls.

RESULTS

Sample characteristics

From October 2011, when depression screening with SAMISS was first implemented in the FMCS, to July 2012, a total of 158 HIV+ patients were enrolled into treatment, and all 158 (100%) of them completed the SAMISS. The 11 individuals who were missing information on CD4+ counts were excluded, resulting in the final sample size of 147. Table 1 depicts the distribution of demographic and behavioral variables by CD4+ count categories among the 147 individuals included in the analysis. As shown, a total of 45 (31%) patients had baseline CD4+ count < 350 cell/mm^3. Majority of the patients were males, between 35 and 55 years of age, and with low monthly income; no significant differences for age, sex or monthly income were observed by CD4+ categories. Group differences were, however, observed for education attainment and ART adherence. Twenty-two percent of those with CD4+ count > 350 cells/mm^3 received some college education, compared to 42% among those with CD4+ count < 350 cells/mm^3 (P < 0.05). However, data on education was missing in 49 patients. As depicted in Table 1, among the patients with CD4 count > 350 cells/mm^3, 21% reported poor ART adherence and 50% reported good ART adherence. The ART adherence status of the remaining 29% of patients was classified as "not applicable", since this group consists of patients with recent HIV+ diagnosis, who have not been prescribed ART. Among the category of patients with poorer CD4+ counts (*i.e.*, < 350 cells/mm^3), the proportion with poor adherence is reversed, accounting for 44%. Approximately 24% of patients in the poor CD4 group had untreated depression in the past year, compared to 9% of untreated depression among those with CD4+ count > 350 (Table 1). In addition, 53% of patients in the poor CD4 group had past year MDD diagnosis, compared to 33% past year MDD in those with CD4 count > 350 cells/mm^3.

Table 2 shows the comparison of ART adherence and other potential demographic and behavioral correlates of poor CD4 outcome between patients with treated MDD, untreated MDD and without MDD. Patients with untreated MDD had the lowest ART adherence rate. No significant differences were observed between these groups in ART adherence. ART adherence was highest among those with treated MDD. Problem drinking rates 55% for the untreated MDD, 46% for treated MDD and 28% for patients without MDD (P < 0.02). No significant differences were observed in age, gender, income, education and substance abuse between the MDD categories.

Relationship between depression and CD4+ counts

Table 3 depicts the result of our multiple logistic regression analyses for determination of the independent

Table 2 Demographic and behavioral characteristics of study participants with or without depression

Characteristics	No MDD (n = 89) (%)	MDD treated (n = 38) (%)	MDD untreated (n = 20) (%)	P
Gender				
Male	63.27	50	60	0.35
Female	36.73	50	40	
Age groups				
> 55	24.49	5	15	0.12
35-55	62.24	77.5	70	
< 35	13.27	17.5	15	
Monthly income				
0-200	32.61	30.77	33.33	0.32
204-670	17.39	25.64	5.56	
672-739	21.74	30.77	27.78	
743-2650	28.26	12.82	33.33	
Educational status				
No college	70.59	78.57	72.73	0.73
College	29.41	21.43	27.27	
Accommodation				
Yes	60.42	72.50	70	0.35
No	39.58	27.50	30	
HIV treatment adherence				
No	26.53	25	45	0.51
Yes	48.98	52.50	40	
Unknown	24.49	22.50	15	
Substance abuse				
No	41.84	30	45	0.37
Yes	58.16	70	55	
Problem drinking				
No	72.45	53.85	45	0.02
Yes	27.55	46.15	55	

HIV: Human immunodeficiency virus; MDD: Major depressive disorder.

association between MDD and poor CD4+ outcome, adjusting for ART adherence, age and gender. The result of simple logistic regression for each variable in the multiple regression was included to aid comparison of indirect versus direct (*i.e.*, independent) associations. In the un-adjusted analysis (second column of Table 3), the odds of having poor CD4 count in the treated MDD group were 1.68 times that of the non-MDD group, and this difference was not significant (P < 0.3). On the other hand, there was an almost 400% increase in odds of poor CD4 outcome in the untreated MDD group compared to the reference (nonMDD) group (P < 0.008). Adjusting for age, gender and ART adherence, the odds ratio (OR) of poor CD4 comparing untreated MDD to non-MDD patients was 3.12 (P < 0.04).The unadjusted analysis revealed a 60% decreased odds of poor CD4 count outcome comparing the group with good ART adherence to the group with poor ART adherence (P < 0.03). Also in the multivariate analysis, there was a significant inverse association between ART adherence and poor CD4 counts (OR = 0.38, P < 0.03). Our multiple logistic model revealed significant associations between the younger age groups (*i.e.*, < 35 years and 35 to 55 years) and poor CD4 outcome, treating the older age group (*i.e.*, > 55 years) as reference group.

Table 3 Logistic regression analysis of potential risk factors for lower CD4 count of < 350 cells/mm^3

Characteristic	OR (P-value, 95%CI)	AOR (P-value, 95%CI)[1]
Depression		
No	REF	REF
Yes (treated)	1.68 (0.22, 0.73-3.87)	1.35 (0.52, 0.54-3.38)
Yes (Untreated)	3.96 (0.008, 1.44-10.88)	3.12 (0.04, 1.07-9.11)
Age		
> 55	REF	REF
35-55	2.71 (0.09, 0.86-8.54)	3.22 (0.03, 1.14-9.11)
< 35	3.38 (0.09, 0.85-13.55)	4.25 (0.03, 1.15-15.69)
Gender		
Male	REF	REF
Female	1.61 (0.19, 0.79-3.28)	1.48 (0.33, 0.68-3.21)
HIV treatment adherence		
No	REF	REF
Yes	0.41 (0.03, 0.18-0.92)	0.38 (0.03, 0.17-0.89)
Unknown	0.18 (0.003, 0.06-0.54)	0.17 (< 0.01, 0.05-0.57)

[1]Model includes: MDD, age sex and adherence. REF: Reference category; HIV: Human immunodeficiency virus; MDD: Major depressive disorder; AOR: Adjusted odds ratio.

DISCUSSION

In this study of HIV+ individuals of African-American ethnic background, we found a 39% prevalence of positive screen for depression in the past year, higher than the prevalence rates in the general population and in keeping with previous studies. Untreated depression was associated with lower CD4 T lymphocyte counts, suggesting a significant relationship between untreated depression and immune status in HIV+ individuals. Poorer immunological status was also significantly associated with younger age and non-adherence to ART. These findings are very important as the ultimate result of lower CD4 T lymphocyte counts in HIV disease is progression to AIDS and mortality[32,33].

CD4 T lymphocytes counts are reported as the number of cells in a cubic millimeter of blood. A normal CD4 count is from 500 to 1500 cells per cubic millimeter of blood. CD4 T lymphocytes are primarily targeted by HIV viral cells and play an important role in host immune defenses against opportunistic infections[34]. With progressive HIV disease, CD4 count levels drop to low levels resulting in AIDS defining illness and increasing mortality. As such, CD4 count is one of the most important prognostic markers of HIV-1 disease progression and an important measure in the decision for commencement of ART in HIV+ patients. Our finding of reduced CD4 T lymphocyte count in association with untreated depression has potential clinical significance, as it suggests that CD4 count could potentially be used as clinical marker of untreated co-morbid depression in HIV+ individuals, in addition to its well-established value as marker of HIV disease severity[35].

Efforts to understand the role of the immune system in major depression have been going on for 3 decades. The majority of studies have focused on the

role of activated innate immune system in depression, with fewer studies on the role of T lymphocyte cells and other adaptive immune responses[36]. It is of note that some initial studies on T lymphocyte responses in hospitalized depressed patients, revealed a reduced proliferation of T cells in response to T cell mitogens - phytohemagglutinin, concanavalin A[37-39], but these findings were not always reproducible. To elucidate this discrepancy, an extensive metaanalysis of more than 180 studies comprising greater than 40 immune measures, revealed mild reductions in Natural Killer cell count, decreased T cell count and T cell proportions and reduced lymphocyte proliferation responses in depressed patients compared to their controls[40].

The evidence based data depicting T lymphocyte dysfunction in depressed individuals, furthered studies on the role of depression in HIV progression. An extensive literature review on studies carried out in both pre-HAART and post-HAART eras showed depression exacerbates HIV progression to AIDS, with at least three studies further depicting an independent association of depression with decreased CD4 T lymphocyte count in individuals with HIV[32]. An example is a longitudinal study of a multiethnic 177 HIV positive men and women, with CD4 counts of between 150 and 500, followed for 2 years. After adjusting for age, gender, antiretroviral treatment and adherence, cumulative depression and hopelessness were associated with decreases CD4 count and increase in viral load[41].

Our results also show a significant association between ART treatment adherence and CD4+ T lymphocyte count, which is in keeping with previous studies[32,42]. Individuals who were adherent were approximately 60% less likely to have a poor CD4 count in the univariate analysis and after controlling for depression, age and gender. Other studies examining different populations have found depression to be associated with poor ART adherence[41-43]. One of such studies of HIV infected injecting drug users, revealed an association between depression and ART non-adherence as a strong indicator of clinical progression[44]. Another study on indigent low income ethnic minorities with HIV, consisting of mainly African-American population, revealed a significant association between depression and poorer ART adherence[45]. Thus, some studies also discussed the possibility of ART adherence being a potential mediator of sorts in the relationship between MDD and poor CD4+ T lymphocyte outcomes[32,40,41].

In lieu of the mediating effect of ART adherence on the relationship between depression and CD4 count, our study examined if the strength of the relationship between depression and CD4 count diminished by adjusting for ART adherence. Our results confirmed an independent relationship between depression and CD4 count. There was however a 21% decrease in the odds of poorer CD4 count in the untreated depression group after adjusting for ART adherence. Hence, our study shows that ART adherence may be a confounder in the association between untreated depression and poorer CD4 count, especially in light of the fact that nearly 50% of individuals with untreated depression also were non adherent to ART. However, larger prospective studies will be beneficial in further examining the nature of these relationships.

This study has some limitations that should be acknowledged. The cross-sectional design and small sample size limit our ability to make inferences about causal direction of the observed associations and their significance, respectively. The study sample consisted exclusively of African-American individuals from a specific urban community. While this limits the generalizability of the findings, it also provides natural control for potential sociodemographic (*e.g.*, poverty, health disparities) and cultural, racial or community-bound factors that could have confounded the results. It also provides clues that may help inform future clinical and research efforts to adapt evidence based-psychological and social interventions, including mental health screening and treatment monitoring protocols in a manner that will accommodate the sociocultural dimensions of HIV, depression, and salient health behaviors that may be unique to predominantly low-income, African-American urban communities.

In summary, we found that depression is highly prevalent in this population of HIV+ individuals and untreated depression and poor ART adherence are independently associated with poorer CD4 T-lymphocyte outcomes. Furthermore, it contributes to growing appreciation of other possible pathways linking depression to HIV outcome, other than the mediating role of ART adherence. Our findings need to be validated in a larger cohort with follow up over time. There is also a need for further research into the factors that may predispose this community to poorer outcomes. The lower mean income and educational attainment in this clinical cohort also suggests the potential relevance of integrating specialized mental health and case management services into community primary care centers in for better management of HIV+ patients.

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COMMENTS

Background

Human immunodeficiency virus (HIV) epidemic is a major public health concern. Approximately 1.2 million people are living with HIV in the United States with 50000 new infections yearly. Evidence strongly suggests significant association between HIV infection and depression. Prevalence rates of depression are significantly higher in HIV-infected individuals in comparison to the general population. The reported associations between depression and HIV disease severity might be mediated by risky behaviors, such as substance abuse,

unsafe practices or antiretroviral therapy (ART) non-adherence. Consequently, these factors may further increase transmission risk or exacerbate infection in HIV+ individuals - especially with new drug-resistant viral strains. Recent studies have shown significant association between depression and markers of poorer HIV disease outcomes including lower CD4 counts and higher viral loads. In contrast, the association between major depressive disorder (MDD) and CD4+ outcome could be driven by immunologic mechanisms that are independent from ART adherence. To examine the indirect and direct associations between MDD and CD4+ count, adjusting for ART adherence, the authors collected clinical and immunologic data from the cohort of African-American HIV+ individuals with or without MDD comorbidity. The aim of this study is to see the association between non-adherence to ART and non-treatment of co-morbid depression with poor CD4+ levels on admission.

Research frontiers

Majority of the current studies suggest that co-morbid depression may negatively impact adherence to ART, while non-adherence to highly active ART, depression and lack of antidepressant use have been associated with accelerated progression of HIV and increase mortality. On the other hand, given the growing body of scientific evidence implicating important role of immunologic mechanisms in the pathophysiology of MDD, especially in people with chronic illnesses, it is plausible that the association between MDD and CD4+ outcome could be driven by immunologic mechanisms that are independent from ART adherence and other relevant health behavior.

Innovation and breakthroughs

Efforts to understand the role of the immune system in major depression have been going on for 3 decades. The majority of studies have focused on the role of activated innate immune system in depression, with fewer studies on the role of T lymphocyte cells and other adaptive immune responses. In this study, the authors found 39% prevalence for depression, which is higher than the general population. Untreated depression was associated with lower CD4 T lymphocyte counts, suggesting a significant relationship between untreated depression and immune status in HIV+ individuals. Poorer immunological status was also significantly associated with younger age and non-adherence to ART.

Applications

ART adherence may be a confounder in the association between untreated depression and poorer CD4 count. This study provides the evidence that non-adherence to ART and non-treatment of co-morbid depression would be independently associated with poor CD4+ levels on admission. Practical application: To determine if recent efforts to improve ART adherence among HIV+ African Americans attending a primary care clinic sufficiently minimizes the negative impact of depression on HIV outcomes.

Terminology

Epidemics: Widespread outbreak of infectious disease in a population or community; Cohort: Group of people with common characteristics.

Peer-review

The manuscript explores interesting relationship between CD4 count and depression. It found that there is association between poor CD4 count and untreated depression.

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