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ORIGINAL PAPER

Antidepressant Treatment and Adherence to Combination Antiretroviral Therapy among Patients with AIDS and Diagnosed Depression

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Abstract
Background The prevalence of depression is elevated among HIV-infected individuals and there is evidence that depression exerts a negative impact on HIV medication adherence.
Methods Merged HIV/AIDS surveillance data and Medicaid claims data from January 1996 to December 1998 were used to identify AIDS-infected patients with diagnosed depression, and filled prescriptions were used to identify their antidepressant use, and highly active antiretroviral therapy (HAART). Chi-square tests and robust logistic regressions were used to examine antidepressant use after HAART initiation, and a person-month approach was used to estimate the association between antidepressant treatment and adherence to HAART after its initiation.
Results Of the 406 AIDS-infected patients diagnosed with depression who initiated HAART during this period, 81% ($N = 329$) were treated with an antidepressant. The HAART adherence rate was low overall. After HAART initiation; only 63% of the person-months had a prescription for it. However, use of an antidepressant in the prior month was significantly associated with HAART in the current month. After controlling for other factors, the odds of current-month HAART adherence were increased by almost 30% for those with antidepressant use in the prior month (Adjusted OR = 1.28, 95% CI [1.16, 1.41]).
Conclusions While the HAART adherence rate was low among patients with AIDS diagnosed with depression, prior month's antidepressant use increases odds of adherence. Unmeasured factors may influence the reported association between antidepressant use and HAART adherence, but our findings point to the need to investigate directly the impact of antidepressant therapy on HAART adherence found among patients with AIDS and depression.

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A large literature has established the significance of clinical depression and depressive symptomatology in the care of patients with HIV (e.g., [1]). Depression is both common and consequential.

Early research documented rates of depression higher than usually found in the general population [2, 3]. Interpretation of this finding was complicated by the high base rates of depression in risk groups most liable to HIV infection [4, 5]. However, a meta-analysis comparing HIV(+) and HIV(−) at risk patients found major depression at almost twice the rate in the HIV+ group [6]. Also, longitudinal work indicates that HIV infection is itself associated with new cases of major depression [7].

Many of the behavioral consequences of depression among patients with HIV/AIDS have significant health implications, including problems adhering to antiviral regimens [8–10]. Across a range of settings and populations, depression has been associated with reduced probability of antiretroviral utilization [11, 12]. In the multi-center AIDS cohort study, depression was linked to interruption and discontinuation of highly active antiretroviral therapy (HAART). [13]. Recently, this pattern of association has also been found in studies of adherence that include biological measures associated with lower adherence, such as lower CD4 count [14] and detectable viral load [15].

Observational studies have produced mixed findings regarding associations between diagnosed depression and adherence in studies relying on administrative claims. One study found that patients with severe affective disorder (a category that included both major depression and bipolar disorder) were more likely to initiate combination antiviral therapy, but less likely to be adherent, when compared to patients with no indication of a major mental illness (i.e., schizophrenia, major depression, or bipolar disorder) [16]. However, another study using Medicaid claims found that, contrary to expectation, patient with HIV and diagnosed depression were more, not less, adherent [17].

Only limited evidence has yet documented the role played by treatment of depression in improving adherence. No controlled trials to date have demonstrated that depression treatment improves adherence, but two types of evidence suggest this possibility is plausible. First, among patients with HIV and depression, symptoms appear to respond to a range of treatments, including older [4] and new generation antidepressants [18, 19], as well as psychotherapy [20]. Himelhoch and Medoff [21] found significant effects of antidepressant therapy reported in three of seven double-blinded randomized trials comparing it to placebo in patients with HIV who met starndardized criteria for depression, and concluded from their meta-analysis that antidepressants are efficacious. Second, some observational studies suggest that, for depressed patients receiving community care, antiretroviral adherence benefits may be associated with treatment of depression [17, 22, 23]. One recent study reported improved adherence by both treated and untreated patients with diagnosed depression over a 6-month period, but also argued the data indicated that even in the context of generally improving adherence over a 6-month period, addition of an antidepressant predicted significantly greater improvements [23]. However, this conclusion has been challenged on several methodological and statistical grounds [24], and there is wide agreement that additional support is needed to confirm the clinical assumption that antidepressant care improves the antiretroviral adherence of depressed patients.

The research challenge is increased because the possible relations among depression, depression treatment, and antiviral adherence are not limited to the logic underlying many discussions that depression treatment → improved depression → improved antiretroviral

adherence. For example, some research indicates depressed patients treated with antidepressants are more likely to receive antiviral therapy, which may reflect some impact of depression treatment on a provider's decision to prescribe antiviral therapy. In addition, HAART regimens can themselves reduce depression [25–27]. And of course adherence to both antidepressant therapy and antiretroviral therapy may be influenced by some third variable.

The medication outcome typically most important to the clinician is a sustained period of adherence by the patient, but ample evidence documents considerable variability in antiretroviral adherence [28]. Well-designed prospective studies have highlighted the limitations of using baseline patient characteristics to predict adherence trajectories. The predictive value of a variable or combination of variables may change over time, and changes in a variable from one point to another may be more powerful predictors than the absolute level. Previous observational studies have argued for a temporal association by comparing antiretroviral adherence rates before and after antidepressant initiation. We examine further possible linkages with a more fine-grained examination of temporal associations with a person-month analytic framework.

Methods

Data

Data for our research comes from a merged Medicaid claims and surveillance data from the NJ AIDS/HIV Registry.

Study Population

The study population consisted of New Jersey Medicaid beneficiaries diagnosed with AIDS from 1990 through March 1996, identified through the match between Medicaid eligibility and the State's AIDS/HIV registry. Additional inclusion criteria were: age 18 and over at the time of receiving AIDS diagnosis, enrolled in Medicaid fee-for-service program between January 1996 and December 1998, and received Medicaid service during this period. We identified 2,459 patients who met these criteria. We further excluded people who either died ($N = 672$) or dropped out of Medicaid ($N = 259$) during this period. Among the 1,528 patients, 77% ($N = 1{,}186$) initiated HAART with at least 1-month follow-up, and among them, 35% ($N = 406$) were diagnosed with comobid depression. This group constituted the final study population.

Depression Diagnosis was identified by the primary and secondary diagnostic codes conforming to the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) recorded in Medicaid claims. To reduce risk of false positive identification of depression, we included only diagnoses assigned by hospitals, physicians, medical clinics, or mental health providers. (Following prior practices, we disregarded claims indicating depression diagnosis from other medical care providers such as emergency department physicians, case managers, and home-health agencies, since these setting may lack the information or expertise needed to provide a high quality diagnosis.) An individual was identified as having depression if he had at least one claim with ICD-9-CM codes of 296.2 (Major depressive disorder, single episode), 296.3 (Major depressive

disorder, recurrent), 300.4 (Neurotic depression) or 311 (Depression disorder, not elsewhere classified).

Highly active antiretroviral therapy was defined as the use of any *Protease Inhibitors (PIs) or* non-nucleoside reverse transcriptase inhibitors *(NNRTIs).* These drugs were identified by National Drug Codes (NDC) recorded in Medicaid pharmacy claims. PI drugs available during the observation period included ritonavir, indinavir, saquinavir, and nelfinavir, and NNRTIs included nevirapine, delavirdine and efavirenz. Individuals having at least 1 claim between March 1996 and December 1998 that indicated PI or NNRTI use were considered HAART users.

Measures

Antidepressant Use was identified from therapeutic class codes recorded in Medicaid pharmacy claims. These codes were provided by NJ Department of Human Services, Division of Medical Assistance and Health Services. The list of antidepressant therapeutic class codes included H2H, H2J, H2K and H2N.

Demographic Characteristics were obtained from the HIV/AIDS Registry data and included gender, race/ethnicity, age at AIDS diagnosis, and county of residence. Since age may have a non-linear effect, patients were categorized into four groups, based on age: aged 18–29; 30–39, 40–45, and 46 and above. HIV/AIDS prevalence varies widely in New Jersey. Using county of residence, we created a categorical variable for people living in high prevalence areas at the time of AIDS diagnosis, with high prevalence defined as those with over 400 persons living with HIV/AIDS per 100,000 population. The high prevalence areas comprised Atlantic, Essex, Hudson, Passaic, and Union counties [29].

Illness stage was measured by year of diagnosis, which was categorized into four levels: before 1991, 1991–1992, 1993–1994, and 1995–1996. Risk group was defined using Registry classifications and grouped into three categories: injections drug users (IDUs), non-IDUs and those with missing information.

Medicare coverage also entered the analysis as a covariate since prior research indicates a dually-eligible patient may have greater access to outpatient medical treatments than those eligible only for Medicaid [30].

In New Jersey, *AIDS Community Care Alternatives Program (ACCAP)* was provided as an HIV-specific Medicaid home and community-based care waiver program. Enrollment is voluntary and ACCAP offers a variety of services, including case management and private duty nursing that could affect treatment patterns [31, 32]. In the current analysis, individuals were defined as participants in the ACCAP program by having at least one claim with procedure codes for the waiver services.

Analytic Procedures

We first examined rates of antidepressant use after PI/NNRTI initiation. Chi-square statistics and multiple logistic regression were used to estimate person-level predictors of antidepressant use. However, our primary goal was to examine the association between antidepressant treatment and adherence to PI/NNRTI, requiring attention to study population, temporal order and proximity. For example, to assess the antidepressant treatment effect on HAART adherence, we chose to focus on HIV infected individuals who had already initiated HAART before the depression episode began because some investigators report protease inhibitor therapy is initiated later for patients with depression [33], and

survey data from infectious physicians who treat patients with HIV/AIDS found that most say a patient's prior psychiatric hospitalization counts against initiation of HAART [34].

Viewing adherence in a dynamic framework, rather than as a fixed patient characteristic, should also motivate further the search for intervention opportunities that can affect month-to-month patterns of adherence. We converted the person-level data to person-month units of analysis. (Dates of service are recorded in each paid Medicaid claim, which makes it possible to specify the temporal ordering of a service.) Counting from the first month after PI/NNRTI initiation, a maximum of 34 person-months can be contributed by each person in the study population.

Under our person-month approach, a single individual may have repeated observations, resulting in correlated observations. To account for these intra-person correlations, generalized estimation equations (GEE) methods were used. To examine the predictors of HAART adherence, including prior month antidepressant use, we used logistic regression. All the analyses were implemented using STATA version 8 [35].

Results

Characteristics of HIV-Infected Individuals with Diagnosed Depression

Table 1 shows the characteristics of the study population and the rate of antidepressant use after PI/NNRTI initiation. Of the total 406 patients, about half were male, African American, or aged 30–39 at the time of their AIDS. Most of them lived in a high prevalence area (75%) and did not participate in the waiver program (81%). The majority of the PINNRTI users (81%, $N = 329$) filled at least one antidepressant prescription after PINNRTI initiation. Bivariate analyses and multiple logistic regression did not find significant group differences in the rate of antidepressant use, even when controlling for length of follow up.

Persistence of Monthly PI/NNRTI Use by those Diagnosed with Depression

Results of the analyses on adherence to PI/NNRTI use among PI/NNRTI users and its association with antidepressant use are shown in Table 2. Overall, PI/NNRTI were prescribed in 63% ($N = 6{,}157$) of the total person-months ($N = 9{,}808$). In this group with diagnosed depression, antidepressant use in the previous month was significantly associated with higher likelihood of PI/NNRTI use in the current month. If the patient was treated with antidepressant in the previous month, the patient's likelihood of receiving PI/NNRTI in the current month was 70%, (versus 59% for those who were not treated by antidepressant in the previous month). The GEE estimation further confirmed these findings. When controlling for other factors, the previous month antidepressant use increased the odds of current month PI/NNRTI use by almost 30% (adjusted OR = 1.28, 95% CI = [1.16, 1.41]). Racial/ethnic minorities were less likely to receive PI/NNRTI than whites (African American: adjusted OR = 0.71, 95% CI = [0.52, 0.95], and Latinos: adjusted OR = 0.61, 95% CI = [0.43,0.85]). Significantly higher rates of PI/NNRTI use were associated with older age, living in the high-prevalence area (adjusted OR = 1.80, 95% CI = [1.37, 2.37]) and ACCAP membership (adjusted OR = 1.46, 95% CI = [1.07,1.99]) than their counterparts.

Table 1 Characteristics of the study population and their antidepressant use

	Total		ADP use among PI/NNRTI users			
	N	%	*N*	% of total	Logistic regression on ADP use	
					OR	95% CI
Total	406	100.0	329	81.0		
Sex						
Male	214	52.7	171	79.9	–	–
Female	192	47.3	158	82.3	1.27	[0.68,2.37]
Race/Ethnicity						
White	107	26.6	88	82.2	–	–
African Americans	206	51.2	167	81.1	1.25	[0.57,2.73]
Latinos	89	22.1	70	78.7	1.65	[0.62,4.35]
Age at primary diagnosis						
18–29	60	14.8	42	70.0	–	–
30–39	222	54.7	185	83.3	1.35	[0.57,3.16]
40–45	86	21.2	71	82.6	1.34	[0.47,3.81]
46 and above	38	9.4	31	81.6	1.04	[0.30,3.59]
Mode of transmission						
Non-IDUs	101	24.9	83	82.2	–	–
Injection drug users	252	62.1	205	81.4	1.10	[0.52,2.34]
Missing	53	13.1	41	77.4	1.58	[0.51,4.94]
County of residence						
High prevalence	304	74.9	244	80.3	0.89	[0.41,1.96]
Other	102	25.1	85	83.3	–	–
Waiver status						
Non-ACCAP	331	81.5	266	80.4	–	–
ACCAP	75	18.5	63	84.0	1.29	[0.51,3.29]
Medicare coverage						
Yes	158	38.9	135	85.4	1.38	[0.70,2.74]
No	248	61.1	194	78.2	–	–
Year of diagnosis						
1991–1992	113	27.8	90	79.7	–	–
1993–1994	193	47.5	154	79.8	0.97	[0.48,1.93]
1995–1996	100	24.6	85	85.0	2.79	[1.03,7.57]

Note: Based on New Jersey Medicaid participants, aged 18 and over at the time of receiving AIDS diagnosis, diagnosed with AIDS from 1990 through March 1996, continuously enrolled in Medicaid fee-for-service program between January 1996 and December 1998, diagnosed with depression, and had at least one PI/NNRTI prescription during this period. The multiple logistic regression also controlled for the length of follow up

Discussion

We found that in a state-wide population with HIV and diagnosed depression, rates of PI/NNRTI initiation and rates of antidepressant initiation were each greater than 85%.

Table 2 Predictors of monthly PI/NNRTI use among NJ Medicaid AIDS population diagnosed with depression and ever treated with PI/NNRTI

	Total person-month		Person-months with PI/NNRTI use		GEE regression on monthly PI/NNRTI use	
	N	%	*N*	%	OR	95% CI
Total	9,808	100.0	6,157	62.8	–	–
Antidepressant use in the previous month[a]						
Yes	3,411	34.8	2,371	69.5	1.28**	[1.16,1.41]
No	6,397	65.2	3,786	59.2	–	–
Sex[a]						
Male	5,299	54.0	3,272	61.8	–	–
Female	4,509	46.0	2,885	64.0	1.13	[0.91,1.41]
Race[a]						
White	2,765	28.5	1,851	66.9	–	–
African Americans	4,785	49.3	2,955	61.8	0.71*	[0.53,0.95]
Latinos	2,162	22.3	1,310	60.6	0.61**	[0.43,0.85]
Age at primary diagnosis[a]						
18–29	1,315	13.4	738	56.1	–	–
30–39	5,366	54.7	3,310	61.7	1.23	[0.89,1.71]
40–45	2,178	22.2	1,440	66.1	1.49*	[1.01,2.21]
46 and above	949	9.7	669	70.5	1.97**	[1.22,3.17]
Mode of transmission[a]						
Non-IDUs	2,569	26.2	1,675	65.2	–	–
Injection drug users	6,052	61.7	3,716	61.4	0.77^{+}	[0.59,1.02]
Missing	1,187	12.1	766	64.5	0.80	[0.55,1.18]
County of residence[a]						
High prevalence	7,202	73.4	4,697	65.2	1.80**	[1.37,2.37]
Other	2,606	26.6	1,460	56.0	–	–
Waiver status[a]						
ACCAP	2,102	21.4	1,445	68.7	1.46*	[1.07,1.99]
Non-ACCAP	7,706	78.6	4,712	61.2	–	–
Medicare Coverage [a]						
Yes	4,024	41.0	2,579	64.1	0.94	[0.74,1.20]
No	5,784	59.0	3,578	61.9	–	–
Year of diagnosis						
1991–1992	2,741	28.0	1,706	62.2	–	–
1993–1994	4,703	48.0	2,994	63.7	1.04	[0.79,1.36]
1995–1996	2,364	24.1	1,457	61.6	0.94	[0.69,1.28]

Note: Based on New Jersey Medicaid participants who were aged 18 and over at the time of receiving AIDS diagnosis, diagnosed with AIDS from 1990 through March 1996, continuously enrolled in Medicaid fee-for-service program between January 1996 and December 1998, diagnosed with depression, and had at least one PI/NNRTI filled during this period. Superscript a denotes significant subgroup difference ($P < .05$) in overall rate of monthly PI/NNRTI use using Chi-square statistics. **, * and + denote significant effect at 1%, 5%, and 10% levels, respectively, in the GEE regression on monthly PI/NNRTI use

However, despite representing optimal care for most patients during this period, PI/NNRTI prescriptions were filled in only 63% of all person-months for the group studied.

Our findings are consistent with the view that treating the depression of patients with HIV and depression may improve their antiviral adherence, but the observational study design used cannot demonstrate causality.

Prior research has given reason for concern that patients with psychiatric conditions may face access barriers [33, 34]. Our findings, however, are consistent with those who found no evidence of access barriers for this group [16, 36]. It should be noted, however, that we lack important information needed to determine illness stage (e.g., CD4 counts), which means we cannot determine whether HAART was initiated at a later illness stage, suggesting delays in initiation.

Our figures on the prevalence of depression in this population fall in a middle range, compared to other recent estimates. Prior studies, many of which date from the early 1990s, have reported rates of current depression in the 10–20% range [37]. Claims-based estimates approximately equivalent to ours were found among drug abusers studied with Medicaid claims (34% for women, 29% for men) in neighboring New York State [17]. A higher rate (57%) was reported based on chart review, administrative, and pharmacy files in from an urban health setting for the period 1997–2001 [23].

The comparative underrepresentation of African Americans among those diagnosed with depression in this population with HIV may represent differences in care seeking, access, or provider diagnosis. In general medical care, national data on trends in office visits [38] agree with patient-focused data from the 2000 Medical Expenditure Panel Survey (MEPS) in reporting that it is more common for African American patients to be diagnosed with depression, yet not received an antidepressant [39].

Our findings share the ascertainment and measurement limitations common to research using administrative data. Our reliance on provider diagnosis, rather than primary data collection, makes it impossible to comment on cases of depression that are not identified. Prior work on HIV care has found under-identification of depression, but indicate under-identification is less common in patients who have been seen for at least 3 visits [40]. Research comparing administrative data with medical records tends to find good agreement for major psychiatric disorders, including associated secondary conditions [41]. In non-psychiatric branches of medicine,, serum drug levels, physiological measures of drug effect, and health outcomes have all been found to have statistically significant correlations with refill compliance [42]. By convention, refill based measures provide an upper bound estimate of compliance, a highly specific but potentially insensitive indicator of partial compliance (since some patients may refill, but not take, medications).

The accumulation of evidence consistent with the claim that treatment of depression can improve antiretroviral adherence requires additional, targeted research strategies if the most pressing clinical questions are to be settled. Prospective randomized trials are needed to determine the extent to which reported associations reflect causal influence. Direct measures of symptom profiles over time are needed to explore further just how treatment-related improvements in depression might impact antiretroviral adherence, and longitudinal follow up is needed to determine the temporal stability and resilience of any effects. A goal for future research is to determine when and how depression treatment needs to be combined with behavioral interventions to promote HAART adherence (by, for example, training in scheduling, promoting adaptive thoughts about adherence, etc.) [43].

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