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A Retrospective Evaluation of the Relationship Between Mental Disorders and Patient Adherence to Antiretroviral Therapy

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A Retrospective Evaluation of the Relationship Between Mental Disorders and Patient Adherence to Antiretroviral Therapy

by

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THESIS

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Dedication

This thesis is dedicated in loving memory to my father, Walter Franklin Fowler.

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Most of all, I would like to thank my mother for making me who I am today. Mom, words cannot express how much your unconditional love, friendship, and support have meant to me. The best in me I know comes from you. Thank you for not letting me come home.

Abstract

A Retrospective Evaluation of the Relationship Between Mental Disorders and Patient Adherence to Antiretroviral Therapy

by

Jill Aglaia Fowler, M.S.Phr.

The University of Texas at Austin, 2009

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Adherence to combination antiretroviral therapy is important for achieving optimal HIV-related outcomes. Epidemiologic data indicate that persons with mental disorders are disproportionately affected by HIV/AIDS, which is concerning since having a mental disorder has been associated with poor adherence to medications for treatment of chronic disease states. The purpose of this study was to examine the relationship between the presence of mental disorders and adherence to combination antiretroviral therapy. Additionally, this study examined the relationship between adherence to psychotropic medications and adherence to antiretroviral therapy.

Study data were collected from the Texas Medicaid Vendor Drug Program database and Texas Medicaid enrollment files. Adherence to and persistence with antiretroviral therapy, as well as adherence to psychotropic medications when applicable, were evaluated over a 12-month period in 1,321 patients starting a new combination antiretroviral regimen. The presence of a mental disorder was defined based on

prescription claims for psychotropic medications. Proportion of days covered was used to calculate adherence, while persistence was defined as the number of days persistent with all antiretrovirals in the index regimen. Logistic regression was used to evaluate the relationship between psychotropic medication use and adherence to antiretroviral therapy (90% cut-off), as well as the relationship between adherence to psychotropic medications (80% cut-off) and adherence to antiretroviral therapy. The relationship between antiretroviral persistence and psychotropic medication use was evaluated using multiple linear regression. Factorial ANOVA was used to evaluate the interactions between race/ethnicity, gender, and psychotropic medication use in their effects on adherence to and persistence with antiretroviral therapy.

No significant relationship was found between the presence of a mental disorder and adherence to or persistence with combination antiretroviral therapy in this study. However, the limitations of using psychotropic medication use as a proxy for mental disorders may have affected the results. Adherence to psychotropic medications overall ($n = 501$; OR = 3.37, 95% CI: 1.86 – 6.10; $p < 0.001$) and specifically to antidepressants ($n = 443$; OR = 4.23, 95% CI: 2.31 – 7.75; $p < 0.001$) was significantly associated with adherence to antiretroviral therapy, indicating a possible relationship between effective treatment for mental disorders and combination antiretroviral therapy adherence. While additional research is needed to clarify this relationship, these data support the need for an integrated approach to treatment of mental disorders and HIV/AIDS.

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CHAPTER ONE

Introduction and Literature Review

BACKGROUND

Human Immunodeficiency Virus (HIV) infection and the associated Acquired Immune Deficiency Syndrome (AIDS) continue to be a significant health issue both in the United States as a whole and in the state of Texas. At the end of 2006, an estimated 491,727 persons in the U.S. were living with HIV/AIDS, of which 59,066 (12.0%) were estimated to be from Texas.[1] While the incidence of HIV/AIDS in the U.S. remained stable from 2003-2006, HIV/AIDS prevalence increased steadily as the number of deaths of persons with AIDS decreased.[1]

Epidemiologic data indicate that racial and ethnic minorities are disproportionately affected by HIV/AIDS (Table 1.1). In 2006, rates of HIV/AIDS in the U.S. black and Hispanic populations were 67.7 per 100,000 and 25.5 per 100,000, respectively, as compared to 8.2 per 100,000 in the white population.[1] Although blacks represent only about 13% of the U.S. population, they accounted for 49% of all HIV/AIDS cases diagnosed in 2006.[1,2] A similar trend is seen in Texas, where blacks represent 11% of the population but accounted for 38% of all the HIV/AIDS cases in 2006.[3] The rate for blacks living with HIV/AIDS in Texas in 2006 was over four times higher than the rate for whites and Hispanics (Figure 1.1).[3] Rates of HIV/AIDS are higher among males than females across all racial/ethnic groups, though women of racial/ethnic minorities may be particularly at risk. The rate of new HIV/AIDS diagnoses in black females in Texas was nine times higher than the rate in

Hispanic females and 19 times higher than the rate in white females in 2006 (Figure 1.2).[3]

As with racial and ethnic minorities, rates of HIV/AIDS are disproportionately high among persons with mental disorders. This is important to consider since data from a recent, nationally representative survey indicates that the prevalence of serious mental disorders in the U.S. over a 12-month period is approximately 6.5%.[4] Multiple studies have shown that persons suffering from serious mental disorders are at an increased risk for contracting HIV as compared to the general population, with the degree of risk varying by geographic region.[5-7] In a review of studies published through 1996 that evaluated the prevalence of HIV infection among persons with serious mental disorders, the overall seroprevalence was found to be 7.8%, which is much higher than the estimated 0.4% prevalence in the general U.S. population at that time.[5] After controlling for age, sex, race/ethnicity, and time spent on welfare, one study of Medicaid recipients found that patients with a schizophrenia spectrum disorder were 1.5 times more likely than those without a serious mental disorder to be diagnosed with HIV infection, whereas patients with a major affective disorder were 3.8 times as likely.[7] Possible explanations for the increased risk of HIV infection among those with mental disorders include the greater likelihood that persons with mental disorders will engage in high-risk sexual behaviors (e.g., multiple sexual partners, infrequent condom use, trading sex for money or drugs) and the higher prevalence of substance use, including injection drug use, in this population.[5-8]

The influence of race/ethnicity and gender on the rates of HIV infection among persons with serious mental disorders has not been clearly defined, though there is some evidence to suggest that these relationships may differ from those seen

in the general population. As discussed above, the rate of HIV/AIDS in the U.S. black population is higher than that in the white and Hispanic populations.[1] When combining data from studies published through 1996 that evaluated the prevalence of HIV infection among persons with serious mental disorders, rates of seropositivity were similarly higher among blacks and Hispanics as compared to whites.[5] In the general U.S. population, the rate of HIV/AIDS is higher among men than women, with a ratio of approximately 3:1.[1] In contrast, studies evaluating the rate of HIV infection among persons with serious mental disorders have found near equality in the rates of HIV by sex.[5,6] This indicates that women with serious mental disorders may be at greater risk for HIV infection than women in the general population.

Table 1.1 Estimated Numbers of Cases and Rates (per 100,000 population) of HIV/AIDS in Adults and Adolescents by Race/Ethnicity and Sex in 33 States with Confidential Name-Based HIV Infection Reporting, 2006[a]

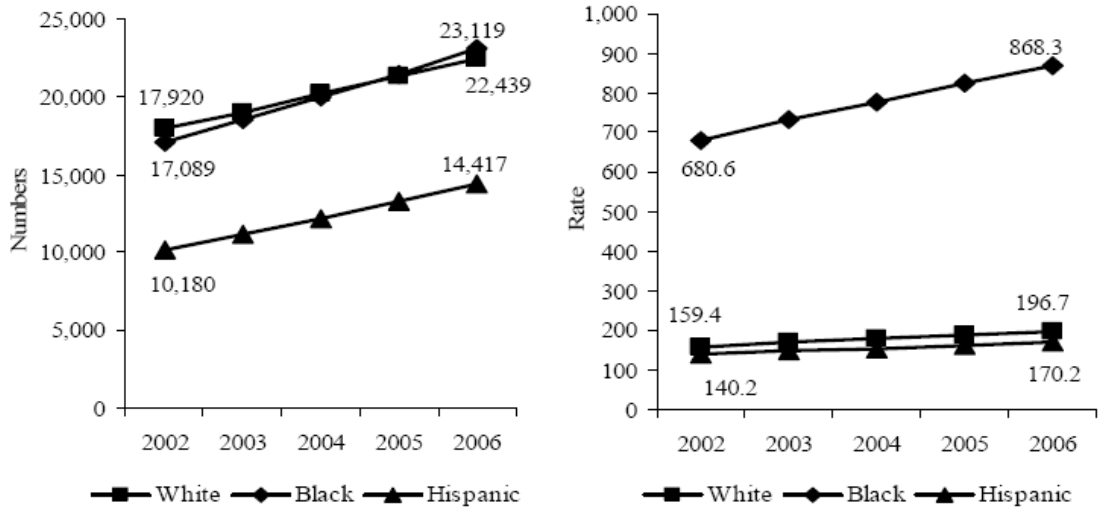
	Males		Females		Total[b]	
Race/Ethnicity	**No.**	**Rate**	**No.**	**Rate**	**No.**	**Rate**
White, not Hispanic	9,078	16.7	1,664	2.9	10,742	9.6
Black, not Hispanic	11,230	119.1	6,033	56.2	17,263	85.6
Hispanic	5,058	50.9	1,400	15.1	6,458	33.7
Asian/Pacific Islander	318	13.5	79	3.2	397	8.2
American Indian/Alaska Native	129	17.7	35	4.6	164	11.0
Total[c]	**25,928**	**33.8**	**9,252**	**11.5**	**35,180**	**22.4**

[a] Adapted from: Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2006. Vol. 18. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention;2008:5-10,24. Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed: May 12, 2008.

[b] Because row totals were calculated independently of the values for the subpopulations, the values in each row may not sum to the row total.

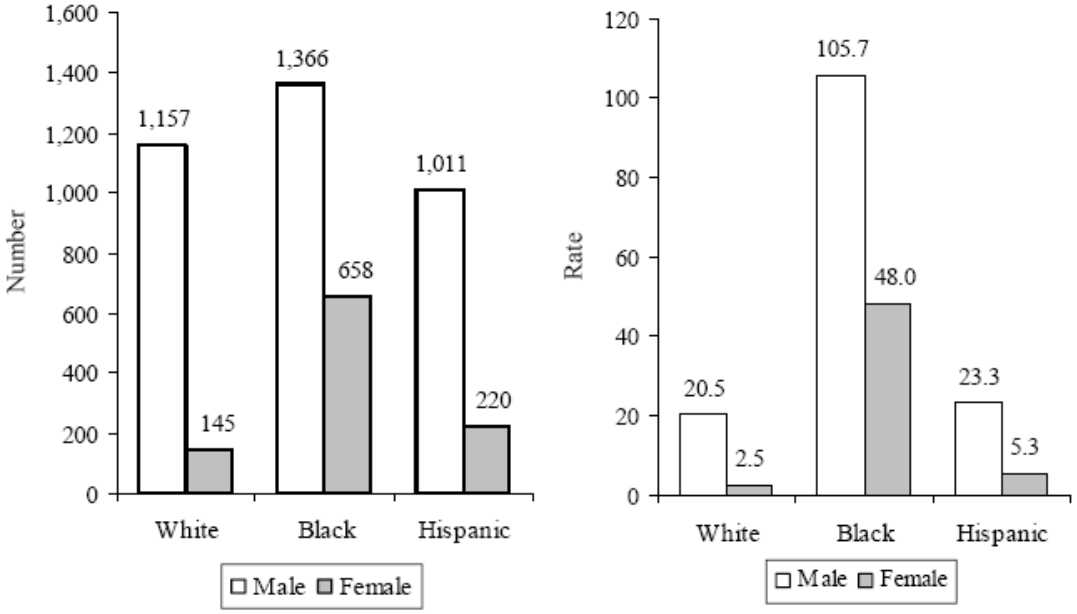
[c] Includes persons of unknown race or multiple races. Because column totals were calculated independently of the values for the subpopulations, the values in each column may not sum to the column total.

Figure 1.1 Number and Rate (per 100,000 population) of Persons Living with HIV/AIDS by Race/Ethnicity, Texas, 2002-2006[a]



[a] Texas Integrated Epidemiologic Profile for HIV/AIDS Services Planning, January 2008. HIV/STD Epidemiology and Surveillance Branch of the Texas Department of State Health Services;2008:6-12. Available at: http://www.dshs.state.tx.us/hivstd/planning/Epi_Profile_02012008.pdf. Accessed: May 12, 2008.

Figure 1.2 Number and Rate (per 100,000 population) of New Diagnoses by Sex and Race/Ethnicity, Texas, 2006[a]



[a] Texas Integrated Epidemiologic Profile for HIV/AIDS Services Planning, January 2008. HIV/STD Epidemiology and Surveillance Branch of the Texas Department of State Health Services;2008:6-12. Available at: http://www.dshs.state.tx.us/hivstd/planning/Epi_Profile_02012008.pdf. Accessed: May 12, 2008.

OVERVIEW OF ANTIRETROVIRAL THERAPY AND ADHERENCE

Antiretroviral therapy for treatment of HIV-infection has progressed significantly since the introduction of zidovudine (AZT) in March 1987. Use of potent combination antiretroviral therapy as the standard of care has led to substantial improvements in survival among patients diagnosed with AIDS.[9] Despite major advances in treatment, currently available combination antiretroviral regimens will not lead to eradication of the HIV virus. Therefore, the Department of Health and Human Services recommended goals of antiretroviral treatment focus on prolonging

survival and improving quality of life through restoring and preserving immunologic function and "maximally and durably" suppressing viral load.[10]

All currently recommended combination antiretroviral regimens consist of at least three drugs active against the HIV virus. Although six mechanistic classes of antiretroviral agents are available for inclusion in combination antiretroviral regimens, several regimens are preferred for initial therapy based on evidence for their efficacy and tolerability (Table 1.2).[10] The combination antiretroviral regimen that is chosen should be tailored to the individual patient based on factors such as potential side effects, pill burden, comorbid conditions, interactions with required medications, and results of drug resistance testing.[10]

Adherence refers to the extent to which patients take their medications as prescribed. Multiple factors are associated with decreased medication adherence, including patient forgetfulness, misunderstanding of dosing instructions, high side effect burden, complexity of regimen, poor patient-prescriber relationship, high medication cost, and indication for a chronic versus an acute condition.[11] Adherence to antiretroviral therapy is complicated by the fact that all recommended regimens consist of multiple medications, many of which are expensive.[11] All of these medications are associated with side effects (e.g. gastrointestinal symptoms and lipodystrophy with protease inhibitors and central nervous system effects with efavirenz), which could reduce patients' willingness to adhere to therapy.[10] Additionally, the stigma associated with HIV infection may foster nonadherence when patients are concerned that others will see them taking their medications.[12] Once the decision is made to initiate antiretroviral therapy, treatment must be maintained for a lifetime, requiring the patient to make a life long commitment to

antiretroviral adherence.[10] Earlier combination antiretroviral therapy regimens were associated with a high pill burden, multiple daily dosing, and food requirements that made adherence difficult. In an effort to ease adherence, coformulations of antiretroviral agents have been developed to reduce pill burden, and studies have been conducted to establish the efficacy of once daily administration for some agents.[12] The recently developed coformulation of efavirenz/emtricitabine/tenofovir allows patients to receive a complete combination antiretroviral therapy regimen in only one pill taken once daily. Despite the significant simplification of many antiretroviral regimens, patient education regarding HIV infection, potential medication side effects, and the consequences of nonadherence will still be essential for optimizing adherence to antiretroviral therapy.[12]

Table 1.2 Antiretroviral Components Recommended for Treatment of HIV-1 Infections in Treatment-Naïve Patients[a]

Select an NNRTI or PI to Add to a Dual-NRTI Backbone			
	NNRTI or PI Options		**Dual-NRTI Options**
Preferred Components	NNRTI: efavirenz OR PI: atazanavir + ritonavir, fosamprenavir + ritonavir (2x/day), lopinavir/ritonavir (2x/day)	+	abacavir/lamivudine[b] OR tenofovir/emtricitabine[b]
Alternative to Preferred Components	NNRTI: nevirapine OR PI: atazanavir, fosamprenavir, fosamprenavir + ritonavir, lopinavir/ritonavir (1x/day), saquinavir + ritonavir		zidovudine/lamivudine[b] OR didanosine + (emtracitabine or lamivudine)
Abbreviations: NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor			

[a]Adapted from: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 1 December 2007. The Panel of Clinical Practices for the Treatment of HIV Infection convened by the Department of Health and Human Services. Available at: http://AIDSinfo.nih.gov. Accessed: March 13, 2008.
[b]Emtricitabine may be used in place of lamivudine and vice versa.

ADHERENCE TO ANTIRETROVIRAL THERAPY AND HIV-RELATED OUTCOMES

Adherence is a chief concern with lifelong combination antiretroviral therapy, since high rates of adherence have been correlated with HIV viral suppression, reduced viral resistance, and improved patient survival.[10] It is widely accepted that at least 95% adherence to antiretroviral therapy is required to achieve virologic suppression, a figure that is based on linking medication adherence to disease

outcomes with unboosted protease inhibitor (PI)-based regimens. Paterson and colleagues evaluated the relationship between adherence to protease inhibitors and patient outcomes in 99 HIV-infected outpatients recruited from clinics in Pittsburgh, PA and Omaha, NE.[13] Both patients who were already receiving a protease inhibitor at baseline and patients who were to be newly initiated on a protease inhibitor were included in this study. Adherence was measured prospectively using the Medication Event Monitoring System (MEMS), with a median duration of follow-up of 6 months. Decreased adherence was significantly associated with risk for virologic failure ($p < 0.001$), which was defined as an HIV RNA level greater than 400 copies/mL at the last study visit (Figure 1.3). Only 5 of 23 (22%) patients with 95% or greater adherence experienced virologic failure, whereas the risk of virologic failure was 61% in patients with 80-94.9% adherence (odds ratio = 5.6, 95% CI: 1.3 – 25.7) and 80% in patients with less than 80% adherence (odds ratio = 14.4, 95% CI: 3.4 – 66.6). Changes in CD4 lymphocyte count were also significantly related to degree of adherence ($p = 0.006$). The mean increase in CD4 lymphocyte count from baseline to final study visit was significantly greater for patients with 95% or greater adherence (83 cells/mm^3) than those with less than 95% adherence (6 cells/mm^3, $p = 0.045$). Based on these data, the authors concluded that adherence of 95% or greater to protease inhibitors is necessary for optimal virologic outcomes.

More recent studies indicate that non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens and ritonavir-boosted PI-based regimens may achieve acceptable viral load suppression at rates of adherence lower than 95%.[14-16] Using data collected prospectively from a cohort of homeless and marginally housed persons living in San Francisco, California, Bangsberg and colleagues found that viral

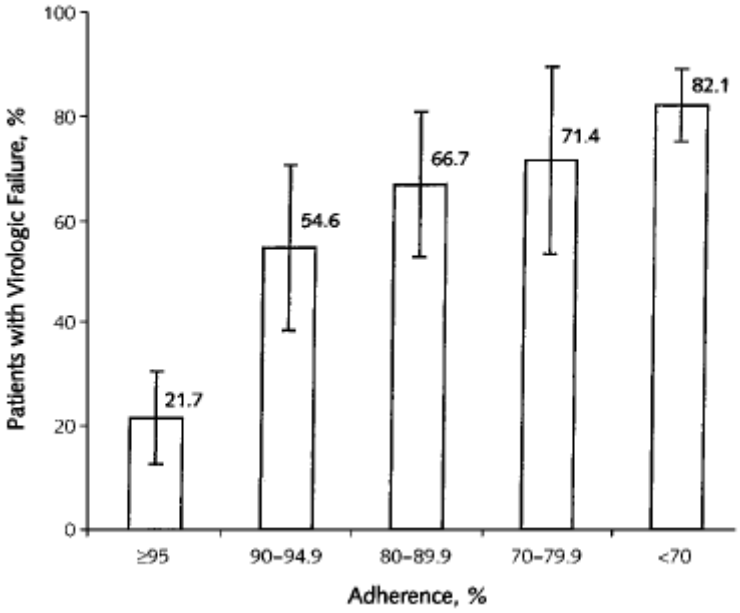
load suppression (HIV RNA < 400 copies/mL) was significantly more common for patients newly started on NNRTI-based regimens than those started on unboosted protease inhibitor regimens ($p = 0.001$).[14] Patients were followed for a median of 9.1 months and adherence was determined using unannounced pill counts. When adherence was divided into quartiles based on unannounced pill count determinations, the majority of patients receiving NNRTI-based therapy achieved viral load suppression at adherence levels of 54-100%. Nachega and colleagues evaluated the relationship between adherence to NNRTI-based antiretroviral therapy and viral load suppression in a large cohort of previously treatment-naïve patients enrolled in an HIV/AIDS disease management program in South Africa.[15] Adherence was calculated based on prescription drug claims. The primary outcome in this study was sustained viral load suppression, which was defined as an HIV RNA level < 400 copies/mL at all measurements from one month after antiretroviral therapy initiation to end of follow-up (median follow-up period was 2.2 years). The authors found that rates of adherence greater than or equal to 80% were associated with sustained viral load suppression in the majority of patients. However, it was also found that every 10% increase in adherence beyond 50% was associated with a mean absolute increase of 0.10 in the proportion of patients achieving sustained viral load suppression, indicating a dose-response relationship between adherence and viral suppression.

The relationship between adherence to ritonavir-boosted PI regimens and virologic suppression was evaluated by Shuter and colleagues.[16] Sixty-four HIV-infected outpatients taking an antiretroviral regimen containing lopinavir/ritonavir were recruited from a clinic in the Bronx, NY. Adherence was evaluated prospectively using MEMS over the 24-week study period. The results of this study

did not reveal a strong relationship between antiretroviral adherence and virologic suppression, as no significant difference was found in the proportion of patients who achieved virologic suppression (HIV RNA < 400 copies/mL) among the lopinavir/ritonavir adherence quartiles ($p = 0.42$). Rates of virologic suppression in this study were high, and even at the lowest level of adherence (23.5-53.3%), 69% of patients achieved a viral load of < 400 copies/mL at 24 weeks.

Although recent evidence suggests that some combination antiretroviral regimens may not require at least 95% adherence for most patients to achieve viral load suppression, efforts should still be made to maximize antiretroviral adherence in order to achieve the goal of maximum and durable suppression of viral load.[10] This is emphasized by the finding of Nachega and colleagues that there is a dose-response relationship between viral load suppression and antiretroviral adherence.[15] Additionally, nonadherence to antiretroviral therapy has important public health implications, as suboptimal adherence has been linked to the development of HIV drug resistance and could lead to transmission of multi-drug resistant viral strains.[17]

Figure 1.3 Adherence to Unboosted Protease Inhibitor Therapy and Virologic Failure[a]



[a] Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;133:21-30.

TREATMENT ADHERENCE AND MENTAL DISORDERS

As discussed above, multiple factors may engender nonadherence to combination antiretroviral therapy, including cost, side effects, and chronicity of treatment. While these factors present barriers to antiretroviral adherence for any population, they may be particularly difficult to overcome for patients with mental disorders, who often suffer from cognitive impairment and behavioral instability. Patients with serious mental disorders, including depression, bipolar disorder, and schizophrenia, often have poor adherence with psychotropic medications.[18-21] Additionally, having a mental disorder has been associated with poor adherence to medications used to treat chronic medical conditions, including diabetes,

hypertension, and coronary heart disease.[22-25] It is not surprising, therefore, that several studies have found an association between the presence of mental disorders and poor adherence to antiretroviral therapy.[13,27-30]

In the previously described study by Paterson and colleagues, which evaluated the relationship between adherence to unboosted PI-based therapy and HIV-related outcomes, factors associated with improved adherence were also assessed.[13] Psychiatric comorbidity was evaluated at baseline using the General Health Questionnaire, a 28-item measure divided into four subscales of psychiatric symptoms: somatic symptoms, anxiety and insomnia, social dysfunction, and depression.[26] Lower psychiatric comorbidity as measured by the General Health Questionnaire was associated with greater than or equal to 95% adherence to antiretroviral medication ($p = 0.0014$), and remained a significant predictor of at least 95% adherence after adjustment for other demographic and disease state factors associated with adherence (odds ratio = 1.7, $p = 0.04$, 95% CI: 1.0 – 3.0).[13]

In a two week prospective study, Wagner and colleagues evaluated adherence to antiretroviral therapy among 47 Los Angeles, CA residents with serious mental disorders using an electronic monitoring cap system.[27] Patients included in this study were diagnosed with bipolar depression (51%), schizophrenia (26%), schizoaffective disorder (11%), and major depression with psychotic features (13%). Most (91%) patients were using antiretroviral regimens with a twice-daily dosing schedule, and the average time on the current antiretroviral regimen was 29 months. Even during the brief, 2-week observation period, less than half of participants (40%) demonstrated at least 90% adherence, and 31% of patients had less than 50% adherence. Although not statistically significant, the rates of adherence in this study

varied by psychiatric diagnosis. The mean rate of adherence was 81% for patients with schizoaffective disorder, 70% for patients with bipolar depression, 59% for patients with schizophrenia, and 52% for those who had major depression with psychotic features.

Tucker and colleagues analyzed data from the HIV Cost and Services Utilization Study to evaluate the effects of specific psychiatric disorders on adherence to antiretroviral medication.[28] The HIV Cost and Services Utilization Study was a probability sample of 2,864 HIV-infected patients who were representative of all the adult HIV-infected patients living in the contiguous United States in early 1996. Study data were collected from a baseline and two follow-up interviews. The analyses in this study were based on data from 1,910 patients who participated in all three interviews and who were taking antiretroviral medications at the time of the second follow-up interview. Antiretroviral adherence was determined by patient responses to interview questions about pill-taking behavior at the time of the second follow-up. Patients were considered to be nonadherent if they reported any deviations from the prescribed regimen over the past week. General mental health status at the time of the second follow-up was evaluated using the five-item Mental Health Index from the 36-item Short Form (SF-36) Health Survey, which evaluates anxiety, depression, loss of behavioral or emotional control, and psychological well-being over the past month. Patients were identified as having a probable diagnosis of depression, dysthymia, generalized anxiety disorder (GAD), or panic disorder based on responses to the Short-Form of the World Health Organization Composite International Diagnostic Interview during the first follow-up interview.

Nineteen percent of patients in this sample had evidence for a probable psychiatric disorder, with major depression being the most common (16.5%).[28] After adjustment for important demographic and disease state variables, having a probable diagnosis of depression (odds ratio = 1.7, p = 0.001, 95% CI: 1.3 – 2.3], GAD (odds ratio = 2.4, p = 0.02, 95% CI: 1.2 – 5.0), or panic disorder (odds ratio = 2.0, p < 0.001, 95% CI: 1.4 – 3.0) increased the likelihood of patient-reported nonadherence to antiretroviral medication. Even after adjustment for self-reported substance use, poorer general mental health (odds ratio = 1.3, p = 0.02, 95% CI: 1.0 – 1.6) and probable diagnosis of a psychiatric disorder (odds ratio = 1.7, p = 0.002, 95% CI: 1.2 – 2.3) remained significantly associated with nonadherence.

In an Italian study conducted by Ammassari and colleagues, the effects of depressive symptoms and cognitive impairment on adherence to antiretroviral therapy were assessed in 135 HIV-infected patients.[29] Adherence to antiretroviral medications was assessed by asking patients about the timing of their last missed dose in the previous four weeks. Patients who reported missing a dose of medication in the previous week were considered to be nonadherent. Depressive symptoms were rated using the Montgomery-Åsberg Depression Rating Scale (MADRS), and patients were considered to have prominent depressive symptoms if their MADRS score was greater than 19. Cognitive impairment was assessed by a battery of neuropsychological tests and defined as performance of 1.5 or more standard deviations below published age-matched norms. Patients in this study had been taking their current antiretroviral regimen for less than one year, on average. The rate of self-reported nonadherence was 30%. Thirty-two (24%) patients were found to have prominent depressive symptoms and 16 (12%) were found to have global

neurocognitive impairment. The presence of prominent depressive symptoms was associated with an increased likelihood for antiretroviral nonadherence (odds ratio = 3.12, p = 0.008, 95% CI: 1.36 – 7.13), though global cognitive impairment was not. The relationship between depressive symptoms and nonadherence was weakened but remained significant (odds ratio = 1.05, p = 0.03, 95% CI: 1.00 – 1.10) after adjustment for other variables associated with nonadherence.

In addition to its impact on adherence, the presence of mental disorders may affect persistence with antiretroviral therapy. Walkup and colleagues utilized data from 2,459 HIV-infected New Jersey Medicaid beneficiaries to evaluate the use of newer PI and NNRTI-based antiretroviral regimens among patients with serious mental disorders.[30] Persistence with these regimens was included as a secondary outcome. Diagnosis of a serious mental disorder was determined based on service claims including *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) codes for schizophrenia, bipolar disorder, or major depressive disorder, recurrent episode. Patients with ICD-9-CM codes for bipolar disorder or major depressive disorder, recurrent episode were considered to have a severe affective disorder. Persistence with antiretroviral therapy was analyzed by examining quarterly use of PIs or NNRTIs among participants. The use of PI and NNRTI-based antiretroviral regimens was found to be higher among patients with schizophrenia (68.3%) and severe affective disorders (75.6%) than patients without serious mental disorders (64.3%, p = 0.003). After controlling for demographic and disease state factors, patients with severe affective disorders (odds ratio = 0.73, p < 0.01, 95% CI: 0.57 – 0.94), but not those with schizophrenia (odds ratio = 1.04, p =

NS, 95% CI: 0.78 – 1.38), were less likely to be persistent with antiretroviral therapy than those with no serious mental disorders.

PSYCHOTROPIC MEDICATION ADHERENCE AND ADHERENCE TO ANTIRETROVIRAL THERAPY

The association of mental disorders, particularly affective disorders, with an increased risk of nonadherence to antiretroviral therapy is supported by several studies using varying definitions of mental disorders and adherence. Symptoms of mental disorders are potentially modifiable risk factors for nonadherence. It is therefore important to know whether appropriate treatment of mental disorders leads to improved adherence to antiretroviral therapy. Relatively few studies have addressed this issue, and most analyses have focused on the use of antidepressants.

In the study by Wagner and colleagues discussed above, which prospectively evaluated adherence to antiretroviral therapy among patients with serious mental disorders, self-reported adherence to psychotropic medication was associated with adherence to antiretroviral therapy.[27] Thirty-six of the 47 patients (77%) included in the study were taking psychotropic medication, with antidepressants being the most commonly used agents (62%). Mood stabilizers and antipsychotics were each used by 26% of the sample and anxiolytics were used by 15%. Adherence to psychotropic medication was assessed at study endpoint by asking patients to recall their pill-taking behavior over the past 3 days. The mean self-reported adherence to psychotropic medications was 86%. A moderate correlation was found between self-reported adherence to psychotropics and both self-reported ($r = 0.45$, $p < 0.05$) and electronically monitored ($r = 0.45$, $p < 0.05$) adherence to antiretroviral therapy.

Yun and colleagues performed a retrospective cohort study to evaluate the effect of antidepressant treatment on antiretroviral adherence in HIV-infected patients with comorbid depression.[31] A cohort of 1,713 primarily indigent HIV-infected patients was identified using surveillance data from the Denver Public Health Department that was previously collected for other studies. Patients were considered to be depressed if administrative data contained an ICD-9 code for Major Depressive Disorder or for Bipolar I Disorder with the most recent episode depressed or mixed. Patients were also considered to have depression if a provider assessment of depression was documented in the patient's medical chart, or if electronic pharmacy records revealed treatment with antidepressants. Patients receiving only low doses of tricyclic antidepressants or trazodone were not considered to have depression. Adherence to antiretroviral and antidepressant medications was calculated based on outpatient electronic pharmacy records. System-wide pharmacy data were likely to account for most prescriptions received by study participants, as AIDS Drug Assistance Program medications were provided to patients at a significantly reduced cost. Adherence to antiretroviral therapy was calculated by adding the number of days dispensed for each antiretroviral drug used during the study period and dividing by the sum of the observation periods (time from first to last refill plus number of days dispensed) for each drug; a similar calculation was used to determine antidepressant adherence. Patients were considered to be adherent to antiretroviral therapy if the calculated adherence rate was at least 95%. Patients with a calculated adherence rate greater than or equal to the median adherence value for antidepressant medications were considered to be adherent to antidepressants.

Of the 1,713 HIV-infected patients identified, 818 (48%) received antiretroviral therapy, with a mean adherence rate of 72%.[31] Nine-hundred eighty-one patients (57%) were considered to have a diagnosis of depression, of which 450 (46%) were prescribed antidepressants (median adherence rate 87%). While the authors originally concluded that both receipt of and adherence to antidepressant treatment was associated with antiretroviral adherence, a subsequently published commentary by peers led the authors to reevaluate their analyses.[32] The proportion of depressed patients who received antidepressant therapy was lower among those who were at least 95% adherent to antiretroviral therapy, which may indicate that merely prescribing antidepressant therapy does not improve antiretroviral adherence among depressed patients. However, when adherence to antidepressant therapy was taken into account, the proportion of depressed patients who received and were adherent to antidepressant therapy was higher among those who were adherent to antiretroviral therapy (69%) than those who were not (48%; odds ratio = 2.45, p = 0.001, 95% CI: 1.39 – 4.29).

In another large retrospective cohort study, Horberg and colleagues evaluated the effects of depression and selective serotonin reuptake inhibitor (SSRI) use on antiretroviral adherence.[33] Data from two large health maintenance organizations were used to identify a cohort of 3,359 HIV-infected individuals initiated on a new combination antiretroviral regimen (either newly initiated or switched from a previous regimen). Patients were considered to be depressed if they had at least one outpatient visit with a coded clinical diagnosis of depression, major depression, or dysthymia. Adherence to antiretroviral therapy and SSRIs over the 12-month observation period was calculated from pharmacy dispensing and refill data, with

antiretroviral adherence calculated across all antiretroviral medications. The adherence measure used expressed the number of doses for which a patient had the drug in possession as a percentage of the total number of intended doses in the interval between the first and last refill. Patients with a calculated adherence of greater than or equal to 90% were considered adherent to antiretroviral therapy, whereas adherence greater than 80% was considered sufficient for SSRIs.

Of the 3,359 patients included in this study, 1,398 (42%) were diagnosed with depression and 508 (15%) were prescribed SSRIs.[33] The overall mean rate of adherence to antiretroviral therapy was high at 80.9%. The mean adherence to SSRIs over the 12-month observation period was 76.9%, and 57.9% of those prescribed SSRIs achieved greater than 80% adherence. When adherence to antiretroviral therapy was treated as a continuous measure, rates of antiretroviral adherence were lower among patients with depression (81.4% for patients treated with SSRIs, 79.2% for patients not treated with SSRIs; $p < 0.001$ for both) than for nondepressed patients (82.6%). While statistically significant, these small differences in antiretroviral adherence are unlikely to be clinically meaningful. Patients who were greater than 80% adherent to SSRIs had a higher mean rate of antiretroviral adherence (84.7%) than nondepressed patients (82.6%, $p < 0.001$) or depressed patients without exposure to SSRIs (79.2%, $p = 0.001$). After adjustment for age, gender, antiretroviral-naïve status, antiretroviral regimen type, and temporal trend, rates of antiretroviral adherence among depressed patients without exposure to SSRIs remained significantly lower than that for nondepressed patients ($p = 0.01$), and patients who were greater than 80% adherent to SSRIs had significantly higher rates of antiretroviral adherence than depressed patients without exposure to SSRIs ($p = 0.01$).

When adherence was dichotomized based on achieving at least 90% adherence to antiretroviral therapy, depressed patients without SSRI exposure had significantly lower odds of achieving at least 90% adherence than nondepressed patients (adjusted odds ratio = 0.81, p = 0.03, 95% CI: 0.7 – 0.98). Patients who were treated with SSRIs were just as likely as nondepressed patients to achieve at least 90% adherence to antiretroviral therapy (adjusted odds ratio = 0.91, p = 0.41, 95% CI: 0.72 – 1.15). Patients with greater than 80% adherence to SSRIs were no more likely than nondepressed patients to achieve at least 90% adherence to antiretrovirals (adjusted odds ratio = 1.13, p = 0.39, 95% CI: 0.86 – 1.49), though they were significantly more likely than depressed patients without SSRI exposure to achieve this level of adherence (p = 0.01).

STUDY OBJECTIVES

The purpose of the current study is to evaluate the relationship between mental disorders and patient adherence to antiretroviral therapy, with the intent to determine if certain subgroups of the population with mental disorders, based on race/ethnicity and gender, are particularly at risk for nonadherence. This study will also evaluate the relationship between adherence to psychotropic medications and adherence to combination antiretroviral therapy to determine if efforts to improve antiretroviral adherence among patients with mental disorders should emphasize adherence to psychotropic medications. Specific study objectives are: 1) to compare the prevalence of psychotropic medication use among subgroups of patients taking antiretroviral therapy based on race/ethnicity and gender; 2) to examine the relationship between psychotropic medication use and antiretroviral adherence and

persistence, taking into account race/ethnicity and gender; and 3) to examine the relationship between antiretroviral adherence and adherence to psychotropic medications while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

Tested Hypotheses

Objective One: To compare the prevalence of psychotropic medication use among subgroups of patients taking antiretroviral therapy based on race/ethnicity and gender.

- H_{01}: There will be no significant difference in the prevalence of psychotropic medication use among HIV-infected patients based on race/ethnicity.
- H_{02}: There will be no significant difference in the prevalence of psychotropic medication use among HIV-infected patients based on gender.

Rationale for H_{01} through H_{02}: Previous studies indicate that the risk of contracting HIV is higher among patients with mental disorders.[5-7] Some data suggest that, among patients with mental disorders, racial/ethnic minorities and women may be disproportionately affected by HIV/AIDS, though these relationships have not been clearly established.[5,6]

Objective Two: To examine the relationship between psychotropic medication use and antiretroviral adherence and persistence, taking into account race/ethnicity and gender.

- H_{03}: There will be no significant difference in the rate of adherence to antiretroviral therapy between those with and those without psychotropic

medication use after controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

- H_{04}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use and race/ethnicity.
- H_{05}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use and gender.
- H_{06}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use, race/ethnicity, and gender.
- H_{07}: There will be no significant difference in persistence with antiretroviral therapy between those with and those without psychotropic medication use after controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.
- H_{08}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use and race/ethnicity.
- H_{09}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use and gender.
- H_{010}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use, race/ethnicity, and gender.

Rationale for H_{03} through H_{010}: Previous studies have indicated that having a mental disorder is associated with poor adherence to antiretroviral therapy but have not evaluated whether specific subgroups of patients with mental disorders are particularly at risk for nonadherence.[13, 27-30]

Objective Three: To examine the relationship between antiretroviral adherence and adherence to psychotropic medications while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

- H_{011}: Among patients using psychotropic medications, there will be no significant relationship between adherence to antiretroviral therapy and adherence to psychotropic medications while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.
- H_{012}: Among patients taking antidepressants, there will be no significant relationship between adherence to antiretroviral therapy and adherence to antidepressants while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.
- H_{013}: Among patients taking antipsychotics, there will be no significant relationship between adherence to antiretroviral therapy and adherence to mood stabilizers while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.
- H_{014}: Among patients taking mood stabilizers, there will be no significant relationship between adherence to antiretroviral therapy and adherence to antipsychotics while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

Rationale for H_{011} through H_{014}: Previous studies indicate that adherence to psychotropic medications, specifically antidepressants, may be associated with adherence to antiretroviral therapy.[31,33]

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CHAPTER TWO

Methods

This chapter describes the research methods used to test the hypotheses stated in Chapter One. The design of the study is specified, along with the criteria for patient selection. Definitions are provided for the primary outcome measures used and the statistical analyses used to test each study hypothesis are explained.

STUDY DESIGN

This is a retrospective cohort study using data extracted from the Texas Medicaid Vendor Drug Program database and Texas Medicaid enrollment files. Texas Medicaid, which is overseen by the Texas Health and Human Services Commission, provides medical coverage for eligible indigent patients in the state of Texas. Coverage is provided for up to three outpatient prescriptions per month (limited to a 185-day supply), though some beneficiaries are exempt from the three prescriptions per month limitation.[1,2]

Data were extracted over the period from January 1, 2003 to December 31, 2005. This timeframe was chosen to avoid the complicating factor of patients who were previously dually-eligible for Medicaid and Medicare being switched to a Medicare Part D prescription drug plan in November 2006. Prescription claims data were used to identify the target study population (adult patients starting a new combination antiretroviral regimen during the year 2004), as well as the subgroup of patients receiving psychotropic medications. Important covariates, including patient

gender and race/ethnicity, were extracted from the Texas Medicaid Vendor Drug Program database and Texas Medicaid enrollment files, respectively. Claims data were also used to determine antiretroviral regimen type and total number of prescribed medications. Adherence to and persistence with combination antiretroviral therapy, as well as adherence to psychotropic medications when applicable, were evaluated over the 12-month period following antiretroviral therapy initiation.

STUDY POPULATION

Subjects eligible for inclusion in this study were those 18-64 years of age with prescription claims for at least three antiretroviral medications indicated for treatment of HIV infection within a 3-month period between January 1, 2004 and December 31, 2004 (Table 2.1). Claims for at least three antiretroviral medications were required since all combination antiretroviral regimens recommended for treatment of HIV infection in 2004 consisted of at least three antiretroviral agents.[3-5] A 3-month index period was chosen to allow patients who were limited to three prescriptions per month an opportunity to acquire the individual components of their combination antiretroviral regimens over multiple months. This often becomes necessary when patients are being treated with other costly medications for comorbid conditions. In order to target a population of patients starting a new combination antiretroviral regimen, patients were excluded if they had any claims for antiretroviral medications in the 3 months prior to the index period. Included patients were required to have continuous enrollment in Medicaid for the 3 months prior to and 12 months following the index period.

Assuming a ratio of 1:2 for patients with mental disorders to those without, the sample size needed to detect a minimum relative risk of adherence to combination antiretroviral therapy of 0.75 with 80% power and $\alpha = 0.05$ is 990. This estimate is based on data from a previous study indicating that the rate of adherence to antiretroviral therapy among non-depressed HIV-infected patients is 34%.[6]

Table 2.1 Antiretroviral Medications for Treatment of HIV Infection Available in 2004

Generic Name	Brand Name
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
Abacavir	Ziagen
Didanosine	Videx
Emtricitabine	Emtriva
Lamivudine	Epivir
Stavudine	Zerit
Tenofovir	Viread
Zalcitabine	Hivid
Zidovudine	Retrovir
Combination NRTIs	
Abacavir/Lamivudine	Epzicom
Emtricitabine/Tenofovir	Truvada
Lamivudine/Zidovudine	Combivir
Abacavir/Lamivudine/Zidovudine	Trizivir
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Delavirdine	Rescriptor
Efavirenz	Sustiva
Nevirapine	Viramune
Protease Inhibitors (PIs)	
Amprenavir	Agenerase
Atazanavir	Reyataz
Fosamprenavir	Lexiva
Indinavir	Crixivan
Lopinavir/Ritonavir	Kaletra
Nelfinavir	Viracept
Ritonavir	Norvir
Saquinavir	Invirase, Fortovase
Fusion Inhibitors	
Enfuvirtide	Fuzeon

Subgroup of Patients with Mental Disorders

In this study, a mental disorder was defined as having a prescription claim for an antidepressant, mood stabilizer, and/or antipsychotic agent between January 1, 2004 and December 31, 2004 (Tables 2.3-2.5). To avoid including patients in this subgroup who were using psychotropic medications for insomnia rather than a mental disorder, minimum doses for inclusion were required for quetiapine (≥ 300 mg/day) and tricyclic antidepressants (≥ 75 mg/day). A dose of 300 mg/day was chosen as the minimum for quetiapine since this is the lowest dose shown to be effective for treatment of bipolar disorder and schizophrenia.[7] The minimum dose of 75 mg/day chosen for the tricyclic antidepressants is based on a Cochrane review which found that low dosages of tricylclic antidepressants, generally 75-100 mg/day, were effective for treatment of depression.[8] Trazodone was excluded from the list of antidepressants used to denote presence of a mental disorder since this medication is more often used to treat insomnia than depression. Prochlorperazine was excluded from the list of antipsychotic agents used to denote presence of a mental disorder since this medication is primarily used for treatment of nausea rather than psychosis. Claims for injectable antipsychotic agents were excluded due to inconsistencies in the days supply entered in the database and the fact that claims for these medications are not consistently processed through the Texas Medicaid Vendor Drug Program. Claims for the olanzapine/fluoxetine combination or the perphenazine/amitriptyline combination were included in analyses for both antipsychotics and antidepressants as appropriate.

In order to separate anticonvulsant agents used for epilepsy from those used for mood stabilization, only anticonvulsants that have at least one formulation with a

current FDA-approved indication for treatment of bipolar disorder were considered to be mood stabilizers for this study. These are valproic acid, divalproex sodium, carbamazepine, and lamotrigine.[9-11] Patients receiving other anticonvulsants in addition to those considered to be mood stabilizers during the 12-month evaluation period were considered to be treated for a seizure disorder and excluded from the subgroup of patients with mental disorders. Additionally, patients taking a mood-stabilizing anticonvulsant were required to have a claim for at least one other psychotropic agent (i.e., antidepressant, lithium, and/or antipsychotic) during the 12-month evaluation period to be included in the subgroup of patients with mental disorders (Tables 2.2-2.4). This increases the likelihood that these anticonvulsants were being used to treat a psychiatric condition rather than a seizure disorder.

Table 2.2 Antidepressants Available in 2004

Generic Name	Brand Name
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Citalopram	Celexa
Escitalopram	Lexapro
Fluoxetine	Prozac
Fluvoxamine	Luvox
Paroxetine	Paxil
Sertraline	Zoloft
Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)	
Duloxetine	Cymbalta
Venlafaxine	Effexor
Tricyclic Antidepressants (TCAs)	
Amitriptyline	Elavil
Amoxapine	Asendin
Clomipramine	Anafranil
Desipramine	Norpramin
Doxepin	Sinequan
Imipramine	Tofranil
Nortriptyline	Pamelor
Protriptyline	Vivactil
Trimipramine	Surmontil
Monoamine Oxidase Inhibitors (MAOIs)	
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Other	
Bupropion	Wellbutrin
Nefazodone	Serzone
Mirtazapine	Remeron

Table 2.3 Mood Stabilizers Available in 2004

Generic Name	Brand Name(s)
Anticonvulsants	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol
Divalproex Sodium	Depakote
Lamotrigine	Lamictal
Valproic Acid	Depakene
Other	
Lithium	Eskalith, Lithobid

Table 2.4 Antipsychotics Available in 2004

Generic Name	Brand Name
First Generation Antipsychotics	
Chlorpromazine	Thorazine
Droperidol	Inapsine
Fluphenazine	Prolixin
Haloperidol	Haldol
Loxapine	Loxitane
Molindone	Moban
Perphenazine	Trilafon
Pimozide	Orap
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Second Generation Antipsychotics	
Aripiprazole	Abilify
Clozapine	Clozaril
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal
Ziprasidone	Geodon

OUTCOME MEASURES

Adherence to combination antiretroviral therapy was assessed using prescription claims data. The primary adherence measure was the Proportion of Days Covered (PDC) across all antiretroviral medications in the index regimen.[12] This measure was chosen over the commonly used Medication Possession Ratio (MPR) because the PDC provides a more conservative estimate of medication adherence when multiple medications in the same class are used concomitantly. While the numerator of the MPR is merely a sum of the number of days supplied for a medication, the numerator of the PDC is calculated using a set of rules that avoids double-counting days of medication coverage. Therefore, values for the PDC range from 0 to 1.[12] The PDC for combination antiretroviral therapy was calculated by determining the total number of days during the 12-month follow-up period for which all index antiretrovirals were available and dividing by 365 days. Adherence to antiretroviral therapy was dichotomized based on calculated PDCs. Patients with a PDC $\geq$ 90% were considered adherent to combination antiretroviral therapy for the primary analyses, though sensitivity analyses were also performed using PDC values of $\geq$ 95%, $\geq$ 85%, and $\geq$ 80% as the cutoffs for antiretroviral adherence. Assessing multiple levels of antiretroviral adherence was considered to be valuable given the recent evidence indicating that many patients taking newer combination antiretroviral regimens will achieve desired clinical outcomes at adherence levels below 95%.[13-15] Patients with a PDC $\geq$ 80% for antidepressants, antipsychotics, and mood stabilizers were considered adherent to psychotropic medications, based on convention. When more than one psychotropic medication was used during the evaluation period, the PDC for psychotropics was calculated as the mean adherence across drug classes.

Persistence was measured as the number of days that a patient was persistent with combination antiretroviral therapy. A gap in treatment of greater than 60 days (days supply dispensed plus a 60 day grace period) constituted the end of the treatment period for each individual drug. In a multicenter, National Institutes of Health-sponsored study of structured antiretroviral treatment interruption, the mean time to early termination of treatment interruption due to a decline in CD4 lymphocyte count, an increase in HIV RNA levels, and/or disease progression was 2.3 months.[16] Therefore, a gap in treatment of 60 days is likely to result in clinically significant adverse outcomes. The number of days persistent was calculated by summing the number of days from the first date on which all index medications were available to the last date before which no gaps in treatment with all index medications greater than 60 days occurred.

STATISTICAL ANALYSES

Statistical analyses for this study were performed using SPSS® Version 15.0 for Windows.[17] All tests were two-sided. The threshold for statistical significance was defined as $\alpha = 0.05$ for all tests. Frequencies and percentages were used to describe the study population in terms of categorical baseline variables (race/ethnicity, gender, psychotropic medication use, types of antiretroviral regimens prescribed), while descriptive statistics were used to evaluate continuous baseline variables (age, total number of medications). Assumptions for each statistical test were checked to evaluate validity, and tests were performed to rule out multicollinearity for variables entered into regression equations. Table 2.5 provides a list of the statistical analyses used for hypothesis testing.

For objective one, Pearson chi-square analyses were used to evaluate differences in the proportion of patients using psychotropic medications among population subgroups based on race/ethnicity and gender. For all analyses, race/ethnicity was categorized as black, white, Hispanic, or other, and gender was dichotomized as male and female.

Objective two examines the relationship between mental disorders and antiretroviral adherence and persistence. Logistic regression was used to evaluate the relationship between adherence based on PDC and psychotropic medication use, controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications. Controlling for these same factors, multiple linear regression was used to evaluate the relationship between psychotropic medication use and number of days persistent. For all analyses, antiretroviral regimen type was classified as NNRTI-based, ritonavir boosted PI-based, unboosted PI-based, triple NRTI, or other. Total number of medications included antiretrovirals, psychotropics, and all other medications prescribed over the 3-month index period to serve as an indicator of overall pill burden.

In addition to the regression analyses, factorial ANOVA was used to test for significant interactions between psychotropic medication use, race/ethnicity, and gender with regard to effects on PDC (treated as a continuous variable) and number of days persistent. Factorial ANOVA allows for testing of the three way interaction between psychotropic medication use, race/ethnicity, and gender, which assessed whether particular subsets of the mentally ill population (e.g. Hispanic females, white males) were at greater risk for antiretroviral nonadherence.

For objective three, logistic regression was used to evaluate the relationship between adherence to antiretroviral therapy and adherence to psychotropic medications, controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications. Models for overall psychotropic medication adherence, as well as adherence to different classes of psychotropic medications, were tested.

Table 2.5 List of Analyses by Hypothesis

Hypothesis	Time-frame	DV	Measmt Level	IV	Measmt Level	Test
Objective 1						
H_{01}-H_{02}	Baseline	Proportion of subjects using psychotropics	Nominal	1. Race/ethnicity 2. Gender	Nominal Nominal	Pearson chi-square
Objective 2						
H_{03}	Baseline to Endpoint	Adherence to ARV drugs (based on PDC)	Nominal	3. Use of Psychotropics <u>Covariates</u> -Race/ethnicity -Gender -ARV regimen type -Total # of medications	Nominal Nominal Nominal Nominal Interval	Logistic regression
H_{04}-H_{06}	Baseline to Endpoint	PDC for ARV drugs	Continuous	<u>Interaction term</u> 4. Use of Psychotropics*race/ethnicity 5. Use of Psychotropics* gender 6. Use of Psychotropics*race/ethnicity*gender	 Nominal Nominal Nominal	Factorial ANOVA
H_{07}	Baseline to Endpoint	Number of days persistent	Continuous	7. Use of Psychotropics <u>Covariates</u> -Race/ethnicity -Gender -ARV regimen type -Total # of medications	Nominal Nominal Nominal Nominal Continuous	Multiple linear regression
H_{08}-H_{010}	Baseline to Endpoint	Number of days persistent	Continuous	<u>Interaction term</u> 8. Use of Psychotropics*race/ethnicity 9. Use of Psychotropics* gender 10. Use of Psychotropics*race/ethnicity*gender	 Nominal Nominal Nominal	Factorial ANOVA
Abbreviations: Measmt = measurement; DV = dependent variable; IV = independent variable; ARV = antiretroviral; MPR = medication possession ratio; ANOVA = analysis of variance						

Table 2.5 List of Analyses by Hypothesis - Continued

Hypothesis	Time-frame	DV	Measmt Level	IV	Measmt Level	Test
Objective 3						
H_{011}-H_{014}	Baseline to Endpoint	Adherence to ARV drugs (based on PDC)	Nominal	Adherence (based on PDC) to: 11. Psychotropics 12. Anti-depressants 13. Anti-psychotics 14. Mood stabilizers <u>Covariates</u> -Race/ethnicity -Gender -ARV regimen type -Total # of medications	 Nominal Nominal Nominal Nominal Nominal Nominal Nominal Continuous	Logistic regression
Abbreviations: Measmt = measurement; DV = dependent variable; IV = independent variable; ARV = antiretroviral						

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CHAPTER THREE

Results

This chapter describes the demographic characteristics of the study population and presents the results of the analyses described in Chapter Two. Data for this study were collected from the Texas Medicaid Vendor Drug Program database and Texas Medicaid enrollment files. During 2004, 171,230 claims for antiretroviral medications were made to Texas Medicaid for 5,138 individual patients aged 18-64. After applying inclusion and exclusion criteria for number of antiretroviral agents in the index regimen, claims for antiretrovirals in the previous three months, and continuous enrollment, a total of 1,321 patients using combination antiretroviral therapy were included in the sample (Table 3.1).

Table 3.1 Summary of Subjects Meeting Inclusion Criteria

Criterion	Number
Total number of subjects with an ARV claim during 2004	5,699
Number of subjects ages 18-64 [-561]	5,138
Number of subjects with claims for at least 3 ARVs within 3 months starting in 2004 [-955]	4,183
Number of subjects with no ARV claims in 3 months prior to index [-2,711]	1,472
Number of subjects with continuous enrollment in Texas Medicaid [-151]	1,321
Total number of subjects meeting inclusion criteria	1,321
Abbreviations: ARV = antiretroviral	

DEMOGRAPHIC CHARACTERISTICS

Demographic characteristics for the 1,321 patients included in the sample are displayed in Table 3.2. The mean age of all subjects was 40.2 ± 9.3 years, with a range of 18 to 64 years. Males and females were almost equally represented, with males accounting for 52.4% of the sample. The most common racial/ethnic group was black (53.1%), followed by white (22.7%) and Hispanic (13.9%). Most patients in the sample were using a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen at baseline (31.5%), though ritonavir-boosted protease inhibitor (PI)-based regimens (28.6%) and unboosted PI-based regimens (21.6%) were also commonly used. The mean number of antiretroviral drugs in the initial regimen across the entire sample was 3.4 ± 0.8, with a range from three to eight. The total number of medications being used over the 3-month index period ranged from one to thirty, with a mean of 7.3 ± 4.6. The reason that some patients in the sample had a total number of medications less than three is because the total number of medications used, which represents total pill burden, does not take into account that some dosage forms represent combination medications. All patients listed as having one or two for total number of medications were receiving combination antiretroviral medications.

Table 3.2 Baseline Demographic Characteristics of Patients Using Combination Antiretroviral Therapy

Characteristic	All Included Subjects (N = 1,321)
Age, mean ± SD (yrs)	40.2 ± 9.3
Male, number (%)	692 (52.4%)
Race/Ethnicity, number (%)	
Black	702 (53.1%)
White	300 (22.7%)
Hispanic	183 (13.9%)
Other	136 (10.3%)
ARV regimen type, number (%)	
NNRTI-based	416 (31.5%)
Ritonavir boosted PI-based	378 (28.6%)
Unboosted PI-based	285 (21.6%)
Triple NRTI	121 (9.2%)
Other	121 (9.2%)
Number of ARV drugs in index regimen, mean ± SD	3.4 ± 0.8
Total number of medications, mean ± SD	7.3 ± 4.6
Abbreviations: SD = standard deviation, ARV = antiretroviral, NNRTI = nonnucleoside reverse transcriptase inhibitor, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor	

Of the 1,321 patients included in the sample, 501 (37.9%) met the study criteria for having a mental disorder based on psychotropic drug use. Table 3.3 displays the demographic characteristics of the sample by psychotropic medication use. The mean age for patients using psychotropic medications (41.7 years, SD = 7.8) was significantly greater than the mean age for those not using psychotropics (39.3 years, SD = 10.0, $p < 0.001$), with a mean difference of 2.4 years. No significant differences were observed between subjects using psychotropics and those who were not with regard to type of antiretroviral regimen used or the number of antiretroviral drugs in the index regimen. Patients using psychotropic medications had a significantly higher mean total number of medications at baseline (8.9, SD = 5.4)

compared to those who did not use psychotropics (6.3, SD = 3.7, $p < 0.001$). Differences among groups based on race/ethnicity and gender are outlined in the results of objective one.

Table 3.3 Baseline Demographic Characteristics of Patients Using Combination Antiretroviral Therapy by Use of Psychotropic Medications (N = 1321)

Characteristic	Subjects Using Psychotropics (n = 501)	Subjects Not Using Psychotropics (n = 820)	Statistic	p-value
Age, mean ± SD (yrs)	41.7 ± 7.8	39.3 ± 10.0	t (1246.3) = 4.94	<0.001
Male, number (%)	261 (52.1%)	431 (52.6%)	χ^2 (1) = 0.03	0.87
Race/Ethnicity, number (%)			χ^2 (3) = 24.16	<0.001
Black	231 (46.1%)	471 (57.4%)		
White	148 (29.5%)	152 (18.5%)		
Hispanic	69 (13.8%)	114 (13.9%)		
Other	53 (10.6%)	83 (10.1%)		
ARV regimen type, number (%)			χ^2 (4) = 6.11	0.19
NNRTI-based	162 (32.3%)	254 (31.0%)		
Ritonavir boosted PI-based	133 (26.5%)	245 (29.9%)		
Unboosted PI-based	103 (20.6%)	182 (22.2%)		
Triple NRTI	46 (9.2%)	75 (9.1%)		
Other	57 (11.4%)	64 (7.8%)		
Number of ARV drugs in index regimen, mean ± SD	3.4 ± 0.9	3.4 ± 0.8	t (962.8) = 1.64	0.10
Total number of medications, mean ± SD	8.9 ± 5.4	6.3 ± 3.7	t (780.3) = 9.76	<0.001

Abbreviations: SD = standard deviation, ARV = antiretroviral, NNRTI = nonnucleoside reverse transcriptase inhibitor, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

OBJECTIVE ONE: EXAMINATION OF THE RELATIONSHIP BETWEEN PSYCHOTROPIC MEDICATION USE AND RACE/ETHNICITY AND GENDER AMONG PATIENTS WITH HIV

This objective examines whether women and/or racial/ethnic minorities being treated for HIV are more likely to have concomitant treatment for mental disorders. Pearson chi-square tests were used to evaluate differences in the proportion of subjects using psychotropic medications based on race/ethnicity and gender. As shown in Table 3.3, no significant relationship was found between subjects' gender and psychotropic medication use ($\chi^2 = 0.03$, df = 1, p = 0.87). However, a chi-square analysis did reveal a significant relationship between race/ethnicity and use of psychotropic medications ($\chi^2 = 24.16$, df = 3, $p < 0.001$). Among white patients, the proportion of patients using psychotropic medications (49.3%) was approximately equal to the proportion of those who were not (50.7%). For patients who were black, Hispanic, or whose race/ethnicity was classified as "other," the proportion of patients using psychotropic medications (32.9%, 37.7%, and 39.0%, respectively) was markedly lower than the proportion of patients who were not using psychotropics (67.1%, 62.3%, and 61.0%, respectively). (Note: Table 3.3 shows column percentages, whereas above data represent row percentages).

Results of Hypothesis Testing

Objective One: To compare the prevalence of psychotropic medication use among subgroups of patients taking antiretroviral therapy based on race/ethnicity and gender.

H_{01}: There will be no significant difference in the prevalence of psychotropic medication use among HIV-infected patients based on race/ethnicity.

Result: Hypothesis is rejected. The proportion of patients using psychotropic medications varied based on race/ethnicity, with blacks, Hispanics, and patients with a race classified as "other" having a lower proportion of psychotropic medication use (32.9%, 37.7%, and 39.0%, respectively) than whites (49.3%).

H_{02}: There will be no significant difference in the prevalence of psychotropic medication use among HIV-infected patients based on gender.

Result: Hypothesis not rejected. No significant relationship was observed between gender and psychotropic medication use among patients treated for HIV infection.

OBJECTIVE TWO: EXAMINING THE RELATIONSHIP BETWEEN PSYCHOTROPIC MEDICATION USE AND ANTIRETROVIRAL ADHERENCE AND PERSISTENCE

This objective was designed to study whether psychotropic medication use is related to adherence to and persistence with combination antiretroviral therapy. Antiretroviral adherence and persistence were calculated for each subject as described in Chapter 2. The mean adherence to combination antiretroviral therapy, as measured by proportion of days covered (PDC), across the entire sample was 39.1% ± 34.6%. The mean persistence with antiretroviral therapy in this sample was 140.3 ± 137.6 days. T-test results revealed no significant differences between subjects using psychotropic medications and those who were not in mean PDC ($t = 0.30$, $df = 1319$, $p = 0.76$) or mean number of days persistent ($t = 0.30$, $df = 1319$, $p = 0.77$; Table 3.4). Because of the large standard deviations for mean PDC and mean number of days

persistent, nonparametric tests were also conducted. A Mann-Whitney U test showed no significant difference in mean PDC between patients using psychotropic medications (median = 25.5%, mean = 39.5%, SD = 33.7%) and those who were not (median = 24.9%, mean = 38.9%, SD = 35.2%) (Z = -0.31, p = 0.76). A nonsignificant difference was also found from a Mann-Whitney U test evaluating mean number of days persistent between users (median = 88.0, mean = 141.7, SD = 135.8) and nonusers (median = 68.0, mean = 139.4, SD = 138.8) of psychotropic medications (Z = -0.62, p = 0.53).

Table 3.4 T-test Comparison of Unadjusted Mean Proportion of Days Covered and Mean Number of Days Persistent by Use of Psychotropic Medications (N = 1321)

Adherence Measure	Subjects Using Psychotropics (n = 501)	Subjects Not Using Psychotropics (n = 820)	Statistic	ρ-value
Mean PDC (%)	39.5 ± 33.7	38.9 ± 35.2	t (1319) = 0.30	0.76
Mean # Days Persistent	141.7 ± 135.8	139.4 ± 138.8	t (1319) = 0.30	0.77
Abbreviations: PDC = proportion of days covered				

Adherence

Binary logistic regression models controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications were used to examine the relationship between PDC and use of psychotropic medications. Adherence to antiretroviral therapy was dichotomized based on PDC value, where subjects having a PDC ≥ 90% were considered to be adherent for the primary analysis. Similar regressions were conducted for adherence defined as PDC ≥ 95%, PDC ≥ 85% , and PDC ≥ 80% to evaluate the sensitivity of the model. After controlling for potential

confounders, the odds of having at least 90% adherence to combination antiretroviral therapy as measured by PDC was not significantly associated with using psychotropic medications (OR = 0.90, p = 0.52, 95% CI: 0.65 – 1.24; Table 3.5). As shown in Tables 3.6-3.8, the relationship between psychotropic medication use and adherence to combination antiretroviral therapy was nonsignificant for all other evaluated levels of adherence (i.e. 95%, 85%, and 80%).

Table 3.5 Results from Binary Logistic Regression Models Analyzing the Relationship between Psychotropic Medication Use and At Least 90% Adherence to Combination Antiretroviral Therapy (N = 1321)[a]

Variable	Coefficient (β) for Psychotropic Medication Use	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
Psychotropic Use[b]	-0.11	0.17	0.42	0.52	0.90	0.65 – 1.24
Race/ethnicity[c]						
Black	-0.13	0.19	0.44	0.51	0.88	0.61 – 1.28
Hispanic	0.03	0.25	0.02	0.90	1.03	0.63 – 1.68
Other	-0.25	0.30	0.69	0.41	0.78	0.43 – 1.41
Gender[d]	0.10	0.16	0.46	0.51	1.11	0.82 – 1.50
ARV regimen type[e]						
Boosted PI	-0.62	0.20	9.90	0.002	0.54	0.36 – 0.79
Unboosted PI	-0.41	0.20	4.01	0.05	0.67	0.45 – 0.99
Triple NRTI	-0.40	0.27	2.14	0.14	0.67	0.39 – 1.15
Other	-0.77	0.33	5.37	0.02	0.47	0.24 – 0.89
Total # of medications	-0.07	0.02	9.51	0.002	0.93	0.90 – 0.98

Abbreviations: CI = confidence interval, ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

[a] Adherence defined as proportion of days covered (PDC)

Model Chi-Square = 33.73, df = 11, $p < 0.001$

Reference categories: [b] nonuse of psychotropics, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

Table 3.6 Results from Binary Logistic Regression Models Analyzing the Relationship between Psychotropic Medication Use and At Least 95% Adherence to Combination Antiretroviral Therapy (N = 1321)[a]

Variable	Coefficient (β) for Psychotropic Medication Use	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
Psychotropic Use[b]	-0.06	0.19	0.09	0.77	0.95	0.66 – 1.37
Race/ethnicity[c]						
Black	-0.19	0.22	0.74	0.39	0.83	0.54 – 1.27
Hispanic	0.16	0.27	0.35	0.56	1.17	0.69 – 2.00
Other	-0.05	0.32	0.02	0.89	0.96	0.51 – 1.80
Gender[d]	0.06	0.18	0.11	0.74	1.06	0.75 – 1.49
ARV regimen type[e]						
Boosted PI	-0.57	0.22	6.78	0.01	0.57	0.37 – 0.87
Unboosted PI	-0.44	0.23	3.73	0.05	0.65	0.42 – 1.01
Triple NRTI	-0.80	0.34	5.40	0.02	0.45	0.23 – 0.88
Other	-1.05	0.41	6.37	0.01	0.35	0.16 – 0.79
Total # of medications	-0.08	0.03	9.77	0.002	0.92	0.88 – 0.97

Abbreviations: CI = confidence interval, ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

[a] Adherence defined as proportion of days covered (PDC)

Model Chi-Square = 34.41, df = 11, $p < 0.001$

Reference categories: [b] nonuse of psychotropics, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

Table 3.7 Results from Binary Logistic Regression Models Analyzing the Relationship between Psychotropic Medication Use and At Least 85% Adherence to Combination Antiretroviral Therapy (N = 1321)[a]

Variable	Coefficient (β) for Psychotropic Medication Use	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
Psychotropic Use[b]	-0.09	0.16	0.34	0.56	0.91	0.67 – 1.24
Race/ethnicity[c]						
Black	-0.21	0.18	1.38	0.24	0.81	0.57 – 1.15
Hispanic	-0.19	0.24	0.64	0.42	0.83	0.52 – 1.32
Other	-0.24	0.27	0.78	0.38	0.79	0.46 – 1.34
Gender[d]	-0.01	0.15	0.01	0.93	0.99	0.74 – 1.31
ARV regimen type[e]						
Boosted PI	-0.59	0.19	10.01	0.002	0.56	0.39 – 0.80
Unboosted PI	-0.32	0.19	2.80	0.10	0.73	0.50 – 1.06
Triple NRTI	-0.30	0.25	1.37	0.24	0.74	0.45 – 1.22
Other	-0.87	0.32	7.44	0.01	0.42	0.23 – 0.78
Total # of medications	-0.07	0.02	11.37	0.001	0.93	0.90 – 0.97

Abbreviations: CI = confidence interval, ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

[a] Adherence defined as proportion of days covered (PDC)

Model Chi-Square = 38.32, df = 11, $p < 0.001$

Reference categories: [b] nonuse of psychotropics, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

Table 3.8 Results from Binary Logistic Regression Models Analyzing the Relationship between Psychotropic Medication Use and At Least 80% Adherence to Combination Antiretroviral Therapy (N = 1321)[a]

Variable	Coefficient (β) for Psychotropic Medication Use	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
Psychotropic Use[b]	-0.08	0.15	0.27	0.61	0.93	0.69 – 1.24
Race/ethnicity[c]						
Black	-0.29	0.17	2.81	0.09	0.75	0.54 – 1.05
Hispanic	-0.09	0.22	0.18	0.68	0.91	0.59 – 1.41
Other	-0.37	0.27	1.90	0.17	0.69	0.41 – 1.17
Gender[d]	0.03	0.14	0.03	0.86	1.03	0.78 – 1.35
ARV regimen type[e]						
Boosted PI	-0.54	0.18	9.35	0.002	0.58	0.41 – 0.82
Unboosted PI	-0.29	0.18	2.54	0.11	0.75	0.52 – 1.07
Triple NRTI	-0.37	0.25	2.22	0.14	0.69	0.42 – 1.12
Other	-0.84	0.30	7.76	0.01	0.43	0.24 – 0.78
Total # of medications	-0.06	0.02	9.96	0.002	0.94	0.91 – 0.98

Abbreviations: CI = confidence interval, ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

[a] Adherence defined as proportion of days covered (PDC)
Model Chi-Square = 37.43, df = 11, $p < 0.001$
Reference categories: [b] nonuse of psychotropics, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

In an effort to determine whether particular subsets of the mentally ill population are at greater risk for antiretroviral nonadherence, factorial analysis of variance (ANOVA) was conducted to evaluate the interactions between psychotropic medication use, race/ethnicity, and gender with regard to effects on PDC. Table 3.9 displays the results for the factorial ANOVA with PDC as the dependent variable. The overall F-test for the model was significant (F = 1.66, df = 15, p = 0.05). Because the ANOVA showed a significant interaction between psychotropic medication use and race/ethnicity (F = 2.59, df = 3, p = 0.05), the main effects are not

interpreted. The interaction revealed that the relationship between psychotropic medication use and adherence to antiretroviral therapy measured by PDC varied by race/ethnicity. The mean PDC was similar for those who were and were not using psychotropics among whites (42.9% ± 34.5% vs. 42.7% ± 36.1%), blacks (35.5% ± 32.8% vs. 38.0% ± 34.7%), and Hispanics (42.3% ± 33.4% vs. 44.9% ± 36.7%). However, for patients with a race/ethnicity classified as "other," mean PDC was higher for patients using psychotropic medications (43.4% ± 34.8%) than for those who were not (28.4% ± 32.0%). While Levene's test for homogeneity of variance was not significant ($p = 0.057$), it does indicate a trend toward heterogeneity in the population variances. Since group sizes were markedly different, differences in the population variances can lead to unstable estimates of significance and increase the risk of a type-1 error. The testing of multiple hypotheses inherent in a three way factorial ANOVA design also increases the risk of a false positive result. Therefore, the results of this analysis must be interpreted with caution.

Table 3.9 Results from a Factorial Analysis of Variance Analyzing the Interactions between Psychotropic Medication Use, Race/Ethnicity, and Gender in their Effects on Adherence to Combination Antiretroviral Therapy (N = 1321)[a]

Source of Variation	df	Sums of Squares	Mean Square	F	p-value	Observed Power[b]
Use of Psychotropics	1	0.23	0.23	1.95	0.16	0.29
Race/Ethnicity	3	1.26	0.42	3.52	0.02	0.78
Gender	1	0.15	0.15	1.24	0.27	0.20
Use of Psychotropics* Race/Ethnicity	3	0.92	0.31	2.59	0.05	0.64
Use of Psychotropics* Gender	1	0.03	0.03	0.24	0.62	0.08
Use of Psychotropics* Race/Ethnicity*Gender	6	0.67	0.11	0.94	0.47	0.38
Error	1305	155.48	0.12	—	—	—
Abbreviations: df = degrees of freedom						

[a] Adherence defined as proportion of days covered (PDC)
[b] Computed using $\alpha = 0.05$
Model F-test = 1.66, df = 15, p = 0.05

Table 3.10 Mean Proportion of Days Covered by Population Subgroups Based on Use of Psychotropic Medications and Race/Ethnicity (N = 1321)[a]

Race/Ethnicity	Subjects Using Psychotropics (n = 501)	Subjects Not Using Psychotropics (n = 820)
Black	35.5 ± 32.8	38.0 ± 34.7
White	42.9 ± 34.5	42.7 ± 36.1
Hispanic	42.3 ± 33.4	44.9 ± 36.7
Other	43.4 ± 34.8	28.4 ± 32.0

[a] Proportion of days covered expressed as mean% ± standard deviation

Persistence

The relationship between psychotropic medication use and number of days persistent was evaluated using a multiple linear regression model, which controlled for race/ethnicity, gender, antiretroviral regimen type, and total number of medications. Results of this regression are presented in Table 3.11. The overall multiple regression model was significant (adjusted $R^2 = 0.03$, $F\ [10,1310] = 4.46$, $p < 0.001$), with the included variables accounting for 2.5% of the variance in number of days persistent. Psychotropic medication use was not found to be significantly related to number of days persistent ($b = 4.99$, $t[1310] = 0.61$, $p = 0.54$).

Table 3.11 Results from a Multiple Linear Regression Model Analyzing the Relationship between Psychotropic Medication Use and Persistence with Combination Antiretroviral Therapy (N = 1321)[a]

	Unstandardized Coefficients		Standardized Coefficients		
Persistence	**B**	**Standard Error**	**β**	**T**	**p-value**
Intercept	188.21	11.54	—	16.32	< 0.001
Use of Psychotropics[b]	4.99	8.13	0.02	0.61	0.54
Race/ethnicity[c]					
Black	-22.37	9.60	-0.08	-2.33	0.02
Hispanic	-0.30	12.84	-0.001	-0.02	0.98
Other	-29.77	14.15	-0.07	-2.10	0.04
Gender[d]	0.54	7.70	0.002	0.07	0.95
ARV regimen type[e]					
Boosted PI	-39.94	9.76	-0.13	-4.09	< 0.001
Unboosted PI	-19.83	10.49	-0.06	-1.89	0.06
Triple NRTI	-15.12	14.04	-0.03	-1.08	0.28
Other	-54.71	14.28	-0.12	-3.83	< 0.001
Total # of medications	-1.78	0.87	-0.06	-2.05	0.04

Abbreviations: ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

[a] Persistence defined as number of days on which all index antiretroviral medications were available
Model F (10, 1310) = 4.46, p < 0.001
Reference categories: [b] nonuse of psychotropics, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

Factorial ANOVA was used to test the interactions between psychotropic medication use, race/ethnicity, and gender with regard to effects on number of days persistent. The results of this analysis are displayed in Table 3.12. Because the overall F-test for the model was nonsignificant (F = 1.37, df = 15, p = 0.16), interaction effects were not interpreted. As discussed with the previous ANOVA model, heterogeneity of variance (Levene's test significant with p = 0.004) combined with unequal group sizes confers instability to estimates of main and interaction effects.

Table 3.12 Results from a Factorial Analysis of Variance Analyzing the Interactions between Psychotropic Medication Use, Race/Ethnicity, and Gender in their Effects on Persistence with Combination Antiretroviral Therapy (N = 1321)[a]

Source of Variation	df	Sums of Squares	Mean Square	F	p-value	Observed Power[b]
Use of Psychotropics	1	24579.54	24579.54	1.30	0.25	0.21
Race/Ethnicity	3	181325.48	60441.83	3.20	0.02	0.74
Gender	1	5409.42	5409.42	0.29	0.59	0.08
Use of Psychotropics* Race/Ethnicity	3	126397.63	42132.55	2.23	0.08	0.57
Use of Psychotropics* Gender	1	20.84	20.84	0.001	0.97	0.05
Use of Psychotropics* Race/Ethnicity*Gender	6	44453.18	7408.86	0.60	0.88	0.17
Error	1305	24616287.30	18863.06	—	—	—
Abbreviations: df = degrees of freedom						

[a] Persistence defined as number of days on which all index antiretroviral medications were available
[b] Computed using $\alpha = 0.05$
Model F-test = 1.37, df = 15, p = 0.16

Results of Hypothesis Testing

Objective Two: To examine the relationship between psychotropic medication use and antiretroviral adherence and persistence, taking into account race/ethnicity and gender.

H_{03}: There will be no significant difference in the rate of adherence to antiretroviral therapy between those with and those without psychotropic medication use after controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

Result: Hypothesis not rejected. The odds of being noncompliant with combination antiretroviral therapy were not related to use of psychotropic medications.

H_{04}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use and race/ethnicity.

Result: Hypothesis is rejected. While the mean PDC was similar for those who were and were not using psychotropics among whites (42.9% ± 34.5% vs. 42.7% ± 36.1%), blacks (35.5% ± 32.8% vs. 38.0% ± 34.7%), and Hispanics (42.3% ± 33.4% vs. 44.9% ± 36.7%), the mean PDC was higher for patients using psychotropic medications (43.4% ± 34.8%) than for those who were not (28.4% ± 32.0%) among patients with a race/ethnicity classified as "other."

H_{05}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use and gender.

Result: Hypothesis not rejected. No significant interaction was observed between psychotropic medication use and gender with regard to effects on antiretroviral adherence.

H_{06}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use, race/ethnicity, and gender.

Result: Hypothesis not rejected. No significant interaction was observed between psychotropic medication use, race/ethnicity, and gender with regard to effects on antiretroviral adherence.

H_{07}: There will be no significant difference in persistence with antiretroviral therapy between those with and those without psychotropic medication use after controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

Result: Hypothesis not rejected. No significant relationship was observed between antiretroviral persistence and psychotropic medication use.

H_{08}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use and race/ethnicity.

Result: Hypothesis not rejected. No significant interaction was observed between psychotropic medication use and race/ethnicity with regard to effects on persistence with antiretroviral therapy.

H_{09}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use and gender.

Result: Hypothesis not rejected. No significant interaction was observed between psychotropic medication use and gender with regard to effects on persistence with antiretroviral therapy.

H_{010}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use, race/ethnicity, and gender.

Result: Hypothesis not rejected. No significant interaction was observed between psychotropic medication use, race/ethnicity, and gender with regard to effects on persistence with antiretroviral therapy.

OBJECTIVE THREE: EXAMINATION OF THE RELATIONSHIP BETWEEN ANTIRETROVIRAL ADHERENCE AND ADHERENCE TO PSYCHOTROPIC MEDICATIONS

This objective was designed to examine whether a relationship exists between adherence to combination antiretroviral therapy and adherence to psychotropic medications. Adherence to each class of psychotropic medication (antidepressants, mood stabilizers, and antipsychotics) was determined by calculating the number of days on which at least one medication in that class was available for use by the patient (proportion of days covered, PDC). The mean PDC was 38.3% ± 34.2% for antidepressants (N = 443), 36.5% ± 33.5% for antipsychotics (N = 187), and 40.7% ± 33.9% for mood stabilizers (N = 56). The mean PDC across medication classes for patients using psychotropic medications was 36.7% ± 32.0% (N = 501), indicating a low level of adherence to psychotropics overall. Table 3.13 displays the number and percent of patients who were at least 80% adherent to psychotropic medications in this sample.

Table 3.13 Number and Percent of Patients Achieving at Least 80% Adherence to Psychotropic Medications[a]

Psychotropic Medications	Patients achieving ≥ 80% adherence, Number (%)
Antidepressants (N = 443)	86 (19.4%)
Antipsychotics (N = 187)	33 (17.6%)
Mood Stabilizers (N = 56)	12 (21.4%)
All Psychotropics (N = 501)	81 (16.2%)

[a] Percentages calculated as the number of patients achieving at least 80% adherence to the medication class divided by the total number of patients meeting study criteria for a mental disorder based on use of a drug from that class

Binary logistic regression was used to test the relationship between PDC for antiretroviral therapy and PDC for psychotropics while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications. This relationship was tested for adherence to psychotropics overall, as well as adherence to the individual drug classes. Results from the binary logistic regression models testing the relationship between psychotropic medication adherence and at least 90% adherence to antiretroviral therapy are presented in Tables 3.14-3.17. Patients who had a mean adherence of at least 80% to psychotropic medications overall were 3.37 times more likely to be at least 90% adherent to combination antiretroviral therapy ($p < 0.001$, 95% CI: 1.86 – 6.10).

When adherence to individual psychotropic medication classes was considered separately, the odds of having at least 90% adherence to antiretroviral therapy was significantly higher when patients were at least 80% adherent to antidepressants (OR = 4.23, $p < 0.001$, 95% CI: 2.31 – 7.75). In sensitivity analyses, the relationship between adherence to psychotropic medications and adherence to combination antiretroviral therapy and the relationship between adherence to

antidepressants and adherence to combination antiretroviral therapy remained significant for all levels of antiretroviral adherence tested (95%, 85%, and 80%).

Binary logistic regression models testing the relationship between adherence to antipsychotics and adherence to antiretroviral therapy were all found to be nonsignificant overall. However, the odds ratio for antipsychotic adherence was found to be significant in the model for 90% (OR = 3.33, p = 0.02, 95% CI: 1.21 – 9.19) adherence to antiretrovirals. This suggests that a significant relationship between antipsychotic and antiretroviral adherence may exist, but that the sample was not adequately powered to evaluate this relationship.

Due to the small number of patients using mood stabilizers who were also using a triple NRTI-based antiretroviral regimen, triple NRTI-based regimens were included in the category "other" for logistic regression analyses evaluating the relationship between adherence to mood stabilizers and adherence to antiretroviral therapy. For binary logistic regression models testing the relationship between adherence to mood stabilizers and adherence to antiretroviral therapy, only the model evaluating predictors for at least 85% adherence to antiretrovirals was found to be significant (χ^2 = 19.27; df = 9; p = 0.02), with adherence to mood stabilizers significantly associated with at least 85% adherence to antiretroviral therapy (OR = 18.60, p = 0.04, 95% CI: 1.10 – 315.41). As the other models evaluating this relationship were found to be nonsignificant, the significant relationship found with at least 85% adherence to antiretrovirals and adherence to mood stabilizers may have been a consequence of small cell sizes that can lead to unstable errors.

Table 3.14 Results from Binary Logistic Regression Models Analyzing the Relationship between At Least 80% Adherence to All Psychotropic Medications and At Least 90% Adherence to Combination Antiretroviral Therapy (N = 501)[a]

Variable	Coefficient (β) for Psychotropic Medication Use	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
≥ 80% adherence to psychotropics[b]	1.21	0.30	16.03	<0.001	3.37	1.86 – 6.10
Race/ethnicity[c]						
Black	-0.10	0.31	0.10	0.75	0.91	0.50 – 1.67
Hispanic	-0.13	0.44	0.08	0.77	0.88	0.37 – 2.09
Other	0.30	0.45	0.43	0.51	1.35	0.55 – 3.28
Gender[d]	0.35	0.27	1.63	0.20	1.41	0.83 – 2.41
ARV regimen type[e]						
Boosted PI	-0.19	0.35	0.30	0.58	0.83	0.42 – 1.64
Unboosted PI	-0.07	0.36	0.04	0.84	0.93	0.46 – 1.86
Triple NRTI	-0.06	0.46	0.02	0.90	0.94	0.39 – 2.30
Other	-0.82	0.58	2.06	0.15	0.44	0.14 – 1.35
Total # of medications	-0.05	0.03	3.19	0.07	0.95	0.90 – 1.01

Abbreviations: CI = confidence interval, ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

[a] Adherence defined as proportion of days covered (PDC)

Model Chi-Square = 22.96, df = 10, p = 0.01

Reference categories: [b] < 80% adherence to psychotropics, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

Table 3.15 Results from Binary Logistic Regression Models Analyzing the Relationship between At Least 80% Adherence to Antidepressants and At Least 90% Adherence to Combination Antiretroviral Therapy (N = 443)[a]

Variable	Coefficient (β) for Psychotropic Medication Use	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
≥ 80% adherence to antidepressants[b]	1.44	0.31	21.80	<0.001	4.23	2.31 – 7.75
Race/ethnicity[c]						
Black	0.001	0.33	0.00	1.00	1.00	0.53 – 1.90
Hispanic	-0.06	0.47	0.02	0.90	0.95	0.38 – 2.37
Other	0.25	0.48	0.26	0.61	1.28	0.50 – 3.29
Gender[d]	0.30	0.29	1.12	0.29	1.36	0.77 – 2.38
ARV regimen type[e]						
Boosted PI	-0.05	0.37	0.02	0.89	0.95	0.47 – 1.95
Unboosted PI	-0.002	0.38	0.00	1.00	1.00	0.48 – 2.08
Triple NRTI	-0.08	0.47	0.03	0.87	0.93	0.37 – 2.31
Other	-1.06	0.66	2.60	0.11	0.35	0.10 – 1.26
Total # of medications	-0.06	0.03	3.33	0.07	0.95	0.89 – 1.00

Abbreviations: CI = confidence interval, ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

[a] Adherence defined as proportion of days covered (PDC)

Model Chi-Square = 29.21, df = 10, p = 0.001

Reference categories: [b] < 80% adherence to antidepressants, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

Table 3.16 Results from Binary Logistic Regression Models Analyzing the Relationship between At Least 80% Adherence to Antipsychotics and At Least 90% Adherence to Combination Antiretroviral Therapy (N = 187)[a]

Variable	Coefficient (β) for Psychotropic Medication Use	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
≥ 80% adherence to antipsychotics[b]	1.20	0.52	5.40	0.02	3.33	1.21 – 9.19
Race/ethnicity[c]						
Black	-0.29	0.56	0.27	0.60	0.75	0.25 – 2.25
Hispanic	-0.25	0.81	0.10	0.76	0.78	0.16 – 3.78
Other	0.39	0.75	0.27	0.61	1.47	0.34 – 6.34
Gender[d]	0.26	0.48	0.31	0.58	1.30	0.51– 3.32
ARV regimen type[e]						
Boosted PI	-0.03	0.59	0.002	0.96	0.97	0.31 – 3.06
Unboosted PI	-0.31	0.74	0.18	0.67	0.73	0.17 – 3.10
Triple NRTI	0.14	0.76	0.03	0.86	1.15	0.26 – 5.11
Other	-0.14	0.76	0.04	0.85	0.87	0.20 – 3.82
Total # of medications	-0.06	0.05	1.90	0.17	0.94	0.86 – 1.03

Abbreviations: CI = confidence interval, ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

[a] Adherence defined as proportion of days covered (PDC)

Model Chi-Square = 7.91, df = 10, p = 0.64

Reference categories: [b] < 80% adherence to antipsychotics, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

Table 3.17 Results from Binary Logistic Regression Models Analyzing the Relationship between At Least 80% Adherence to Mood Stabilizers and At Least 90% Adherence to Combination Antiretroviral Therapy (N = 56)[a]

Variable	Coefficient (β) for Psychotropic Medication Use	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
≥ 80% adherence to mood stabilizers[b]	1.90	1.40	1.86	0.17	6.71	0.43 – 103.80
Race/ethnicity[c]						
Black	-3.10	1.58	3.86	0.05	0.05	0.002 – 1.00
Hispanic	0.61	1.96	0.10	0.76	1.84	0.04 – 84.78
Other	-0.26	1.75	0.02	0.88	0.77	0.03 – 23.76
Gender[d]	3.50	1.59	4.83	0.03	32.99	1.46 – 745.32
ARV regimen type[e]						
Boosted PI	0.67	1.57	0.18	0.67	1.95	0.09 – 42.50
Unboosted PI	-1.49	2.01	0.55	0.46	0.23	0.004 – 11.45
Other	1.22	1.65	0.55	0.46	3.37	0.13 – 84.80
Total # of medications	0.01	0.11	0.01	0.91	1.01	0.81 – 1.26
Abbreviations: CI = confidence interval, ARV = antiretroviral, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor						

[a] Adherence defined as proportion of days covered (PDC)
Model Chi-Square = 11.89, df = 9, p = 0.22
Reference categories: [b] < 80% adherence to mood stabilizers, [c] white, [d] male, [e] nonnucleoside reverse transcriptase inhibitor (NNRTI)

Results of Hypothesis Testing

Objective Three: To examine the relationship between antiretroviral adherence and adherence to psychotropic medications while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

H_{011}: Among patients using psychotropic medications, there will be no significant relationship between adherence to antiretroviral therapy and adherence to psychotropic medications while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

Result: Hypothesis is rejected. The odds of being at least 90% adherent to combination antiretroviral therapy were 3.37 times higher for those who were at least 80% adherent to all psychotropic medications.

H_{012}: Among patients taking antidepressants, there will be no significant relationship between adherence to antiretroviral therapy and adherence to antidepressants while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

Result: Hypothesis is rejected. The odds of being at least 90% adherent to combination antiretroviral therapy were 4.23 times higher for those who were at least 80% adherent to antidepressants.

H_{013}: Among patients taking antipsychotics, there will be no significant relationship between adherence to antiretroviral therapy and adherence to antipsychotics while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

Result: Hypothesis not rejected. The odds of being at least 90% adherent to combination antiretroviral therapy were not related to adherence with antipsychotics.

H_{014}: Among patients taking mood stabilizers, there will be no significant relationship between adherence to antiretroviral therapy and adherence to mood stabilizers while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.

Result: Hypothesis not rejected. The odds of being at least 90% adherent to combination antiretroviral therapy were not related to adherence with mood stabilizers.

SUMMARY OF FINDINGS

A summary of the results of hypothesis testing for Objectives One through Three is provided in Table 3.18.

Table 3.18 Summary of Results of Hypothesis Testing

Hypothesis	Statistic	p-value	Outcome
Objective 1			
H_{01}: There will be no significant difference in the prevalence of psychotropic medication use among HIV-infected patients based on race/ethnicity.	χ^2 (3) = 23.16	<0.001	Rejected
H_{02}: There will be no significant difference in the prevalence of psychotropic medication use among HIV-infected patients based on gender.	χ^2 (1) = 0.03	0.87	Not Rejected
Objective 2			
H_{03}: There will be no significant difference in the rate of adherence to antiretroviral therapy between those with and those without psychotropic medication use after controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.	OR = 0.90; 95% CI: 0.65 – 1.24	0.52	Not Rejected
H_{04}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use and race/ethnicity.	F (3) = 2.59	0.05	Rejected
H_{05}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use and gender.	F (1) = 0.24	0.62	Not Rejected
H_{06}: There will be no significant difference in the rate of adherence to antiretroviral therapy based on the interaction between psychotropic medication use, race/ethnicity, and gender.	F (6) = 0.94	0.47	Not Rejected
H_{07}: There will be no significant difference in persistence with antiretroviral therapy between those with and those without psychotropic medication use after controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.	b = 4.99, t(1310) = 0.61	0.54	Not Rejected
H_{08}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use and race/ethnicity.	F (3) = 2.23	0.08	Not Rejected
H_{09}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use and gender.	F (1) = 0.001	0.97	Not Rejected
H_{010}: There will be no significant difference in persistence with antiretroviral therapy based on the interaction between psychotropic medication use, race/ethnicity, and gender.	F (6) = 0.39	0.88	Not Rejected
Abbreviations: OR = odds ratio, CI = confidence interval			

Table 3.18 Summary of Results of Hypothesis Testing - Continued

Hypothesis	Statistic	p-value	Outcome
Objective 3			
H_{11}: Among patients using psychotropic medications, there will be no significant relationship between adherence to antiretroviral therapy and adherence to psychotropic medications while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.	OR = 3.37; 95 % CI: 1.86 – 6.10	<0.001	Rejected
H_{12}: Among patients taking antidepressants, there will be no significant relationship between adherence to antiretroviral therapy and adherence to antidepressants while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.	OR = 4.23; 95% CI: 2.31 – 7.75	<0.001	Rejected
H_{13}: Among patients taking antipsychotics, there will be no significant relationship between adherence to antiretroviral therapy and adherence to antipsychotics while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.	OR = 3.33; 95% CI: 1.21 – 9.19 Note: overall model was not significant, p = 0.64	0.02	Not Rejected
H_{14}: Among patients taking mood stabilizers, there will be no significant relationship between adherence to antiretroviral therapy and adherence to mood stabilizers while controlling for race/ethnicity, gender, antiretroviral regimen type, and total number of medications.	OR = 6.71; 95% CI: 0.43 – 103.80	0.17	Not Rejected
Abbreviations: OR = odds ratio, CI = confidence interval			

CHAPTER FOUR

Discussion

This chapter provides a detailed discussion of the results presented in Chapter Three. Results are evaluated in the context of previous studies with consideration for the clinical relevance of the findings. Limitations of the current study are examined, and suggestions provided for future research in this area.

STUDY POPULATION

As discussed in Chapter One, racial and ethnic minorities are disproportionately affected by HIV/AIDS, with markedly higher rates of HIV/AIDS among blacks and Hispanics as compared to whites.[1] The Texas Medicaid data used in this study provided a unique opportunity to evaluate the relationship between mental disorders and adherence to combination antiretroviral therapy in a racial and ethnically diverse population. Blacks were overrepresented in this sample, accounting for 53.1% of the included patients. This was expected based on epidemiologic data showing that blacks are disproportionately affected by HIV/AIDS, both in Texas and in the U.S. as a whole.[1,2] The proportion of Hispanic patients (13.9%) included in this sample is congruent with U.S. population estimates for the study time period.[3] As predicted based on epidemiologic data on HIV-infected patients from Texas,[2] the proportion of black females (57.4%) in this sample was higher than the proportion of white (38.3%) and Hispanic females (36.1%).

PREVALENCE OF MENTAL DISORDERS AMONG HIV-INFECTED PATIENTS

Results from the National Comorbidity Survey Replication (February 2001 – April 2003) indicate that the 12-month prevalence of serious mental disorders in the U.S. is around 6.5%.[4] In our sample, 501 of 1321 HIV-infected patients (37.9%) met the study criteria for having a mental disorder based on use of psychotropic medications, which is more than five times the expected rate of serious mental disorders in the general population. Another estimate of the 12-month prevalence of mental disorders among U.S. adults, produced by combining data from the Epidemiologic Catchment Area (early 1980s) and National Comorbidity Survey (early 1990s) studies, puts the one-year rate of mental disorders at 21%.[5] This estimate includes the prevalence of anxiety disorders in addition to serious mental disorders (e.g., major depressive disorder, bipolar disorder, schizophrenia), and may be a better comparator for the prevalence rates of mental disorders in the current study since the indication for use of antidepressants, which are commonly used to treat anxiety disorders, could not be distinguished based on the available data. Nonetheless, the 37.9% of HIV-infected patients meeting criteria for a mental disorder over a 12-month period in this study is appreciably higher than the 21% estimate for the general population. This is in keeping with data from previous studies that showed a higher prevalence of HIV infection among persons suffering from serious mental disorders.[6-8]

Pence and colleagues used a brief screening instrument to identify probable mood, anxiety, and substance abuse disorders in a cohort of 1,125 HIV-positive patients presenting to the University of North Carolina Hospitals Infectious Diseases Clinic between 2000 and 2002.[9] The 12-month prevalence of clinically relevant

depression in this population was estimated to be 29% based on patients' self-reported symptoms. This is similar to the rate of antidepressant usage in the current study, which was 33.5%. In a study utilizing New Jersey Medicaid data from 1991 to 1996, Sambamoorthi and colleagues found the rate of depression among patients with HIV/AIDS to be 18%.[10] This is notably lower than the rate of antidepressant use seen in the current study. The diagnosis of depression in the Sambamoorthi study was based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes rather than medication usage data, and only 58% of those patients diagnosed with depression were treated with antidepressants. This indicates an imperfect correlation between psychotropic medication use and diagnosis of a mental disorder. Taken together, these data show that the estimated prevalence of psychiatric disorders among HIV-infected patients may vary due in part to differing methods of identifying mental disorders. However, the rate of mental disorders reported among patients with HIV/AIDS is consistently higher than the rate of mental disorders in the general population, highlighting the need to understand the effects of mental disorders on treatment outcomes for HIV infection.

Patients meeting criteria for a mental disorder in this study were found to differ from those who did not on several of the evaluated baseline characteristics. Patients using psychotropic medications were shown to be significantly older than those not using psychotropics, though the 2.4 year difference in mean age is unlikely to be clinically significant. The mean age for all patients in this sample was higher than expected at 40.2 ± 9.3 years. This may reflect a tendency of low-income patients to seek care for HIV/AIDS later in the disease course following development of symptoms, or it may reflect a bias on the part of prescribers to reserve antiretroviral

treatment for more mature patients who are perceived as more likely to maintain adherence. In addition to the difference in age, the mean total number of medications used at baseline was found to be significantly higher for patients using psychotropics. Differences in the total number of medications at baseline were controlled for in regression analyses.

In this study, there was also a variation in the proportion of patients identified as having a mental disorder varied based on race/ethnicity, with blacks, Hispanics, and patients with a race classified as "other" having a lower proportion of psychotropic medication use (32.9%, 37.7%, and 39.0%, respectively) than whites (49.3%). Since both racial/ethnic minorities and persons with serious mental disorders are disproportionately affected by HIV/AIDS, the lower rate of mental disorders found among minorities in this study was unexpected. However, given that the study definition of a mental disorder was based on psychotropic medication use, the lower rate of mental disorders seen among racial/ethnic minorities in this study may represent a disparity in the treatment of mental disorders rather than a true difference in rate of diagnosis. Racial/ethnic minorities have poorer access to mental health services than whites and are more likely to seek treatment in the general healthcare setting than to see a mental health care specialist.[5] In data from the National Comorbidity Survey, only 11% of Hispanic patients and only 16% of black patients with a diagnosable mood disorder received care from a mental health specialist.[5] Using data from a later (1997-1998), privately-funded, nationally representative survey (HealthCare for Communities), Wells and colleagues found that black patients were more likely than whites to report an unmet need for alcoholism, drug abuse, or mental health treatment, and Hispanic patients were more likely than

whites to report delayed care in these areas.[11] Access to care may be less of an issue in this sample of patients with Medicaid funding, though other barriers to access, such availability of providers in rural areas and mistrust of the healthcare system, still persist.[5]

When they are able to access care, racial/ethnic minorities are less likely than whites to receive guideline-based treatment for mental disorders.[5] Young and colleagues analyzed data from the HealthCare for Communities survey and found that blacks were less likely than whites to receive appropriate treatment for depressive and anxiety disorders (OR = 0.39, 95% CI: 0.23 – 0.64).[12] Hispanics were also less likely to receive appropriate treatment in this study, though the difference was not statistically significant (OR = 0.58, 95% CI: 0.32 – 1.04). Utilizing data from the National Ambulatory Medical Care Survey, investigators have shown that black and Hispanic patients are less likely than whites to receive a prescription for psychotropic medications when visiting an outpatient provider for mental health services.[13.14] Studies evaluating samples of Medicaid recipients using data from the 1990s have also found variance in psychotropic medication based on race. Melfi and colleagues showed that among a large cohort of Medicaid recipients newly diagnosed with a depressive disorder, blacks were half as likely as whites to receive an antidepressant in the six months following diagnosis (OR = 0.50, 95% CI: 0.46 – 0.54).[15] Kuno and Rothbard found that among Medicaid recipients with schizophrenia, blacks were significantly more likely than whites to receive long-acting injectable antipsychotics, agents which were excluded from analyses in this study.[16] Based on these data, utilization of psychotropic agents is likely to underestimate the true rate of mental

disorders among racial/ethnic minorities, which may explain the lower rates of mental disorders seen among minorities in the current study.

Males and females were almost equally represented in this sample of HIV-positive patients, with no difference found in the proportion of males and females meeting study criteria for a mental disorder. The equal proportion of males and females in this study differs from that seen in the general United States population, where males with HIV/AIDS outnumber females 3:1.[1] However, this discrepancy does not appear to be explained by higher rates of mental disorders among females, a factor which would be expected to increase the risk of HIV infection. Female patients may be overrepresented in this sample since women are more likely than men to be Medicaid recipients. This difference may also be partially explained by the overrepresentation of black subjects in this sample, with black women disproportionately affected by HIV/AIDS in Texas.[2]

RELATIONSHIP BETWEEN MENTAL DISORDERS AND ANTIRETROVIRAL ADHERENCE AND PERSISTENCE

The majority of patients in this sample were using antiretroviral regimens containing either an NNRTI (31.5%) or a protease inhibitor boosted with ritonavir (28.6%). Data from recent studies have shown that adequate HIV viral suppression can be achieved with lower than 95% adherence to NNRTI-based and ritonavir-boosted PI-based combination antiretroviral regimens.[17-19] However, one of these studies demonstrated a dose-response relationship between antiretroviral adherence and sustained viral load suppression,[18] which indicates that achieving high rates of treatment adherence remains a valid goal for HIV-infected patients taking

combination antiretroviral therapy. Furthermore, the ability to maintain persistence with antiretroviral therapy is an important factor in treatment success, as life-long adherence is required once therapy has been initiated.[20]

Adherence

Adherence to combination antiretroviral therapy was found to be low overall in this study, with a mean proportion of days covered (PDC) of 39.1% ± 34.6%. Studies that evaluated adherence using the Medication Event Monitoring System (MEMS) or unannounced pill counts found mean rates of adherence to be closer to 70%, which is markedly higher than the rate found in this study.[17,19,21] Paterson and colleagues and Shuter and colleagues both evaluated adherence using MEMS to the protease inhibitor components of antiretroviral regimens over a six month time period and found adherence rates of 74% and 73%, respectively.[19,21] Using unannounced pill counts over a median of 9 months, Bangsberg and colleagues found adherence to be 70% for all antiretrovirals in an NNRTI-based regimen.[17] Nachega and colleagues looked at adherence in terms of prescription claims data but used a more liberal method than PDC to measure adherence.[18] Adherence was defined as the number of months with antiretroviral claims submitted divided by the number of months of study participation (median 2.2 years). The overall mean adherence to antiretroviral therapy in this study was not given, but it falls in the range of 80-89%, which is more than double the rate of adherence found in the current study. Since the above studies linking antiretroviral therapy adherence to HIV outcomes all used alternate definitions of adherence, it is difficult to determine how the adherence rate in the current study translates into clinical outcomes. Because no previous studies have

evaluated adherence to combination antiretroviral therapy based on PDC, it is also difficult to determine the degree to which the measurement itself contributed to the low adherence rate seen in this study.

Compared with other commonly used methods for calculating medication adherence based on prescription claims data (e.g., medication possession ratio or MPR), PDC gives a more conservative estimate of patient adherence, particularly when multiple medications within the same class are being considered.[22,23] By comparing several methods for calculating medication adherence using the same data, Choudhry and colleagues showed that interval-based approaches, such as PDC, consistently showed lower rates of adherence compared to prescription-based approaches, such as MPR, for patients taking multiple related medications (oral hypoglycemics).[22] Martin and colleagues also showed that in cases of therapeutic duplication within a drug class (antipsychotics), adherence measured by MPR was 85% higher than measurements based on PDC.[23] Previous studies using prescription claims data to evaluate the relationship between adherence to antidepressants and adherence to combination antiretroviral therapy used modified versions of the MPR that incorporated use of all antiretroviral medications during the study period to calculate adherence. Both of these studies found higher levels of adherence to antiretroviral therapy (72% and 81%) compared with the 39% adherence seen in the current study.[24,25] Since combination antiretroviral therapy requires therapeutic duplication by definition and MPR has a tendency to overestimate adherence in this situation, use of PDC for calculating adherence may provide a more accurate estimation of actual patient medication-taking behavior.

While PDC is more conservative than MPR in general since it avoids double-counting days of medication coverage, the definition of PDC was made even more conservative in this study by requiring patients to have possession of all antiretroviral mediations in the initial regimen on a given day to be considered adherent for that day. To achieve perfect adherence, patients were required to have access to each antiretroviral medication in the initial regimen for all 365 days of the 12-month follow-up. Use of an average PDC across individual antiretroviral medications was considered for this study, though requiring patients to have possession of all medications in the regimen on a single day was thought to be more clinically relevant. Ideally, HIV-infected patients should take all of their prescribed antiretroviral agents at the same time, attacking the virus simultaneously through multiple mechanisms of action and reducing the risk of developing resistance to the medications. It could be argued that one year is too long to expect a patient to remain adherent to an initial combination antiretroviral regimen, as some previous studies have reported shorter median times to switching among patients initiating antiretroviral therapy.[26] However, the likelihood of switching antiretroviral therapy is almost certainly dependent on the type of regimen initiated (factors including pill burden and side effect profiles), and data from a recent randomized trial of initial antiretroviral treatment strategies found that the median time for switching from a PI-based (ritonavir boosted or unboosted) regimen was 18 months compared with 24 months for NNRTI-based regimens.[27] Therefore, a 12-month period for evaluating adherence to an initial antiretroviral regimen in the current study appears to be reasonable. So, while the conservative nature of our adherence measure may have contributed to the relatively low rate of adherence rate found in this study, the measure was defined

based on parameters deemed to be relevant for patients using combination antiretroviral therapy and deserves further study for validation.

The high degree of variance associated with PDC in this study, as evidenced by large standard deviations, decreases the likelihood of finding a statistical difference in adherence between groups. Indeed, adherence to combination antiretroviral therapy was not found to be significantly related to the use of psychotropic medications indicating the presence of a mental disorder in logistic regression analyses controlling for potential confounding factors. This was true for all levels of adherence tested (95%, 90%, 85%, and 80%). This is in contrast to two previous studies that have shown a significant relationship between having symptoms of a mental disorder and poorer adherence to antiretroviral medications.[28,29] However, both of these studies used patient self-report to define adherence, which may be more subject to bias than prescription claims data. Also, it is important to consider that patients in this study met criteria for a mental disorder through psychotropic medication use, and patients treated for a mental disorder may behave differently in terms of medication adherence than those who are untreated.

Results of logistic regression models consistently showed no relationship between race/ethnicity or gender and adherence to combination antiretroviral therapy, though factorial ANOVA did reveal a significant interaction effect between race/ethnicity and use of psychotropic medications on PDC. Examination of the mean PDC for groups separated by race/ethnicity and psychotropic medication use showed that the only notable difference was a higher rate of antiretroviral adherence among patients using psychotropic medications for those patients with a race/ ethnicity defined as "other." Given the heterogeneity of the race/ethnicity category

"other" and the unexpected higher degree of adherence for patients meeting study criteria for a mental disorder, this finding does not appear to have any clinically meaningful interpretation. It is also possible that this significant interaction effect is a spurious result brought about by unequal group sizes and population variances increasing the risk for a false positive result.

Persistence

The mean persistence with combination antiretroviral therapy in this study was 140.3 ± 137.6 days. This is shorter than expected based on previous studies that evaluated the duration of therapy with an initial combination antiretroviral regimen using prospectively collected clinical trial data. Kirstein and colleagues found that the median time to switching or discontinuing an initial combination antiretroviral regimen among a large cohort of HIV-infected women was 8 months.[26] The short duration of persistence in the current study also differs significantly from results of the study by MacArthur and colleagues described earlier, in which the median times for switching from a PI-based or an NNRTI-based regimen were 18 and 24 months, respectively.[27] As seen with PDC, the variance in our measure of persistence was quite large. This is expected since the number of days on which patients had possession of all antiretroviral agents in the initial regimen was used to calculate both adherence and persistence. The conservative definition of persistence requiring patients to have access to all initial antiretroviral medications with no gaps in access greater than 60 days may have contributed to the shorter duration of persistence seen in this study. However, definitions of switching in previous studies accounted for most changes in therapy, so duration of therapy would not be expected to differ

appreciably in the current study. It is possible that patients enrolled in clinical trials may have more motivation to maintain persistence with a particular antiretroviral regimen than those identified through prescription claims.

In contrast to the findings by Walkup and colleagues discussed in Chapter One,[30] mental illness was not significantly associated with decreased persistence with combination antiretroviral therapy in this study. Walkup and colleagues defined persistence based on quarterly use of either PIs or NNRTIs, and expressed their results as percentages rather than duration, limiting comparison with results from the current study. In that study, patients with severe affective disorders were less likely than patients without serious mental disorders to maintain persistence with antiretroviral therapy, though the absolute difference in persistence was modest (75.2% versus 78.5%, respectively). Results of separate regression analyses in the Walkup and colleagues study hinted at a possible interaction between mental disorders and race in their effects on persistence with antiretroviral therapy, but no significant interactions were found using factorial ANOVA in the current study. With disparate findings in the limited studies addressing this issue, further research is needed to clarify the relationship between mental disorders and persistence with combination antiretroviral therapy.

RELATIONSHIP BETWEEN PSYCHOTROPIC MEDICATION ADHERENCE AND ADHERENCE TO COMBINATION ANTIRETROVIRAL THERAPY

Because symptoms of mental disorders may diminish with appropriate medication therapy, it is logical to hypothesize that increased adherence to psychotropic medications (presumably leading to better symptom control) would

attenuate the negative effect of mental disorders on adherence to combination antiretroviral therapy seen in previous studies. Both adherence to psychotropic medications overall and adherence to antidepressants in particular were found to be associated with adherence to antiretroviral medications in this study. These findings are in keeping with data from previous retrospective prescription claims-based studies which suggest a link between adherence to antiretroviral therapy and adherence to antidepressants among patients diagnosed with a depressive disorder.[24,25] While these associations suggest that improving adherence to psychotropics, particularly antidepressants, may lead to increased adherence with combination antiretroviral therapy, a causative relationship cannot be inferred from the current evidence. Patients who are adherent to antiretroviral medications may be inherently more likely to adhere to prescribed medications in general, or there could be some other unrecognized and unaccounted for variable that influences adherence to both antiretroviral and psychotropic medications.

This study attempted to expand on findings from previous studies by evaluating the effect of additional psychotropic medication classes on adherence to combination antiretroviral therapy. Unfortunately, group sizes for evaluating these effects were small, with only 187 patients identified as users of antipsychotics and only 56 patients identified as users of mood stabilizers. No consistent relationship was found between adherence to antipsychotics or mood stabilizers and adherence to antiretroviral therapy, though this could have been due to a lack of power to detect these effects. One explanation for the small sample sizes of patients meeting criteria for a mental disorder based on use of antipsychotics or mood stabilizers in this study may be that prescribers are reluctant to initiate combination antiretroviral therapy in

patients with schizophrenia or bipolar disorder due to the association of these disorders with medication nonadherence.

As with adherence to combination antiretroviral therapy, adherence to psychotropic medications in this study was found to be low overall, with a mean PDC across all classes of psychotropics of 36.7% ± 32.0%. This low rate of adherence was consistent across all drug classes. Previous studies evaluating the relationship between antidepressant adherence and adherence to combination antiretroviral therapy found much higher mean rates of antidepressant adherence (77-79%) using prescription-based calculations related to the MPR.[24,25] Another study using MPR to calculate adherence to mood stabilizers among veterans diagnosed with bipolar disorder found adherence rates ranging from 76% to 83%.[31] In a review of studies evaluating adherence to antipsychotics among patients diagnosed with schizophrenia using a variety of adherence measures, the mean rate of nonadherence to antipsychotics was around 40%.[32] This corresponds to an antipsychotic adherence rate that is 1.5 times higher than that seen in the current study. As discussed with adherence to antiretroviral medications, use of a conservative measure for calculating adherence over a one-year time period may have contributed to the lower rate of adherence to psychotropic medications seen in this study as compared to previous studies. Additionally, the calculated adherence for psychotropic medications may have been reduced because the index date for evaluating adherence was based upon initiation of combination antiretroviral therapy rather than initiation of psychotropics. For example, a patient who had 100% adherence to an antidepressant which was started six months after starting his index antiretroviral regimen would have a calculated PDC of 50% for the antidepressant over the one year follow-up period.

SIGNIFICANCE OF FINDINGS

Our study revealed a high rate of psychotropic medication use among a large cohort of patients using combination antiretroviral therapy. This supports findings from previous research that indicate a higher rate of mental disorders among HIV-infected patients compared to the general population. The high degree of comorbidity between mental disorders and HIV infection underscores the need for an integrated treatment approach for addressing these issues. While we did not find a significant relationship between having a having mental disorder and decreased adherence to and persistence with antiretroviral therapy in this study, we believe that methodological differences may explain why our findings contrast with those from previous studies showing these relationships to be significant. Additional research is needed to help inform clinicians about the potential consequences of comorbid mental disorders in HIV-infected patients.

Racial and ethnic differences were observed in the rate of mental disorders identified in this population, though not in the expected direction. It is plausible that the lower rate of mental disorders found among ethnic minorities in our study was a result of identifying the diagnosis of a mental disorder through medication use in a population of patients that has been shown to receive disparate treatment for mental disorders. Because of the important clinical implications that poor identification and treatment of mental disorders among racial/ethnic minorities may have for optimizing HIV treatment outcomes, the relationships between race/ethnicity, mental disorders, and adherence to antiretroviral therapy deserve further study using data with more reliable diagnostic identifiers.

The low rates of adherence to and persistence with combination antiretroviral therapy found in this study emphasize the continuing need for innovative practice ideas to enhance compliance with prescribed antiretroviral regimens for all patients. Though previous studies used alternate methods of assessing the link between antiretroviral medication adherence and HIV outcomes, the significantly lower rate of antiretroviral adherence seen in the current study raises concerns about the effectiveness of HIV treatment for Texas Medicaid recipients. Resources directed toward improving adherence to combination antiretroviral therapy in this population are likely to benefit the greater public health, since suboptimal levels of adherence have been associated with the development of drug-resistant HIV strains that can be passed on to others.[33] Unfortunately, this study did not identify a particular subgroup of patients with a greater need for intervention, so efforts to improve antiretroviral adherence would probably need to be wide in scope.

As expected, we found that patients who were adherent to their psychotropic medications (including all categories), particularly antidepressants, were more likely to be adherent to combination antiretroviral therapy. In subanalyses of psychotropic medication categories, we were unable to show a specific effect of adherence to antipsychotics or mood stabilizers on antiretroviral adherence, and additional study of these relationships using larger sample sizes is needed. Given the relationship between overall psychotropic medication adherence and antiretroviral adherence, providers who prescribe combination antiretroviral therapy should ask patients regularly about concomitant medications for treatment of mental disorders and assess adherence to both therapies. Education and interventions aimed at improving

adherence to antiretroviral therapy among patients with mental disorders should incorporate mechanisms to improve adherence to psychotropic medications, as well.

LIMITATIONS

A significant limitation of this study is the use of psychotropic medications as a surrogate marker for the diagnosis of a mental disorder. Indications for psychotropic medication could not be ascertained in this study, and many of these medications have indications for conditions other than the targeted mental disorders (e.g., anxiety disorders, neuropathic pain, insomnia, and seizure disorders). We attempted to minimize inclusion of patients using psychotropic medications for alternative conditions by (1) requiring minimum therapeutic doses for medications commonly used in lower doses for insomnia and (2) requiring that anticonvulsants commonly used as mood stabilizers be used in combination with other psychotropic medications and in the absence of other anticonvulsant agents to be considered as mood stabilizers in this study.

In the study by Yun and colleagues evaluating the relationship between adherence to antidepressant therapy and adherence to antiretroviral medications, less than half (46%) of the patients who were diagnosed with depression were also prescribed antidepressant therapy.[24] In a related study by Horberg and colleagues, only 36% of the patients identified as having a diagnosis of depression were prescribed an SSRI.[25] This suggests that using antidepressant prescription claims as a marker for a diagnosis of depression is likely to preclude identification of a significant number of HIV-infected patients who have been diagnosed with depression but who are not currently being treated. Walkup and colleagues showed

that for HIV-infected patients diagnosed with depression, having a prescription for an antidepressant agent in the previous month predicted continued use of antiretroviral therapy in the current month.[34] This finding suggests that adherence behavior may be different for patients who are prescribed psychotropic medications compared with the general population of HIV-infected individuals with mental disorders. Therefore, to determine the true effect of mental disorders on adherence to combination antiretroviral therapy, a more reliable method of identifying the diagnosis of a mental disorder than drug utilization is needed.

Another limitation of our study is the inability to control for several potentially important confounding variables. No information regarding concomitant substance use was available for patients included in this study, and previous work has shown that drug and alcohol abuse are associated with decreased antiretroviral adherence and viral suppression.[35,36] Because drug and alcohol abuse are often comorbid with serious mental disorders, controlling for these factors is necessary to determine if having a mental disorder is an independent risk factor for nonadherence to antiretroviral therapy. Yun and colleagues still found a significant association between antiretroviral adherence and adherence to antidepressant therapy even with controlling for drug and alcohol use.[24] As is often true with prescription claims data, no information about hospitalizations or about drugs patients received while hospitalized were available for included patients. Frequent or extended hospitalizations could have been factors in the relatively low medication adherence rates found in this study.

Although this study utilized a large database of prescription drug claims to identify a sizable cohort of patients using combination antiretroviral therapy, the

sample size was small for several of the subgroup analyses. This led to decreased power to detect relationships between adherence to antipsychotic or mood stabilizing medications and adherence to antiretrovirals. Factorial ANOVA is generally robust to violations of assumptions with large sample sizes. However, due to markedly unequal group sizes and differences in population variances, there is a concern for errors in estimating the significance of interaction effects with factorial ANOVA in this study. Additionally, all patients using antiretroviral medications for treatment of HIV/AIDS may not have been identified since the sample was limited to those with prescriptions for at least three antiretroviral medications within the three month index period. Patients who filled only part of their prescribed antiretroviral regimen or who obtained one or more medications from some other source would have been excluded, so results would not be generalizable to these patients.

Finally, while the association between adherence to combination antiretroviral therapy and antidepressant medications seen in this study has potentially important clinical implications, we were unable to assess for actual improvements in HIV laboratory measures or clinical outcomes for psychotic and mood disorders. Horberg and colleagues found that having a diagnosis of depression was associated with decreased odds of achieving HIV viral suppression, but that depressed patients who were adherent to SSRIs had a similar likelihood of achieving HIV viral suppression as patients without depression.[25] This suggests that adherence to psychotropic medications among HIV-infected patients receiving combination antiretroviral therapy may lead to improved HIV laboratory measures. Currently, no studies evaluating the relationship between adherence to psychotropics and adherence to

antiretrovirals have attempted to link adherence to psychotropic medications with measures of psychiatric symptom improvement.

AREAS FOR FURTHER RESEARCH

Future studies using prescription claims data to evaluate the relationship between mental disorders and adherence to combination antiretroviral therapy should incorporate diagnostic data to avoid misclassifying patients who are not currently treated for their mental disorder. Since many psychotropic medications have multiple indications, diagnostic data should help clarify when these medications are being used to treat a mental disorder versus some other indication. Diagnostic data should also include information about alcohol and illicit drug abuse to assess whether the effects of mental disorders on antiretroviral adherence are independent of the effects of commonly comorbid substance use disorders. Prior work evaluating the relationship between psychotropic medication adherence and adherence to antiretroviral therapy has focused on use of antidepressants, and our study had relatively small sample sizes for addressing this relationship among patients using antipsychotics and mood stabilizers. Therefore, additional research evaluating adherence among HIV-infected patients with schizophrenia treated with antipsychotic medications and patients with bipolar disorder treated with mood stabilizers is needed.

Ours is the first study to use proportion of days covered to evaluate adherence to combination antiretroviral therapy. Since we did not have access to laboratory data for patients included in this study, additional studies are needed to determine how the degree of antiretroviral adherence as measured by PDC relates to HIV outcomes. Ideally, outcomes measures for mental disorders would also be included in future

studies evaluating the relationship between adherence to psychotropic medications and adherence to antiretroviral therapy, though this type of information is not typically available retrospectively. While retrospective evaluations of prescription claims data can provide important information about medication adherence patterns and factors related to adherence, the nature of these studies does not allow for determination of cause and effect. Prospective studies that evaluate medication adherence in combination with rating scales for mental disorders and HIV laboratory tests will be needed to confirm the hypothesis that increased adherence to psychotropic medications leads to improvements in symptomatology of mental disorders, which in turn leads to improved adherence with antiretroviral medications and subsequent reductions in viral load and improvements in CD4 lymphocyte count.

CONCLUSIONS

This study supports findings from previous work showing that the burden of mental illness is high among HIV-infected patients. The finding that white patients were more likely than minority patients to meet study criteria for a mental disorder based on psychotropic medication use may indicate a disparity in appropriate treatment of mental disorders for racial/ethnic minorities with HIV/AIDS. This potential disparity warrants further study, particularly since the rate of mental disorders among HIV-infected patients is higher than in the general population and racial/ethnic minorities are disproportionately burdened by HIV/AIDS.

This is the first study to use proportion of days covered to measure simultaneous adherence with every drug in the antiretroviral regimen. This method may be particularly useful for evaluating antiretroviral adherence using prescription

claims data, as it avoids double-counting days of medication coverage when multiple drugs in the same class are used concomitantly. That said, additional research will be needed to test how this measure of adherence relates to HIV outcomes such as viral load. While being treated for a mental disorder was not found to be significantly associated with adherence to or persistence with combination antiretroviral therapy in this study, limitations in defining mental disorders by psychotropic medication use may have affected the results. Use of diagnostic data to identify patients with mental disorders in future studies may give more accurate information about the relationship between having a mental disorder and adherence to combination antiretroviral therapy. Adherence to psychotropic medications overall and to antidepressants specifically was associated with adherence to antiretroviral therapy in this study. This may indicate a relationship between effective treatment for mental disorders and antiretroviral adherence among HIV-infected patients, though this relationship requires further investigation.

Adherence to combination antiretroviral therapy is important to achieve optimal HIV outcomes and to avoid promoting viral resistance. Patients with mental disorders have been consistently shown to be disproportionately affected by HIV/AIDS, and often have difficulty maintaining adherence not only to psychotropic medications, but to medications for chronic disease states, as well. Given the high burden of illness and the potential for improved adherence to psychotropic medications to lead to improved adherence to antiretroviral therapy, integrated treatment for HIV/AIDS and mental disorders should be considered as the standard of care.

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