RESEARCH

Association Between Prescription Cost Sharing and Adherence to Initial Combination Antiretroviral Therapy in Commercially Insured Antiretroviral-Naïve Patients with HIV

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ABSTRACT

BACKGROUND: In treatment of human immunodeficiency virus (HIV), high levels of adherence to combination antiretroviral therapy (cART) are required to prevent failure of virologic suppression, development of drug resistance, and permanent loss of therapeutic options. No published research has assessed the association between cART prescription cost sharing and adherence to cART.

OBJECTIVE: To analyze the association between cART prescription cost sharing and adherence to initial cART in commercially insured antiretroviral (ARV)-naïve patients with HIV.

METHODS: This retrospective observational cohort study used 2002-2008 data from a large U.S. claims database of more than 56 million commercially insured individuals. Study subjects were patients aged 18 years or older who initiated cART during the period January 1, 2003, to December 31, 2007, had no ARV claims during the 6-month period prior to the initiation date, and had at least 1 ICD-9-CM diagnosis code for HIV infection (042, 795.71, V08) from 12 months before to 12 months after cART initiation. A minimum 12-month period of continuous enrollment after cART initiation was used to construct a patient-quarter repeated measures panel dataset in which each quarter of data that a patient contributed represented an observation. The evaluation period extended from cART initiation until the occurrence of 1 of the following events: addition of an ARV that was not part of the initial cART regimen, 30-day gap in possession of an ARV within the initiated cART regimen, hospitalization of 30 or more days, loss to follow-up due to study end (December 31, 2008), or disenrollment. The study's outcome was quarterly adherence to cART, defined as the number of days within the quarter that a patient possessed all components of the initial cART regimen. Each patient's cART cost-sharing amount was calculated per 30-day supply of the entire cART regimen. Adherence was dichotomized for analysis at the clinically meaningful thresholds of 95% and 78%. The dichotomized adherence outcomes were separately modeled using population-averaged generalized estimating equations (GEEs) with time-varying and time-constant covariates and an exchangeable working correlation structure. Independent variables included cost-sharing amount; sequential quarter number after cART initiation; interaction between cost-sharing amount and sequential quarter number (to capture any changes in the association of cost sharing with adherence that may occur over time after initiation of cART); and patient demographic, clinical, and insurance characteristics. For each sequential quarter after cART initiation, the GEE models were used to generate average predicted probabilities of adherence reaching each threshold (95% and 78%) at cost-sharing levels of $25, $75, and $144, which represented the 25th, 75th, and 90th percentiles of the cost-sharing distribution, respectively.

RESULTS: The study sample included 19,199 patient-quarters and 3,731 patients: mean age 41.1 years; 83.2% male; mean (SD) duration of post-index period 5.1 (4.2) quarters; mean (SD) daily cART pill count 3.2 (2.2); mean (median) cost sharing per 30-day supply of the entire cART regimen $67 ($40). In the unadjusted analyses of patient-quarters, mean adherence ranged from 97.2% for cost-sharing levels within the 0-20th percentiles (from $0 to $20 per 30-day cART supply) to 94.0% for cost-sharing levels exceeding the 80th percentile (from $84 to $3,832 per 30-day cART supply). In the adjusted analyses for the second quarter (25th percentile of follow-up duration, n = 3,117 cases still under observation) at the cost-sharing levels of $25, $75, and $144, the predicted probabilities of at least 95% adherence were 0.782, 0.770, and 0.752, respectively, and the predicted probabilities of at least 78% adherence were 0.936, 0.931, and 0.924, respectively. The differences in the predicted probabilities of adherence grew over time. By the seventh quarter (the 75th percentile of follow-up duration, n = 1,096 cases still under observation), the predicted probabilities were 0.773, 0.746, and 0.707 for 95% adherence and 0.933, 0.922, and 0.904 for 78% adherence at cost-sharing levels of $25, $75, and $144, respectively.

CONCLUSION: Increasing cART prescription cost sharing was associated with modestly decreased probability of maintaining clinically meaningful levels of cART adherence.

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What is already known about this subject

- In treatment of human immunodeficiency virus (HIV), high levels of adherence to combination antiretroviral therapy (cART) are required to prevent failure of virologic suppression, development of drug resistance, and permanent loss of therapeutic options. In a study by Maggiolo et al. (2005), the risk of virologic failure was 2.4% in patients with cART adherence of more than 95%, compared with 4.3%, 12.2%, and 17.4% for patients with adherence rates of 86%-95%, 76%-85%, and 75% or less, respectively. World Health Organization guidelines state that adherence of at least 95% is desirable over long periods of time, and studies of newer treatment regimens suggest clinically meaningful adherence thresholds of 85% and 75% for patients treated with protease-inhibitor (PI)-based and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, respectively.
- Little is known about the association between cART prescription cost sharing and adherence to cART. Using a questionnaire and conjoint analysis in a sample of 299 highly treatment-experienced patients with HIV/acquired immune deficiency syndrome (AIDS), Stone et al. (2004) found that pill count, dosing frequency, and adverse effects had the greatest impact on perceived ability to adhere to cART; the number of copayments ranked as the seventh most important cART regimen attribute.

What is already known about this subject *(continued)*

- Das-Douglas et al. (2009) examined the relationship between Medicare Part D implementation and antiretroviral (ARV) treatment interruptions in a sample of HIV-infected homeless and marginally housed individuals with drug coverage. Of 44 individuals with Medicare coverage, 41 had dual Medicare/Medi-Cal eligibility, and 10 reported ARV interruptions; the authors reported that 8 of those 10 cited the cost of Part D copayments as the primary cause of the ARV interruptions.

What this study adds

- This study is the first to analyze the relationship between cART prescription cost sharing and adherence to initial cART in commercially insured ARV-naïve HIV patients.
- In the unadjusted analyses of 19,119 patient-quarters (n=3,731 patients), mean adherence (proportion of days covered by the entire cART regimen) ranged from 97.2% for cost-sharing levels in the bottom quintile ($0-$20 per 30-day supply) to 94.0% for cost-sharing levels in the top quintile ($84-$3,832 per 30-day supply).
- In generalized estimating equation analyses adjusted for patient characteristics, at the cost-sharing levels of $25, $75, and $144, the predicted probabilities of at least 95% adherence in the second quarter (the 25th percentile of follow-up) were 0.782, 0.770, and 0.752, respectively; the differences grew over time and by the seventh quarter (the 75th percentile of follow-up) were 0.773, 0.746, and 0.707.
- At the cost-sharing levels of $25, $75, and $144, the predicted probabilities of at least 78% adherence in the second quarter were 0.936, 0.931, and 0.924, respectively; the differences in the predicted probabilities grew over time and by the seventh quarter were 0.933, 0.922, and 0.904.

Human immunodeficiency virus (HIV) is a retrovirus that attacks the immune system by destroying CD4 positive T cells, which are vital to fighting infections. In 2006, more than 1 million people in the United States were living with HIV, and the number of new HIV infections was estimated at 56,300, translating to an incidence rate of 22.8 per 100,000.[1,2] While there is currently no cure for HIV, antiretroviral (ARV) therapy can be used to suppress the virus. The primary goal of ARV therapy is prolonged maximal suppression of plasma viremia, which can reduce HIV-related morbidity and mortality and improve quality of life in HIV-infected adults and adolescents.[3] Since 1996, combination antiretroviral therapy (cART), formerly referred to as highly active antiretroviral therapy (HAART), has been the standard of care for HIV.[4] In treatment-naïve patients with HIV who are initiating cART, the preferred regimen is typically defined as the following: at least 2 nucleoside reverse transcriptase inhibitors (NRTIs) with 1 ritonavir-boosted protease inhibitor (PI), 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), or 1 integrase strand transfer inhibitor (INSTI).[3]

Adherence is an important element in successful ARV therapy.[3] An early study by Paterson et al. (2000) focusing on unboosted protease inhibitors (PIs) suggested that 95% adherence was required for full viral suppression.[5] However, treatment guidelines from the Department of Health and Human Services (DHHS, 2011), describing more recent research, have suggested that newer regimens "may be more forgiving of lapses in adherence because of their longer half-lives."[3] For example, in a study by Maggiolo et al. (2005), there were marked decrements of the risk of virologic failure among PI-treated patients with more than 85% adherence and among NNRTI-treated patients with adherence falling within a "gray zone" between "very poor" (75% or less) adherence and "optimal" (100%) adherence.[6] Among all patients, the risk of virologic failure increased with poor adherence and was 2.4% in patients with adherence of more than 95%, 4.3% in patients with adherence of 86%-95%, 12.2% in patients with adherence of 76%-85%, and 17.4% in patients with adherence of 75% or less.[6]

The importance of optimizing adherence is discussed in the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, which state that "clinicians should encourage patients to adhere as closely as possible to the prescribed doses for all antiretroviral (ARV) regimens."[3] The World Health Organization (WHO) HIV/acquired immune deficiency syndrome (AIDS) programme guidelines for antiretroviral therapy for HIV-infected adults and adolescents, citing older research based on unboosted PI regimens, note that it is desirable to maintain adherence levels at or above 95% over long periods of time.[7] Interventions to improve adherence are also key recommendations within the DHHS and WHO guidelines.

Suboptimal adherence can result from multiple factors including psychosocial issues, active substance abuse, adverse drug effects, and complex medication regimens.[3,8] In many conditions, the consequences of suboptimal medication adherence are primarily manifested in reduced treatment response; however, in HIV infection, suboptimal cART adherence can lead not only to poor treatment response but also to a permanent loss of therapeutic options resulting from the development of resistance mutations.[3,9,10] Subsequent therapies tend to be more complex and costly. Thus, given the myriad detrimental and sometimes irreversible clinical consequences of poor cART adherence, requirements for cART adherence may be higher than for other therapeutic areas, and factors that yield even seemingly small effects on adherence to cART may still be considered clinically significant.

While no gold standard exists for the measurement of adherence, the use of administrative pharmacy refill records

for measurement of adherence to cART has several advantages over other methods, including no social desirability bias, no recall bias, no participant burden, and no potential for tampering. Additionally, administrative pharmacy refill record-based adherence measures have been shown to correlate well with clinical outcomes in HIV/AIDS.[11-13]

Prescription cost sharing refers to out-of-pocket medication expenses (copayments, coinsurance, and deductibles) that are paid by a participant within an insurance plan. A recent report by the Institute of Medicine's Committee on HIV Screening and Access to Care (2011) noted that little is known about the influence of cost sharing on cART adherence in HIV-infected patients in the United States.[14] To date, there have been no published studies investigating the association between cART prescription cost sharing and adherence to cART. By examining this association among treatment-naïve commercially insured HIV patients initiating cART, this study is the first to begin to fill this information gap for an important segment of the HIV-infected population. If higher patient cost-sharing amounts are associated with lower levels of adherence, this could lead to unintended adverse clinical and economic consequences. Information about such associations could aid managed care stakeholders in their decision-making efforts regarding the design of benefit policies that promote medication adherence to maximize the clinical benefits of cART.

Thus, the primary objective of this study was to analyze the association between cART prescription cost sharing and adherence to initial cART in commercially insured antiretroviral-naïve HIV patients. Specifically, we tested the hypothesis that commercially insured HIV patients initiating cART with higher cART prescription cost-sharing levels would be less likely to maintain clinically meaningful levels of adherence.

Methods

Study Design

This was a retrospective observational cohort study using a patient-quarter repeated measures panel data design in which each quarter of data that a patient contributed represented an observation used for the statistical analyses.

Data Sources

Data for the study subjects were extracted from the 2003-2008 Thomson Reuters MarketScan Commercial Database. The database includes inpatient and outpatient medical and outpatient pharmacy claims for tens of millions of employees and their dependents aged 64 years or younger with employer-sponsored health insurance provided through various fee-for-service and capitated payment arrangements annually (n = 56,849,520 during the period from 2002-2008). All database records are de-identified and have been certified to satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the Health Insurance Portability and Accountability Act (HIPAA) privacy rule regarding the determination and documentation of statistically de-identified data. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, institutional review board approval was not sought to conduct this study.

Subject Selection

Study subjects were patients aged 18 years or older who initiated cART during the period from January 1, 2003, through December 31, 2007, had no ARV claims in the 6 months prior to the cART initiation date, and had at least 1 inpatient or outpatient medical claim with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code for HIV infection, including 042 (HIV disease), 795.71 (nonspecific serologic evidence of HIV), or V08 (asymptomatic HIV infection status), in any diagnosis code field at some point within the period extending from up to 12 months before to 12 months after cART initiation. Patients were required to have at least 6 months of continuous enrollment before and at least 12 months of continuous enrollment after cART initiation. As such, some patients may have had fewer than 12 months of continuous enrollment before cART initiation to meet the HIV diagnosis criterion. Lists of ARVs used to identify initial cART and to exclude patients who had claims for ARVs not recommended for initial therapy in the 6 months prior to cART initiation are contained in Appendix 1. Initial cART was defined as 1 NNRTI and 2 to 3 NRTIs or 1 boosted PI (ritonavir counted only as a boosting agent) and 2 to 3 NRTIs; this algorithm reflects the most steadfast recommendations for initial cART across the various guidelines that were released during the study period.[15,16] Initial cART with 2 to 3 NRTIs and 1 INSTI was not included because the only available INSTI (raltegravir) did not receive U.S. Food and Drug Administration (FDA) approval for initial treatment until July 2009 (i.e., after our study period).

While treatment guidelines throughout the study period have had in common the general recommendation that initial cART comprise the aforementioned combinations of drug classes, the specific agents used in regimens that are considered "preferred" or "acceptable" have changed over time based on the availability of new clinical evidence. In the "real world" setting of routine clinical practice, physicians may not always initiate their patients on what is considered to be the state-of-the-art "preferred" combination of agents as recommended per the latest guidelines. In order to allow for such circumstances and provide greater generalizability of study results, while initial cART was defined based on the recommended combination of classes, patients were not required to initiate the specific combination of agents that were considered to be "preferred" at the time of initiation. Additionally, in order to allow for scenarios in which patients may have obtained prescriptions for 1 or more components of their initial cART regimen on 1 day but

were then required to wait for another component because the pharmacy had to order it, all of the components of the cART regimen were not required to have been initiated on the same day but rather within 2 weeks of one another.

Study Period

The 6-month period prior to cART initiation (designated as the baseline period) was established to attempt to include patients who were ARV-naïve and to measure patient baseline characteristics. The minimum 12-month period of continuous enrollment after cART initiation was used to establish a variable-length evaluation period during which cost sharing and adherence were measured. The variable-length evaluation period extended from cART initiation until the occurrence of 1 of the following events: (a) the addition of an ARV that was not part of the initial cART regimen, (b) a 30-day gap in possession of an ARV within the initial cART regimen, (c) a hospitalization of 30 days or more, (d) loss to follow-up due to study end (December 31, 2008), or (e) disenrollment from the health plan. Termination of the evaluation period could have occurred at any time after cART initiation for any of the aforementioned reasons except disenrollment, which could have occurred only after the 12-month minimum post-initiation enrollment period.

The analysis of adherence was terminated at the end of the evaluation period. In this respect, this study focuses on adherence specifically to *initial* cART regimens because adherence was measured only throughout the period during which the patient was considered to be persistent with the initial regimen. It is important to note that patients were not required to stay on their initial cART regimen for any minimum duration of time.

Known changes that occurred in the manufacturing and availability of ARV drugs and the associated regimen changes were accounted for to prevent these clinically insignificant circumstances from causing patients to be classified as experiencing a change to their initial regimens. In addition, because changing to a fixed-dose combination or regimen was likely to be motivated by a desire for convenience and simplification of the regimen, changes in ARV agents that were solely associated with switching to a fixed-dose combination or regimen did not cause a patient to be classified as experiencing a change to the initial regimen. For example, if a patient initiated on efavirenz and combination emtricitabine/tenofovir but then switched to the fixed dose regimen efavirenz/emtricitabine/tenofovir disoproxil fumarate (DF), the patient was not classified as experiencing a change to the initial regimen because of the switch.

While changes to fixed-dose combinations were accounted for, one limitation of administrative claims data is that they do not provide information regarding the reasons for switching. Switching may indicate various circumstances, such as adverse effects, regimen simplification, or even resistance mutations and virologic failure. Therefore, as noted previously, the analysis of adherence was terminated at the point when a switch occurred that was not simply a change to a fixed-dose combination. Accordingly, patients' adherence values would not have been penalized for such switches. Similarly, if the event that caused the end of a patient's evaluation period was a gap of at least 30 days in possession of an ARV, the end of the evaluation period was set to the last day on which he or she did have possession of this ARV. Accordingly, patients' adherence values would not have been penalized for such discontinuations, which may have been ordered by their physicians.

The evaluation period formed the basis of a patient-quarter repeated measures panel data set in which each quarter of data that a patient contributed represented an observation. The quarterly panel dataset permitted the repeated measurement of cost-sharing amounts over time, which may change as a result of benefit design changes.

Study Measures

The study outcome was quarterly adherence to cART as measured through administrative pharmacy refill records. Since cART involves multiple medications, an appropriate measure of concurrent adherence to multiple related medications was required.[17] Adherence to cART was therefore measured as the percentage of days within the quarter that a patient possessed all components of the initial cART regimen, which is also sometimes referred to as the proportion of days covered.[18] That is, any days on which the patient did not possess all components of the cART regimen as indicated by fill dates and days supply were counted as nonadherent days. Appendix 2 provides specific examples of how adherence was measured under various scenarios.

The primary independent variable was the cART cost-sharing amount (sum of copayment and coinsurance) per 30-day supply of the entire cART regimen, measured on a quarterly basis as follows: For N ARVs in a cART regimen during calendar quarter t: cART cost sharing per 30-day supply = Σ from $i = 1$ to N ([Σ patient's total incurred out-of-pocket cost for ARVi during the calendar quarter ÷ Σ patient's days supply for ARVi during the calendar quarter] × 30 days). Thus, if a patient's cART regimen comprised 3 separate prescriptions, the cART cost-sharing amount per 30-day supply would represent the sum of cost sharing for all 3 prescriptions (Appendix 2). Table 1 displays descriptive cost-sharing data for the 5 most commonly used cART regimens, which represented 67.8% of all studied patients. All other regimens (n = 136 regimens used by the remaining 32.2% of patients) were each used by less than 3% of patients.

Other covariates included patient's demographic, clinical, and insurance characteristics that have been shown or were hypothesized to have an effect on adherence or confound the relationship between cost sharing and adherence.[19-23] These

TABLE 1 cART Cost Sharing Per 30-Day Supply for Top 5 Most Frequently Used cART Regimens

	Patients (n)	Patient-Quarters (n)	Mean ($)	SD ($)	p25 ($)	p50 ($)	p75 ($)	p90 ($)	Min ($)	Max ($)
All patients	3,731	19,199	66.7	98.7	24.9	40.2	74.7	144.0	0.0	3,831.6
Emtricitabine + tenofovir + efavirenz	1,359	8,042	49.2	70.5	19.8	30.0	50.1	100.0	0.0	1,299.3
Lamivudine + zidovudine + efavirenz	494	2,620	61.9	67.5	30.0	40.2	70.2	150.0	0.0	1,053.6
Emtricitabine + tenofovir + atazanavir + ritonavir	266	1,307	92.2	128.6	45.0	70.2	99.0	150.0	0.0	1,762.2
Emtricitabine + tenofovir + lopinavir + ritonavir	209	975	80.8	94.1	33.6	49.8	90.0	151.8	0.0	645.0
Lamivudine + zidovudine + lopinavir + ritonavir	202	788	69.9	75.6	30.0	49.8	74.4	150.0	0.0	623.7

cART = combination antiretroviral therapy; max = maximum; min = minimum; p25 = 25th percentile; p50 = 50th percentile; p75 = 75th percentile; p90 = 90th percentile; SD = standard deviation.

covariates, the time period(s) during which they were measured, and the methods of measurement are detailed in Table 2.

Information regarding the NNRTIs, PIs, and NRTIs that the cART regimens comprised was also captured for descriptive purposes. All health care cost/expenditure-related variables were standardized to 2008 constant dollars, adjusted using the Medical Care component of the Consumer Price Index.[24]

Statistical Analyses

As noted in the introduction, although newer regimens can sometimes achieve viral load suppression with imperfect adherence, the DHHS guidelines recommend that patients adhere as closely as possible to the prescribed doses for all ARV regimens. Accordingly, 3 thresholds of adherence, measured as percentage of days within the quarter that a patient possessed all components of his or her initial cART regimen, were chosen for analysis. The first clinically meaningful threshold was 78%, which was informed by the findings of Maggiolo et al. that clinically meaningful adherence thresholds differ for NNRTI and PI-based regimens (i.e., 75% and 85%, respectively).[6] Specifically, 78% is a weighted average of 75% adherence for the 67% of the present study sample that was treated with NNRTIs and 85% for the 33% of the present study sample that was treated with PIs. The second clinically meaningful threshold was 95%, which has been suggested by the WHO as a desirable goal to achieve over long periods of ARV treatment.[7] A third, intermediate, level of 85% adherence was also included as a form of sensitivity analysis. For each of the 3 adherence thresholds, adherence was dichotomized (1 = adherence reaching the threshold and 0 = otherwise).

The statistical analyses comprised multivariate regression techniques, known as generalized estimation equations (GEE), that are well suited for the analysis of longitudinal data.[25] Since the study outcomes were dichotomous (e.g., achieved at least 78% adherence or not), the models used a binomial family distribution with a logit link function. A population-averaged approach was chosen to assess the *average effect* of cost sharing across all patients within the study sample. Since patients could contribute multiple observations to the quarterly panel dataset, potential within-patient correlation was handled through an exchangeable working correlation structure and robust standard errors, which are meant to reduce the potential for type 1 error.

In all models, the dependent variables were the dichotomized adherence variables. Since patients with HIV can exhibit positive changes in health-seeking and health-promoting behaviors early in the course of HIV diagnosis and treatment,[26] we hypothesized that for patients who are starting initial cART therapy, the association between cost sharing and adherence may be minimal during early periods in treatment. Accordingly, the independent variable of primary interest was an interaction term between cost-sharing amount and sequential quarter number after cART initiation. This variable captures the association between cost sharing and adherence over time after initiation of initial cART. Other variables included in the models were the main effects terms (cost-sharing amount and sequential quarter number) and the patient demographic, clinical, and insurance characteristics outlined in Table 2.

A method referred to as LOESS (locally weighted scatterplot smoothing) was used to examine functional form (e.g., linear, quadratic) of the relationship between the cost-sharing and adherence variables.[27] This technique was used to identify the most appropriate functional form of the independent variable for the model so as to reduce specification error. As a result of this exercise, a linear spline of cost sharing at $500 (which is essentially a second cost-sharing variable for values above $500) was added to the model, a point at which the rate of adherence evidently changed according to the LOESS curve.

The GEE models were used to generate average predicted probabilities of adherence at each of the 3 adherence thresholds (≥ 95%, ≥ 85%, and ≥ 78%) at fixed cost-sharing levels of $25, $75, and $144, which represented the 25th, 75th, and 90th percentiles of the cost-sharing distribution, respectively. These predicted probabilities were calculated at each sequential quarter after index.

All models were conducted using Stata/MP 10 (StataCorp, College Station TX) using an *a priori* alpha threshold of 0.05.

TABLE 2 Covariates, Measurement Time Periods, and Measurement Methods

Covariate	Measurement Time Period	Method and Notes
Demographics		
Age in years	Time of cART initiation	
Sex	Time of cART initiation	
U.S. Census Bureau geographic region of residence	Time of cART initiation	Northeast, North Central, West, South
Urbanicity	Time of cART initiation	Urban = residence in an MSA, rural = otherwise
Median household income in patient's 3-digit ZIP code	Time of cART initiation	U.S. Census Bureau data
Year of cART initiation	Time of cART initiation	2003-2007
Clinical characteristics		
Daily average cART pill burden	During quarter under evaluation	Mean number of pills per day on adherent days
Total non-cART out-of-pocket health care expenditures	Baseline[a] and 180 days pre-quarter[b]	Copayments, coinsurance, and deductibles for all medical and non-cART pharmacy claims
Count of unique NDC numbers for non-cART drugs	Baseline[a] and 180 days pre-quarter[b]	
Count of unique 3-digit ICD-9-CM diagnosis codes	Baseline[a] and 180 days pre-quarter[b]	
Binary indicator for hospitalization	Baseline[a] and 180 days pre-quarter[b]	MarketScan indicator[c]
Binary indicator for outpatient visit	Baseline[a] and 180 days pre-quarter[b]	
Binary indicator for hepatitis B diagnosis	Baseline[a] and 180 days pre-quarter[b]	1 inpatient or 1 nondiagnostic outpatient claim with an ICD-9-CM diagnosis code of 070.2x (viral hepatitis B with hepatic coma) or 070.3x (viral hepatitis B without mention of hepatic coma)[d]
Binary indicator for hepatitis C diagnosis	Baseline[a] and 180 days pre-quarter[b]	1 inpatient or 1 nondiagnostic outpatient claim with an ICD-9-CM diagnosis code of 070.7x (unspecified viral hepatitis C), 070.41 (acute hepatitis C with hepatic coma), 070.44 (chronic hepatitis C with hepatic coma), 070.51 (acute hepatitis C without mention of hepatic coma), or 070.54 (chronic hepatitis C without mention of hepatic coma)[d]
Binary indicator for depression diagnosis	Baseline[a] and 180 days pre-quarter[b]	1 inpatient or 1 nondiagnostic outpatient claim with an ICD-9-CM diagnosis code of 296.2x (major depressive disorder, single episode), 296.3x (major depressive disorder, recurrent episode), 300.4x (dysthymic disorder), or 311.xx (depressive disorder, not elsewhere classified)[d]
Binary indicator for alcohol or drug use disorder diagnosis	Baseline[a] and 180 days pre-quarter[b]	1 inpatient or 1 nondiagnostic outpatient claim with an ICD-9-CM diagnosis code of 291.xx (alcohol-induced mental disorders), 292.xx (drug-induced mental disorders), 303.xx (alcohol dependence syndrome), 304.xx (drug dependence), or 305.xx (nondependent abuse of drugs)[d]
Binary indicator for other psychiatric diagnosis	Baseline[a] and 180 days pre-quarter[b]	1 inpatient or 1 nondiagnostic outpatient claim with an ICD-9-CM diagnosis code of 290.xx-319.xx (mental disorders), excluding those used in depression and alcohol and drug use disorders[d]
Insurance characteristics		
Binary indicator for any mail-order ARV prescriptions	Evaluation period[e]	
Health plan type	Baseline[a] and 180 days pre-quarter[b]	Comprehensive, HMO, POS, PPO, other, or unknown/missing
Binary indicator for capitated payment	Baseline[a] and 180 days pre-quarter[b]	MarketScan indicator of capitated payment arrangement on at least 1 claim

[a]Baseline period was the 6 months prior to cART initiation.

[b]Measured for each quarter under evaluation; refers to the 180-day period immediately prior to the start of the quarter.

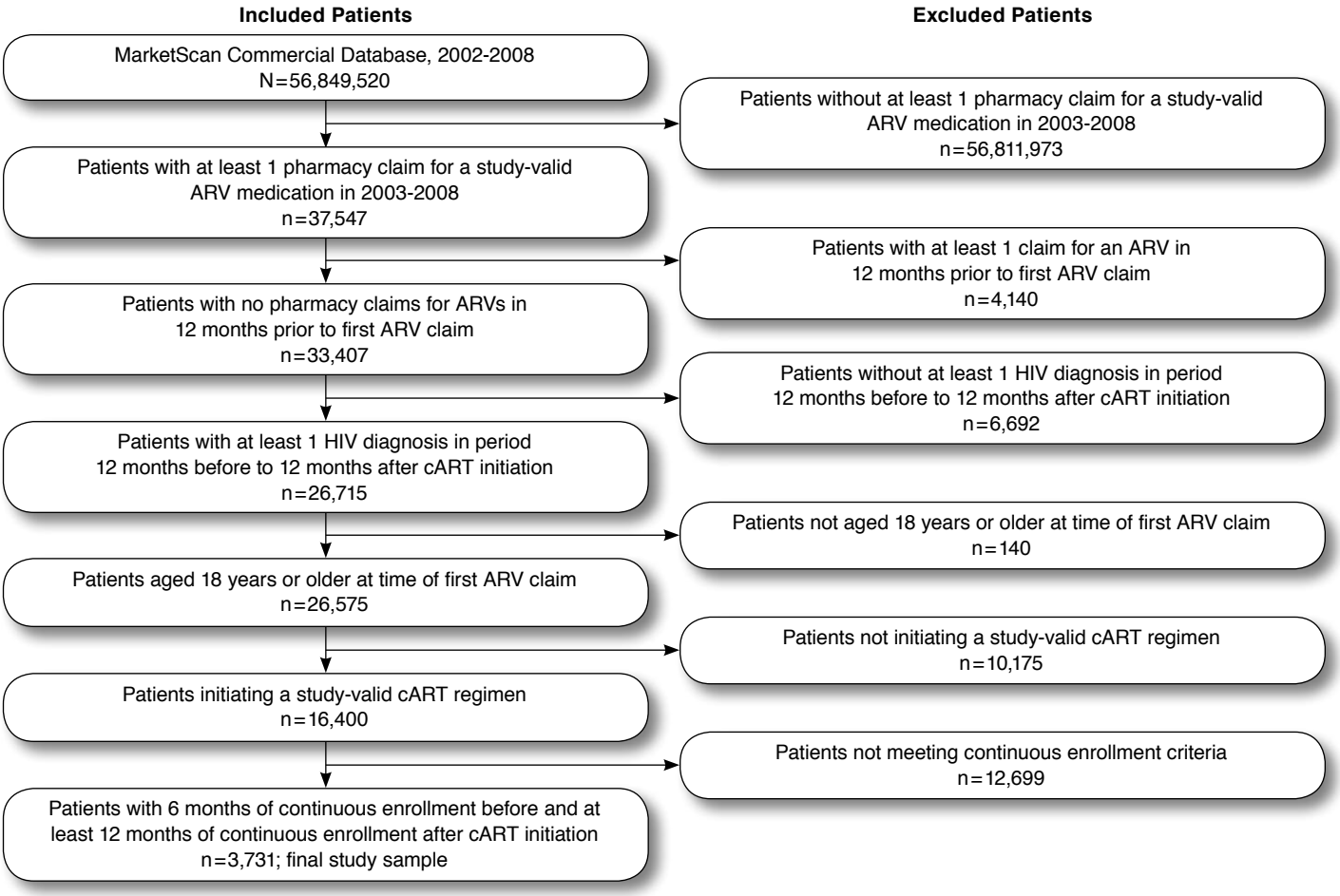
[c]Hospitalizations of any duration were identified by the presence of an indicator within the MarketScan database that indicates whether the claim was incurred because of an admission to an inpatient facility.

[d]"Nondiagnostic" refers to claims not associated with services that may be used to diagnose or rule out the presence of a condition, such as venipuncture or laboratory testing. All diagnoses were measured in any position on the claim (i.e., primary, secondary, and all others).

[e]The evaluation period extended from cART initiation until the occurrence of 1 of the following events: addition of an ARV that was not part of the initial cART regimen; 30-day gap in possession of an ARV within the initiated cART regimen; hospitalization of 30 or more days; loss to follow-up due to study end (December 31, 2008); disenrollment.

ARV = antiretroviral; cART = combination antiretroviral therapy; HMO = health maintenance organization; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; MSA = metropolitan statistical area; NDC = national drug code; POS = point of service; PPO = preferred provider organization.

FIGURE 1 Patient Selection Flow Chart



ARV = antiretroviral; cART = combination antiretroviral therapy; HIV = human immunodeficiency virus.

Sensitivity Analyses

The longitudinal nature of the study design incorporated a variable-length of follow-up in which patients contributed all available patient-quarters for analysis. A potential concern with this approach was the presence of attrition bias resulting from mortality or from systematic differences between those who switched or terminated the initial cART regimen (ending the evaluation period) versus those who continue using the same regimen throughout the study. The reasons for ending the evaluation period were (a) the addition of an ARV that was not part of the initial cART regimen (n = 642 patients); (b) a 30-day gap in possession of an ARV within the initial cART regimen (n = 1,890 patients); (c) a hospitalization of 30 days or more (n = 8 patients); (d) loss to follow-up due to study end on December 31, 2008 (n = 870 patients); or (e) disenrollment from the health plan (n = 321 patients). Thus, death may have been a possible outcome for patients whose study periods ended for hospitalization or disenrollment (reasons c or e). In order to address the potential for such bias, the models were fitted using interaction terms between the study end reasons and the primary independent variable. Statistical significance of these interaction terms would indicate possible bias. Within some of the models, these interaction terms were jointly significant. Accordingly, all models were fit in two ways: (a) using all patients in one analysis and (b) using only patients for whom death was not probable in another analysis.

Since patients who obtain cART medications via mail order introduce the potential to erroneously classify periods covered by fill date plus days supply as adherent days, 2 sensitivity analyses were conducted. In the first sensitivity analysis, patients who filled mail order ARV prescriptions at any point during the evaluation period were excluded from the analysis. In the second sensitivity analysis, instead of the entire patient being excluded from the analysis, only the last quarter of

TABLE 3 Study Sample Demographics and Clinical Characteristics

Demographics Measured at Patient Level as of cART Initiation	**N = 3,731 Patients**	
Age in years		
Mean [SD]	41.1	[8.9]
Median (range)	41	(18-63)
Female, % (n)	16.8	(628)
Geographic region, % (n)		
Northeast	9.8	(365)
North Central	13.1	(490)
South	54.5	(2,035)
West	22.0	(822)
Unknown	0.5	(19)
Urban residence (vs. rural), % (n)	92.7	(3,460)
Median household income in 3-digit ZIP code[a]		
Mean, $ [SD]	43,717	[15,924]
Median, $ (range)	40,925	(8,495-154,817)
Year of cART initiation, % (n)		
2003	13.1	(487)
2004	17.9	(668)
2005	17.3	(644)
2006	24.3	(906)
2007	27.5	(1,026)
Clinical Characteristics, All Quarters[b]	**N = 19,199 Patient-Quarters**	
cART pill burden		
Mean [SD]	3.2	[2.2]
Median (range)	3	(1-63)
Total non-cART out-of-pocket health care expenditures		
Mean, $ [SD]	658	[1,498]
Median, $ (range)	15	(0-68, 634)
Count of unique non-cART NDC numbers		
Mean [SD]	6.6	[6.0]
Median (range)	5	(0-59)
Count of unique 3-digit ICD-9-CM diagnosis codes		
Mean [SD]	6.9	[5.7]
Median (range)	5	(0-60)
Hospitalization, % (n)	11.9	(2,285)
Outpatient visit, % (n)	96.1	(18,446)
Hepatitis B diagnosis, % (n)	1.2	(234)
Hepatitis C diagnosis, % (n)	2.4	(464)
Depression diagnosis, % (n)	6.6	(1,265)
Alcohol or drug use disorder diagnosis, % (n)	2.8	(537)
Other psychiatric diagnosis, % (n)	7.7	(1,483)
Insurance Characteristics During Baseline Period[c]	**N = 3,731 Patients**	
Health plan type		
Comprehensive	5.1	(189)
Health maintenance organization	25.8	(961)
Point of service	12.9	(480)
Preferred provider organization	50.5	(1,884)
Other type	4.4	(163)
Unknown/missing	1.4	(54)
At least 1 claim indicating capitated payments, % (n)	19.1	(714)
Any mail-order ARV prescriptions in evaluation period, % (n)	24.4	(910)

[a]*Based on U.S. Census data.*
[b]*For each patient-quarter, these characteristics were measured during the 180-day period immediately prior to the start of the quarter.*
[c]*Baseline period was the 6 months prior to cART initiation.*
ARV=antiretroviral; cART=combination antiretroviral therapy; ICD-9-CM=International Classification of Diseases, 9th Revision, Clinical Modification; NDC=national drug code; SD=standard deviation.

observation was excluded for patients who filled mail order ARV prescriptions at any point during the evaluation period. This approach was taken after examination of the study follow-up periods. Patients who filled mail order ARV prescriptions at any point during the evaluation period were followed for a median of 6 quarters, whereas those who did not use mail order were followed for a median of 3 quarters. It may be reasonable to assume that if a patient is consistently filling mail order ARV prescriptions over a long period of time, but then discontinues or switches the ARV, perhaps only the final pharmacy claim is the one for which the most uncertainty about adherence is evident. A similar approach to handling these uncertainties has been used in a prior study of medication persistence.[28]

An additional sensitivity analysis focused on patients for whom cART regimens comprised 2 (as opposed to 3) NRTIs as the "backbone" of the regimen. If regimens with 3 NRTIs have higher cost sharing and are more likely to lead to nonadherence because of reasons such as complexity (other than pill burden, which was accounted for in the multivariate models) or adverse events, it is possible that a spurious relationship between the cost-sharing and adherence variables may be observed within the models combining all patients.

In a final sensitivity analysis, all of the aforementioned models were fit using random-effects, as opposed to population-averaged, GEE models. The purpose of this analysis was to examine how robust the study results were to different assumptions regarding population parameters.

Results

Figure 1 presents a sample selection flow chart depicting how the study sample was identified. A total of 37,547 patients with at least 1 pharmacy claim for an ARV after January 1, 2003, were initially identified within the commercial claims database. The final study sample comprised 3,731 patients with at least 6 months of continuous enrollment before and at least 12 months of continuous enrollment after cART initiation.

Table 3 displays the demographics and clinical characteristics of the study sample. Included patients had a mean (standard deviation [SD]) age of 41.1 (8.9) years, and 83.2% were male. A total of 910 (24.4%) patients had at least 1 mail order ARV pharmacy claim in the evaluation period. The mean (SD) duration of the evaluation period was 5.1 (4.2) quarters (minimum = 1, 25th percentile = 2, median = 4, 75th percentile = 7, 90th percentile = 11, maximum = 24), with a total of 19,199 patient-quarter records. NNRTI-based regimens were initiated by 2,482 (66.5%) patients (2,385 [96.1%] initiated with 2 NRTIs, and 97 [3.9%] initiated with 3 NRTIs). PI-based regimens were initiated by 1,249 (33.5%) patients (1,097 [87.8%] initiated with 2 NRTIs, and 152 [12.2%] initiated with 3 NRTIs). (Data on regimen types are not shown in the table.) The mean (SD) average daily cART pill burden was 3.2 (2.2).

Mean (median, interquartile range) cost sharing per 30 days

TABLE 4 Measures of cART Adherence by Cost-Sharing Level

			Adherence Distribution (%)[a]							Number and Percentage of Patient-Quarters by Adherence Level					
cART Cost-Sharing Percentile	cART Cost-Sharing Range ($)		N PQ	Mean	SD	p25	p50	Min	Max	n with ≥78% Adherence	% with ≥78% Adherence	n with ≥85% Adherence	% with ≥85% Adherence	n with ≥95% Adherence	% with ≥95% Adherence
All patients, N = 19,199 patient-quarters															
≤p20	0.0	20.1	4,131	97.2	6.8	98.7	100	26.9	100	3,996	96.7	3,865	93.6	3,468	84.0
>p20-≤p40	20.4	34.2	3,564	96.1	8.6	96.7	100	0.0	100	3,350	94.0	3,223	90.4	2,827	79.3
>p40-≤p60	34.5	50.1	4,080	95.3	9.4	95.3	100	0.0	100	3,803	93.2	3,607	88.4	3,067	75.2
>p60-≤p80	50.4	84.0	3,599	95.1	9.2	94.6	100	7.0	100	3,330	92.5	3,178	88.3	2,663	74.0
>p80	84.3	3,831.6	3,825	94.0	10.9	93.2	100	0.0	100	3,438	89.9	3,234	84.5	2,685	70.2
Emtricitabine + tenofovir + efavirenz, n = 8,042 patient-quarters															
≤p20	0.0	16.8	1,804	97.9	5.6	100	100	41.0	100	1,770	98.1	1,719	95.3	1,568	86.9
>p20-≤p40	17.1	24.9	1,756	95.8	8.5	95.7	100	26.9	100	1,642	93.5	1,574	89.6	1,358	77.3
>p40-≤p60	25.2	36.0	1,273	96.3	7.8	96.7	100	41.8	100	1,209	95.0	1,163	91.4	1,012	79.5
>p60-≤p80	36.3	60.0	1,609	96.3	7.4	96.7	100	48.9	100	1,545	96.0	1,469	91.3	1,263	78.5
>p80	60.3	1,299.3	1,600	95.1	9.5	94.6	100	11.4	100	1,474	92.1	1,403	87.7	1,192	74.5
Lamivudine + zidovudine + efavirenz, n = 2,620 patient-quarters															
≤p20	0.0	24.0	571	97.5	6.8	98.9	100	47.1	100	553	96.8	534	93.5	491	86.0
>p20-≤p40	24.3	40.2	773	94.7	10.3	93.4	100	31.0	100	708	91.6	668	86.4	559	72.3
>p40-≤p60	40.5	49.8	368	95.5	8.8	95.3	100	50.0	100	345	93.8	326	88.6	277	75.3
>p60-≤p80	50.4	79.8	424	94.2	10.6	93.4	98.9	7.0	100	389	91.7	369	87.0	295	69.6
>p80	80.4	1,053.6	484	95.0	10.1	95.6	100	25.0	100	447	92.4	424	87.6	367	75.8
Emtricitabine + tenofovir + atazanavir + ritonavir, n = 1,307 patient-quarters															
≤p20	0.0	39.6	285	97.2	7.4	100	100	46.7	100	270	94.7	262	91.9	244	85.6
>p20-≤p40	40.2	60.3	313	95.5	8.9	94.6	100	48.9	100	292	93.3	281	89.8	234	74.8
>p40-≤p60	61.2	74.7	239	93.0	11.3	89.7	98.9	47.8	100	209	87.4	196	82.0	156	65.3
>p60-≤p80	75.0	105.3	219	93.7	11.3	92.4	100	39.1	100	202	92.2	186	84.9	151	68.9
>p80	105.6	1,762.2	251	93.2	10.6	91.2	98.9	56.7	100	219	87.3	204	81.3	165	65.7
Emtricitabine + tenofovir + lopinavir + ritonavir, n = 975 patient-quarters															
≤p20	0.0	30.0	222	95.3	11.4	96.7	100	30.0	100	204	91.9	197	88.7	182	82.0
>p20-≤p40	30.6	45.0	169	96.7	7.9	98.8	100	56.5	100	160	94.7	157	92.9	139	82.2
>p40-≤p60	45.6	60.0	214	93.3	12.1	91.7	100	26.4	100	191	89.3	178	83.2	147	68.7
>p60-≤p80	60.3	100.2	202	95.6	9.2	96.7	100	50.0	100	185	91.6	177	87.6	159	78.7
>p80	108.0	645.0	168	92.8	11.1	90.1	98.9	52.8	100	144	85.7	136	81.0	109	64.9
Lamivudine + zidovudine + lopinavir + ritonavir, n = 788 patient-quarters															
≤p20	0.0	30.0	207	96.1	9.2	97.8	100	40.7	100	195	94.2	187	90.3	168	81.2
>p20-≤p40	31.8	40.2	109	92.6	11.8	90.2	98.9	52.2	100	91	83.5	90	82.6	70	64.2
>p40-≤p60	41.7	49.8	174	93.1	12.5	91.8	98.9	0.0	100	159	91.4	147	84.5	113	64.9
>p60-≤p80	52.5	88.2	141	95.6	7.5	94.5	100	60.4	100	135	95.7	130	92.2	102	72.3
>p80	88.5	623.7	157	92.5	11.8	89.0	98.9	50.0	100	136	86.6	122	77.7	104	66.2

[a]*Adherence is defined as proportion (percentage) of days in quarter during which patient possessed all components of initial cART regimen.*

cART = combination antiretroviral therapy; max = maximum; min = minimum; PQ = patient-quarters; p = percentile (e.g., p20 = 20th percentile); SD = standard deviation.

supplied of the entire cART regimen was $67 ($40, $25-$75). Overall, adherence levels were high with a mean (SD) adherence level across all patient-quarters of 95.6% (9.1%). Adherence levels of at least 78% were achieved in 17,917 (93.3%) of patient-quarters, at least 80% in 17,727 (92.3%) of patient-quarters, at least 85% in 17,107 (89.1%) of patient-quarters, at least 90% in 16,327 (85.0%) of patient-quarters, and at least 95% in 14,710 (76.6%) of patient-quarters.

Table 4 describes the unadjusted association between adherence and cART cost sharing for all patients and for each of the top 5 most frequently used cART regimens. When observed across all regimens, adherence decreased monotonically with each successively higher quintile of the cost-sharing distribution. Mean adherence ranged from 97.2% in patient-quarters with cost-sharing levels within the 0-20th percentiles of the cost-sharing distribution (from $0 to $20 per 30-day cART supply) to 94.0% in patient-quarters with cost-sharing levels exceeding the 80th percentile of the cost-sharing distribution

TABLE 5 *Multivariate Logit Models Using Population-Averaged Generalized Estimation Equations to Predict Adherence*[a]

Variable	At Least 95% Adherence (N = 19,199 Patient-Quarters)				At Least 85% Adherence (N = 19,199 Patient-Quarters)				At Least 78% Adherence (N=19,199 Patient-Quarters)			
	OR	*P* Value	95% CI		OR	*P* Value	95% CI		OR	*P* Value	95% CI	
cART-related variables[b]												
Sequential quarter number × cART cost sharing	**0.9997**	**<0.001**	**0.9996**	**0.9998**	**0.9997**	**<0.001**	**0.9995**	**0.9999**	**0.9996**	**0.001**	**0.9994**	**0.9999**
Sequential quarter number	0.9965	0.657	0.9812	1.0120	0.9868	0.181	0.9677	1.0062	0.9993	0.956	0.9747	1.0245
cART cost sharing	0.9992	0.017	0.9985	0.9998	0.9993	0.132	0.9984	1.0002	0.9991	0.103	0.9980	1.0002
cART cost sharing—$500 (linear spline)	1.0013	0.030	1.0001	1.0025	1.0016	0.138	0.9995	1.0038	1.0019	0.152	0.9993	1.0045
Daily average cART pill burden	0.9711	0.025	0.9465	0.9964	0.9542	0.002	0.9260	0.9833	0.9388	0.001	0.9051	0.9738
Clinical characteristics[c]												
Total non-cART out-of-pocket health care expenditures	1.0000	0.578	1.0000	1.0000	1.0000	0.852	1.0000	1.0000	1.0000	0.193	0.9999	1.0000
Count of unique non-cART NDC numbers	0.9971	0.552	0.9875	1.0067	1.0068	0.339	0.9929	1.0210	1.0055	0.501	0.9896	1.0216
Count of unique 3-digit ICD-9-CM diagnosis codes	0.9974	0.642	0.9867	1.0083	0.9903	0.170	0.9767	1.0042	1.0561	0.639	0.8406	1.3268
All-cause hospitalization	1.0781	0.306	0.9334	1.2453	1.0853	0.394	0.8991	1.3099	1.2240	0.148	0.9310	1.6092
All-cause outpatient visit	0.9729	0.777	0.8042	1.1769	1.1172	0.360	0.8814	1.4160	0.9911	0.298	0.9746	1.0079
Hepatitis B diagnosis	0.9513	0.815	0.6258	1.4460	1.1060	0.718	0.6406	1.9096	1.2420	0.539	0.6218	2.4808
Hepatitis C diagnosis	0.8832	0.400	0.6614	1.1794	0.9757	0.886	0.6973	1.3654	1.1989	0.434	0.7614	1.8880
Depression diagnosis	0.8916	0.217	0.7432	1.0696	0.8665	0.244	0.6810	1.1025	0.8841	0.412	0.6589	1.1863
Alcohol or drug use disorder diagnosis	0.7665	0.024	0.6084	0.9656	0.8390	0.239	0.6265	1.1237	0.9212	0.690	0.6156	1.3784
Other psychiatric diagnosis	1.0792	0.384	0.9091	1.2811	1.0480	0.690	0.8321	1.3200	1.1002	0.506	0.8303	1.4578
Demographic and insurance characteristics at baseline[d]												
Age in years	1.0044	0.173	0.9981	1.0107	1.0058	0.137	0.9981	1.0136	1.0094	0.042	1.0004	1.0186
Female	0.9570	0.573	0.8214	1.1150	0.9387	0.531	0.7701	1.1441	0.8184	0.086	0.6512	1.0286
Geographic region[e]												
Northeast	1.1940	0.084	0.9765	1.4599	1.1632	0.233	0.9073	1.4914	1.1302	0.411	0.8443	1.5129
North Central	1.0637	0.486	0.8939	1.2658	1.2242	0.067	0.9862	1.5197	1.2101	0.135	0.9426	1.5533
West	1.2422	0.006	1.0630	1.4515	1.4048	0.001	1.1481	1.7188	1.4141	0.005	1.1116	1.7988
Urban (MSA)	0.9268	0.503	0.7420	1.1577	0.8692	0.296	0.6683	1.1307	0.8786	0.424	0.6396	1.2070
Median household income in three-digit ZIP code based on U.S. Census data	1.0000	0.003	1.0000	1.0000	1.0000	0.011	1.0000	1.0000	1.0000	0.014	1.0000	1.0000
Year of cART initiation (reference = 2003)												
2004	1.1252	0.260	0.9164	1.3815	1.2525	0.092	0.9642	1.6269	1.2732	0.110	0.9465	1.7125
2005	0.9201	0.421	0.7514	1.1268	0.9478	0.674	0.7385	1.2164	0.9575	0.768	0.7177	1.2775
2006	1.0884	0.401	0.8933	1.3261	1.1731	0.205	0.9163	1.5017	1.1227	0.416	0.8493	1.4842
2007	1.0965	0.366	0.8978	1.3391	1.2576	0.071	0.9807	1.6128	1.3626	0.036	1.0197	1.8207
Health plan type (reference = comprehensive)												
Health maintenance organization	0.8956	0.446	0.6746	1.1891	0.8427	0.341	0.5924	1.1988	0.7809	0.247	0.5136	1.1872
Point of service	0.9362	0.652	0.7030	1.2468	0.8654	0.429	0.6046	1.2386	0.8341	0.405	0.5440	1.2788
Preferred provider organization	1.0343	0.796	0.8004	1.3366	1.0236	0.888	0.7407	1.4145	0.9415	0.758	0.6414	1.3819
Other type	1.0020	0.992	0.6807	1.4750	0.7974	0.360	0.4909	1.2953	0.7615	0.393	0.4076	1.4225
Unknown/missing	0.9652	0.898	0.5624	1.6564	0.7850	0.436	0.4269	1.4436	0.8441	0.598	0.4494	1.5851
Claims with capitated payments	1.1838	0.078	0.9810	1.4287	1.2850	0.041	1.0103	1.6344	1.3591	0.036	1.0203	1.8104
Any mail-order ARV prescriptions in evaluation period	2.3736	<0.001	2.0668	2.7260	2.6236	<0.001	2.1752	3.1643	2.9522	<0.001	2.3299	3.7408

[a]*Adherence is defined as proportion of days in quarter during which patient possessed all components of initial cART regimen. To assess the goodness of fit of the marginal logistic regression with GEE, the aptness of the functional form of the covariates and link function were examined by conducting graphical and numerical analysis on cumulative sums of residuals over the covariates. No certain covariate misspecification was apparent through its cumulative residual plot.*

[b]*Measured during quarter under evaluation.*

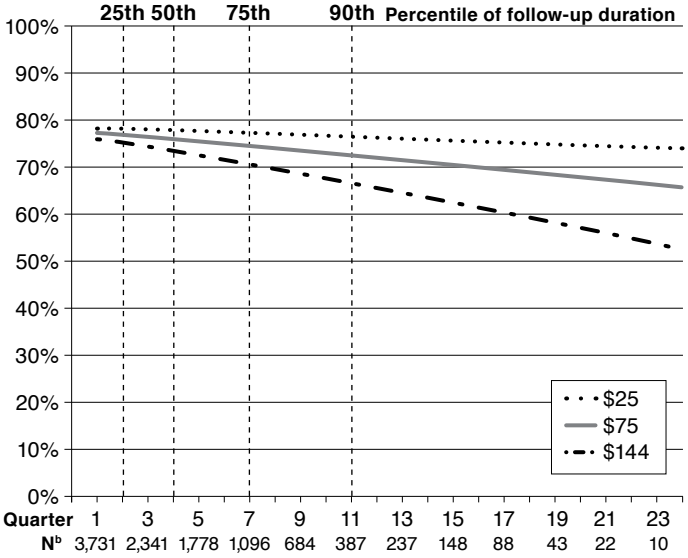
[c]*For each patient-quarter, these characteristics were measured during the 180-day period immediately prior to the start of the quarter.*

[d]*Baseline period was the 6 months prior to cART initiation.*

[e]*Reference category is South/unknown.*

ARV = antiretroviral; cART = combination antiretroviral therapy; CI = confidence interval; GEE = generalized estimating equations; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; MSA = metropolitan statistical area; NDC = national drug code; OR = odds ratio.

FIGURE 2 Predicted Probability of Adherence of 95% or More at 3 Cost-Sharing Levels[a]

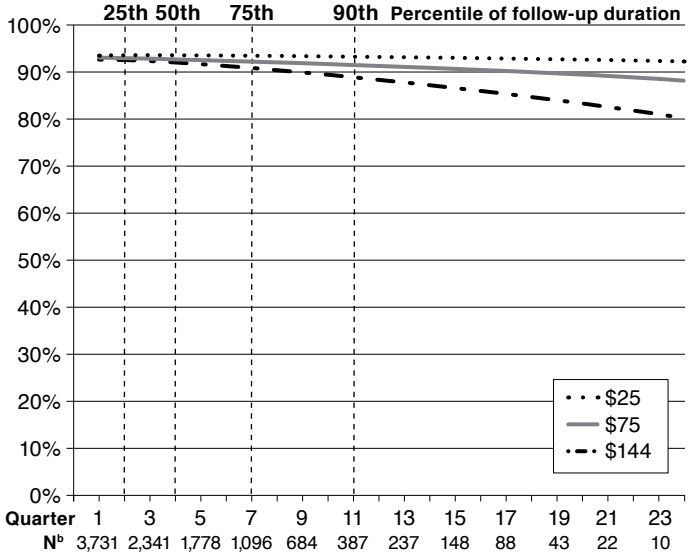


[a]*Cost-sharing levels are per 30-day supply and are predicted through 24 quarters of follow-up observation, beginning at the date of cART initiation. Cost-sharing amounts of $25, $75, and $144 represent the 25th, 75th, and 90th cost-sharing percentiles, respectively.*

[b]*Indicates number of cases available for follow-up at quarters 1, 3, 5, and each odd-numbered quarter through quarter 23.*

cART = combination antiretroviral therapy.

FIGURE 3 Predicted Probability of Adherence of 78% or More at 3 Cost-Sharing Levels[a]



[a]*Cost-sharing levels are per 30-day supply and are predicted through 24 quarters of follow-up observation, beginning at the date of cART initiation. Cost-sharing amounts of $25, $75, and $144 represent the 25th, 75th, and 90th cost-sharing percentiles, respectively.*

[b]*Indicates number of cases available for follow-up at quarters 1, 3, 5, and each odd-numbered quarter through quarter 23.*

cART = combination antiretroviral therapy.

(from $84 to $3,832 per 30-day cART supply). In patient-quarters with cost-sharing levels within the 0-20th percentiles of the cost-sharing distribution, 3,996 (96.7%) had at least 78% adherence; 3,865 (93.6%) had at least 85% adherence; and 3,468 (84.0%) had at least 95% adherence. In patient-quarters with cost-sharing levels exceeding the 80th percentile of the cost-sharing distribution, 3,438 (89.9%) had at least 78% adherence; 3,234 (84.6%) had at least 85% adherence; and 2,685 (70.2%) had at least 95% adherence. When observed within specific regimens, adherence generally decreased with higher quintiles of cART cost sharing but did so in a nonmonotonic way in some instances, exhibiting fluctuations between the lowest and highest quintiles of the cost-sharing distribution. Adherence was generally higher in patient-quarters with cost-sharing levels within the lowest percentiles of the cost-sharing distribution.

Table 5 reports the results of the multivariate analyses of at least 95% adherence, at least 85% adherence, and at least 78% adherence. The primary independent variable, which was the interaction term between cost sharing and sequential quarter number, was statistically significant in all 3 models and suggested a negative association between cost sharing and adherence that increases over time.

Figures 2 and 3 depict the predicted probabilities of at least 95% adherence and at least 78% adherence, respectively, for cost-sharing levels of $25, $75, and $144 and by quarter since cART initiation. These predictions can be interpreted as the expected probability of reaching each adherence threshold if a patient had the same cost-sharing amount throughout all quarters since cART initiation (e.g., initiating and staying on a cART regimen with $25 cost sharing vs. $75 cost sharing).

At the cost-sharing levels of $25, $75, and $144, the predicted probabilities of at least 95% adherence in the second quarter (the 25th percentile of follow-up, n = 3,117 cases still under observation) were 0.782, 0.770, and 0.752, respectively, and the predicted probabilities of at least 78% adherence were 0.936, 0.931, and 0.924, respectively. The differences in the predicted probabilities of adherence grew over time. By the seventh quarter (the 75th percentile of follow-up, n = 1,096 cases still under observation), the predicted probabilities of 95% adherence were 0.773, 0.746, and 0.707, respectively, and the predicted probabilities of at least 78% adherence were 0.933, 0.922, and 0.904, respectively. For the 11th quarter (the 90th percentile of follow-up, n = 387 cases still under observation), predicted probabilities were 0.765, 0.726, and 0.668 for 95% adherence and 0.931, 0.914, and 0.885 for 78% adherence.

In the models of adherence at least 95%, at least 85%, and at least 78%, each 1-pill increase in cART pill burden was associated with a 2.9% ($P = 0.025$), 4.6% ($P = 0.002$), and 6.1% ($P = 0.001$) decrease in the odds of adherence, respectively (Table 5). Residence in the West region (vs. South) was associated with increases of 24.2% ($P = 0.006$), 40.5% ($P = 0.001$), and 41.4% ($P = 0.005$), and having at least 1 mail-order ARV pharmacy claim was associated with increases of 137.4% ($P < 0.001$), 162.4% ($P < 0.001$), and 195.2% ($P < 0.001$) in the odds of 95%, 85%, and 78% adherence, respectively.

An alcohol or drug use disorder diagnosis was associated with a 23.4% ($P = 0.024$) decrease in the odds of 95% adherence (Table 5). In the analyses of adherence at least 85% and at least 78%, having incurred a claim with a capitation payment arrangement was associated with a 28.5% ($P = 0.041$) and 35.9% ($P = 0.036$) increase in the odds of adherence, respectively.

In sensitivity analyses, study results were highly robust in all scenarios tested (numeric findings available upon request). Using the population-averaged approach to the GEE, odds ratios for the interaction term (cost-sharing amount × sequential quarter) in the 36 model variations ranged from 0.99963 to 0.99974, all of which were statistically significant (maximum P value = 0.029). Using the random effects approach to the GEE, odds ratios for the 36 model variations ranged from 0.99937 to 0.99963, 2 of which were statistically insignificant at P values of 0.054 and 0.083. These odds ratios were similar to those in the original models, which ranged from 0.9996 to 0.9997.

Discussion

This is the first study to analyze the association between cART prescription cost sharing and adherence to initial cART. In a real-world sample of commercially insured ARV-naïve patients with HIV initiating cART, increasing cost-sharing amounts were associated with significantly lower odds of reaching the clinically meaningful adherence thresholds of at least 78% and at least 95%. Using the multivariate models for prediction, the differences across the chosen cost-sharing levels (i.e., $25, $75, and $144) in the predicted probability of each adherence threshold were initially minimal (e.g., 1.2 percentage point difference in the predicted probability of 95% adherence), comparing cost-sharing amounts of $25 versus $75 (the 25th and 75th cost-sharing percentiles) during the second quarter of observation but grew over time after initiation of cART (e.g., 2.7 percentage point difference for the same comparison in the seventh quarter of observation). HIV patients often exhibit positive changes in health-seeking and health-promoting behaviors early in the course of HIV diagnosis and treatment.[29] If such behavior mitigates the effects of cost sharing early after initiating cART, this could be a plausible explanation for the growth in the differences in the predicted probability of each adherence threshold over time. The importance of these results is underscored by the fact that initiation of cART requires commitment to lifelong treatment and that high levels of adherence to antiretroviral medications are required to prevent failure of virologic suppression, development of drug resistance, and permanent loss of therapeutic options.[3,9,10]

While this study is the first of its kind, 2 prior studies have presented findings of analyses that incorporated aspects of cost sharing as a predictor of ARV adherence. Stone et al. (2004) administered a questionnaire to 299 highly treatment-experienced patients with HIV/AIDS that evaluated perceptions of the impact on adherence of 10 cART regimen attributes, including the number of copayments and using a modified adaptive conjoint analysis.[30] Pill count, dosing frequency, and adverse effects had the greatest impact on perceived ability to adhere to cART; the number of copayments ranked as the seventh most important cART regimen attribute. Das-Douglas et al. (2009) examined the relationship between Medicare Part D implementation and ARV treatment interruptions in a sample of HIV-infected homeless and marginally housed individuals with drug coverage.[31] Forty-four respondents reported Medicare coverage, with 41 having dual Medicare-MediCal eligibility. Of these 44 individuals, 10 reported ARV interruptions. Although all dual-eligibles could receive brand drugs for copayments of $3-$5 in 2006,[32] 8 of 10 individuals with ARV interruptions cited increased cost of new copayments resulting from transition from MediCal to Part D as the primary driver of the ARV interruptions. The present study's results are qualitatively similar to those of Stone et al. and Das-Douglas et al. but represent a quantitatively different set of results in that they are not based on perceptions of hypothetical cART regimens; they are not qualitative self-reported information about adherence and ARV cost; and the subjects of the present study were not homeless or marginally housed.

Though this study's primary focus was to test a hypothesis about the association between cost sharing and adherence to cART, the model results are consistent with the findings of other prior studies that have found the cART pill burden and alcohol and drug use disorders to be substantial drivers of poor adherence to cART.[30,33,34]

The direction of the results of the present study (increased cost sharing is associated with decreased adherence) are also in line with results of prior research outside of the realm of HIV, which demonstrate an association between prescription cost sharing and decreased medication adherence, persistence, and prescription abandonment. Gleason et al. (2009) conducted a retrospective observational study among commercially insured individuals to assess the relationship between per claim out-of-pocket expense for tumor necrosis factor (TNF) blocker and multiple sclerosis (MS) biologic agents and prescription abandonment.[35] In the adjusted analyses for TNF blocker medication, compared with out-of-pocket expenses of $100 or less, out-of-pocket expenses between $101 and $500 were associated with 2.3 to 4.4-fold higher odds of prescription abandon-

ment, and out-of-pocket expenses greater than $500 were associated with 7-fold higher odds of prescription abandonment. In adjusted analyses for MS medications, compared with out-of-pocket expenses of $100 or less, out-of-pocket expenses greater than $200 per claim were associated with 6- to 7-fold higher odds of prescription abandonment. Zhang et al. (2007) conducted a retrospective observational study of beneficiaries (from 29 employers) newly initiating single-agent angiotensin system blocking medication and found that each $1 in member cost share for the initial prescription claim was associated with a 1.9% increase in total medication gap in therapy and 2.8% greater odds of nonpersistence at 6 months after therapy initiation.[36] Similar findings have also been noted in observational studies focusing on other specific chronic conditions, such as diabetes, hypertension, and hyperlipidemia.[37,38]

Note that HIV patients within the study sample were covered under employer-sponsored health insurance. Though recent data on variations in insurance coverage among individuals with HIV in the United States are sparse, a 1996 study estimated that 31% of individuals with HIV in the United States are covered by private insurance.[39] Thus, this study's population was drawn from a nontrivial proportion of all individuals with HIV. Commercially insured patients are likely to have more structured lives and be in situations that are more economically favorable than the uninsured or patients who have insurance through state Medicaid programs—the latter group representing an estimated 44 percent of individuals with HIV receiving care.[39] Thus, the large proportion of HIV patients with potentially more difficult socioeconomic situations may be even more sensitive to cost sharing for ARV therapy.[40] The importance of this circumstance would depend on the extent to which these patients are responsible for cost sharing, which may be low in the Medicaid setting.

There are various analytic strengths to this study. Patients were drawn from a database that, while not nationally representative of all patients with commercial insurance, does cover a large, geographically diverse population with health plans that include a variety of benefit plan designs and reimbursement schemes, thereby enhancing the generalizability of results compared with data from a single payer, geographical region, or study site. Finally, this study's quarterly panel dataset design was superior to a cross-sectional analysis in that it permitted the repeated measurement of cost-sharing amounts over time, which may change as a result of benefit design changes.

Limitations

There are also several analytic limitations to this study. First, as noted in editorial critiques of studies that have examined the association between cost sharing and adherence,[41,42] this study is limited by its observational (nonrandomized) nature and therefore can only be interpreted as suggesting an association between cART prescription cost sharing and adherence to cART. Second, this study did not set out to assess the impact of adherence on clinical outcomes, and future research is needed to explore whether prescription benefit policies that reduce cART prescription cost sharing would be cost-effective and to quantify how cost sharing correlates with actual clinical outcomes. Third, our variable-length evaluation period extended from cART initiation until the occurrence of various events, one of which was a hospitalization of 30 days or more. If during a hospitalization a patient stockpiled the medication that would otherwise have been used in the outpatient setting, then upon discharge the patient could have resumed using the stockpiled medication. Although our adherence measurement would have expected a refill on day X, that patient may instead have refilled on day X + the length of stay for the hospitalization. Thus, it is possible that patients with shorter than 30-day hospitalizations may have had some adherent days counted as nonadherent as a result of this approach. Among the 19,199 patient-quarters, 2,285 (11.9%) had a hospitalization in the 180-day period prior to the start of a given patient-quarter period. Additionally, the bivariate correlation between cost sharing and the proportion of patients with a hospitalization in the 180-day period prior to the start of a given patient-quarter period was minimal and insignificant (correlation = 0.0086, $P = 0.2347$). As such, we believe that the impact of such hospitalizations on our adherence measurement approach is likely low. Ultimately, hospitalizations are an area of uncertainty for adherence measurement in our data source.

Fourth, this study examined the association between cART prescription cost sharing and adherence to initial cART and did not extend its investigation beyond the initial therapy. Consequently, study results may not be generalizable beyond initial cART regimens (e.g., when regimens must be modified in long-term ongoing therapy), and future research to examine ongoing therapy is warranted. Fifth, this study used prior clinical evidence to inform the 78% adherence threshold and WHO guidance to inform the 95% threshold. Previously published work, on which the present study's adherence thresholds were based, might have used a definition of adherence different than that used in the present study. Although the DHHS guidelines emphasize that clinicians should encourage patients to strive for ARV adherence as close to 100% as possible, there is not an actual known cutoff level of adherence that should be achieved, and as such, the choice of 3 different adherence cutoff values within the present study serves also as a way to test the sensitivity of study findings to the outcome definition. Sixth, study results may not be nationally representative of all commercial health plans nor are they necessarily generalizable to individuals outside of commercial health plans, including the uninsured and those covered by Medicaid. Seventh, the adherence calculation relied on the dates that prescriptions were filled and the number of days supply obtained; such records are unable to fully describe patients' actual medication-taking

behavior. Eighth, race, actual income, biometric information, and mortality are unavailable within the data due to privacy protections. The omission of these and other unmeasured variables represent a form of potential residual confounding, the impact of which would depend on the correlations among the omitted variables, cost sharing, and adherence. The extent to which such confounding is present in this analysis is unknown, and future research of the relationship between cost sharing and adherence that uses data sources with such information would be useful to advance this line of inquiry. Ninth, diagnoses on claims may be coded incorrectly or not coded, thereby potentially excluding some patients with HIV who initiate cART but do not have a diagnosis on a medical claim during the search period. Tenth, patients who died or became unemployed within 1 year after initiating cART were excluded from the study due to the post-index continuous enrollment requirement. This decision may have resulted in a healthier sample in this study than the general population of commercially insured HIV patients initiating cART. Finally, since this is the first study to assess the association between cART prescription cost sharing and adherence to cART, further research is warranted to confirm the study's findings in other commercially insured populations and in vulnerable populations, such as individuals covered by Medicaid.

Conclusion

Increasing cART prescription cost sharing was associated with modestly decreased odds of maintaining clinically meaningful levels of cART adherence.

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DISCLOSURES

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Concept and design were performed by Johnston, Juday, and Seekins. Data were collected primarily by Espindle and Johnston and interpreted by Chu, Johnston, Juday, and Seekins. The manuscript was written primarily by Johnston and Juday and revised primarily by Johnston.

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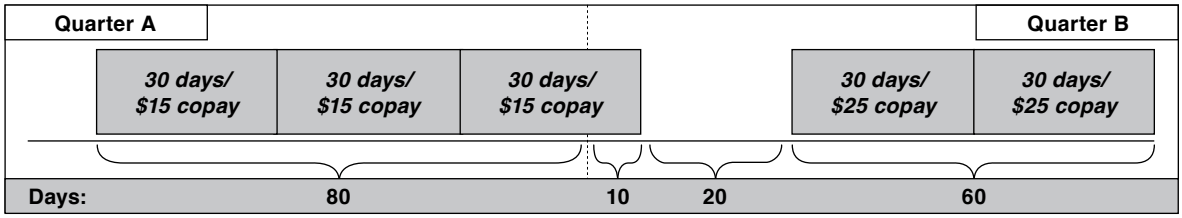
APPENDIX 1 List of Antiretroviral Agents

ARV Class	Generic Name
ARVs used to identify initial cART	
NNRTI	efavirenz
NNRTI	nevirapine
NNRTI + NRTI fixed dose regimen	efavirenz + emtricitabine + tenofovir DF
NRTI	abacavir
NRTI	didanosine
NRTI	emtricitabine
NRTI	lamivudine
NRTI	stavudine
NRTI	tenofovir
NRTI	zidovudine
NRTI fixed dose combination	abacavir + lamivudine
NRTI fixed dose combination	emtricitabine + tenofovir DF
NRTI fixed dose combination	zidovudine + lamivudine
NRTI fixed dose combination	zidovudine + lamivudine + abacavir
PI	amprenavir
PI	atazanavir
PI	darunavir
PI	fosamprenavir
PI	indinavir
PI	lopinavir + ritonavir
PI	nelfinavir
PI	saquinavir
PI boosting agent	ritonavir
Additional ARVs used to select ARV-naïve patients	
HIV fusion inhibitor	enfuvirtide
HIV fusion inhibitor	maraviroc
NNRTI	etravirine
PI	tipranavir

ARV = antiretroviral; cART = combination antiretroviral therapy; DF = disoproxil fumarate; HIV = human immunodeficiency virus; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PI = protease inhibitor.

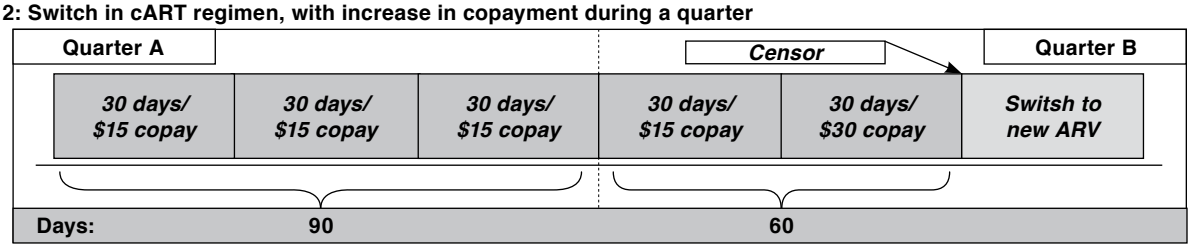
APPENDIX 2 Calculation of Adherence and Cost-Sharing Amount Under Various Scenarios

Scenario 1. Days supplied spanning 2 quarters, with increase in copayment during a quarter



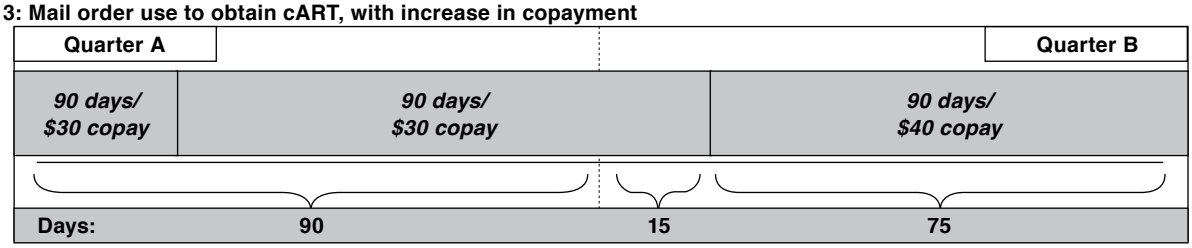
- **Adherence quarter A:** 80 days supplied ÷90 days in quarter=0.89
- **Cost sharing per 30-day supply quarter A:** 80 days supplied @ cost sharing per 30 days of $15; (80/80×$15=$15)
- **Adherence quarter B:** 70 days supplied ÷90 days in quarter=0.78
- **Cost sharing per 30-day supply quarter B:** 10 days supplied @ cost sharing per 30 days of $15; 60 days supplied @ cost sharing per 30 days of $25 ([10/70×$15]+[60/70×$25]=$23.50)

Scenario 2: Switch in cART regimen, with increase in copayment during a quarter



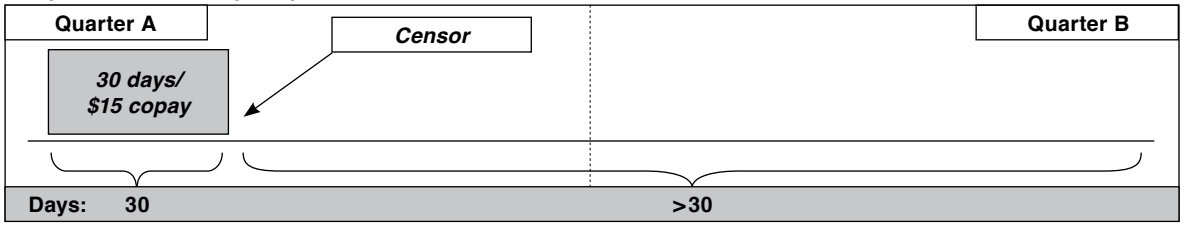
- **Adherence quarter A:** 90 days supplied ÷90 days in quarter=1.00
- **Cost sharing per 30-day supply quarter A:** 90 days supplied @ cost sharing per 30 days of $15; (90/90×$15=$15)
- **Adherence quarter B:** 60 days supplied ÷60 days in quarter prior to switch (censoring)=1.00
- **Cost sharing per 30-day supply quarter B:** 30 days supplied @ cost sharing per 30 days of $15; 30 days supplied @ cost sharing per 30 days of $35 ([30/60×$15]+[30/60×$30]=$22.50)

Scenario 3: Mail order use to obtain cART, with increase in copayment



- **Adherence quarter A:** 90 days supplied ÷90 days in quarter=1.00
- **Cost sharing per 30-day supply quarter A:** 90 days supplied @ cost sharing per 90 days of $30, which is $10 per 30-day supply; (90/90×$10=$10)
- **Adherence quarter B:** 90 days supplied ÷90 days in quarter=1.00
- **Cost sharing per 30-day supply quarter B:** 15 days supplied @ cost sharing per 30 days of $10; 75 days supplied @ cost sharing per 30 days of $13.30 ([15/90×$10]+[75/90×$13.30]=$12.80)

Scenario 4: Gap of at least 30 days in possession of an ARV



- **Adherence quarter A:** 30 days supplied ÷30 days in quarter prior to 30-day gap (censoring)=1.00
- **Cost sharing per 30-day supply quarter A:** 30 days supplied @ cost sharing per 30 days of $15; (30/30×$15=$15)
- **Adherence quarter B:** Not applicable
- **Cost sharing per 30-day supply quarter B:** Not applicable

ARV=antiretroviral; cART=combination antiretroviral therapy.