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Daily Antiretroviral Pill Burden Effects on Medication Adherence, Hospitalization Risk, and Health Care Utilization and Costs in a United States Medicaid Population With HIV

Short Title: Antiretroviral Pill Burden in Medicaid Patients

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ABSTRACT

Objectives: Lower pill burden leads to improved adherence to antiretroviral therapy (ART) among human immunodeficiency virus (HIV) patients. Simpler dosing regimens have not been widely explored in real-world populations. We retrospectively assessed health care utilization and costs in Medicaid enrollees with HIV treated with ART as a once-daily single-tablet regimen (STR) or two or more pills per day (2+PPD).

Design: Patients with an HIV diagnosis from 2005- 2009 receiving complete ART (i.e., 2 nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent) for 60 days or more as STR or 2+PPD were selected and followed until the first of 1) discontinuation of the complete ART, 2) loss of continuous enrollment, or 3) end of the database. Adherence was measured using the medication possession ratio. Monthly utilization and costs were observed from regimen initiation until discontinuation and reported overall and by care setting (inpatient, emergency department, office, pharmacy, other). To assess predictors of hospitalization, Poisson models, counting the number of hospitalizations and covariates for demographics, comorbidities, and ART-naïve status, were estimated.

Results: Of the 7,381 patients who met inclusion criteria, 1,797 were treated with STR and 5,584 with 2+PPD. STR patients were significantly more likely to reach a 95% adherence threshold and had fewer hospitalizations than 2+PPD patients (both: $P < 0.01$). STR patients had mean (SD) total monthly costs of $2,959($4,962); 2+PPD patients had $3,544($5,811) ($P < 0.001$). Hospital costs accounted for 53.8% and pharmacy costs accounted for 32.5% of this difference. Multivariate analyses found that STR treatment led to a 23% reduction in hospitalizations and a 17% reduction in health care costs.

Conclusions: While it was expected that STR patients would have lower pharmacy costs, we also found that STR patients had fewer hospitalizations and lower hospital costs than 2+PPD patients, resulting in significantly lower total health care costs for STR patients.

ARTICLE SUMMARY

Article Focus

- To assess the effect of a single-tablet-per-day ART regimen (STR) on adherence and hospitalization risk in a large population of Medicaid enrollees in the United States who received treatment for HIV infection

Key Messages

- Patients who received ART as a single pill per day were significantly more likely to be highly adherent to therapy than patients who received multiple-pill regimens.
- Improved adherence among patients treated with STR conferred a lower risk of hospitalization.
- The use of an STR may reduce health care costs as well as patient morbidity by decreasing hospitalization rates, which were higher in patients with less-than-complete medication adherence.

Strengths and Limitations of This Study

- This retrospective analysis used pharmacy refill dates as the best available proxy for pill-taking behavior; one advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis the timing in between refills, which also notes the amount of medication dispensed each time.
- Rates of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should measures of overall monthly health care utilization and costs.

- While our prescription claims-based measure of adherence has been found to be a valid proxy for actual medication-taking behavior, we had no measure of actual patient adherence (i.e., daily ingestion/consumption) to the prescriptions they filled.
- Because we did not randomize patients to the two different treatment regimens, we cannot exclude unmeasured confounding factors that may have influenced our outcomes; although we attempted to control for some of these variables through the use of multivariable models that included some of these factors (substance abuse and psychiatric diagnoses), residual confounding may remain.
- We had no laboratory results from patients and thus cannot confirm the degree of virologic suppression obtained across the regimens.

ADMINISTRATIVE STATEMENTS

Protection of Human Subjects

The research organization that conducted this study, RTI Health Solutions, a business unit of RTI International (RTI), holds a Federal-Wide Assurance (FWA #3331 effective until June 17, 2014) from the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) that allows us to review and approve human subjects protocols through our Institutional Review Board (IRB) committees. Since pre-existing, retrospective, de-identified patient data were analyzed for this study, which involved no patient contact or medical interventions and therefore no patient consent forms, the RTI IRB committee approved this study as exempt.

Author Contributions

Calvin Cohen assisted in development of the study design, evaluated and interpreted the study results, and drafted and critically revised the manuscript text. Juliana Meyers and Keith Davis assisted in development of the study design, obtained study funding, conducted all analytic programming and statistical analyses, assisted with evaluation and interpretation of the study

Funding Statement

This study was funded by Gilead Sciences, which is conducting clinical research in and markets current treatments for HIV/AIDS.

Data Sharing

Raw data used for this study are unavailable for public sharing (per terms of the private data use agreement governing original data acquisition).

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INTRODUCTION

The 2012 Department of Health and Human Services guidelines state that there are four preferred regimens for initiating human immunodeficiency virus (HIV) treatment in adults. Furthermore, there are multiple alternatives to these four regimens.[1] Patients and their treating physicians can choose from among these four preferred regimens, using the criteria of greatest efficacy, safety, and simplicity. The latter category is important because regimen simplicity is associated with greater long-term adherence. For example, all four preferred regimens are constructed with a relatively low pill burden (i.e., between one and four tablets per day), and three of the four regimens have once-daily dosing. While randomized trials have compared the components of some of these four regimens with each other, to date no studies compared the four regimens to each other as they are prescribed (i.e., in a real-world setting), given that these study trials have been blinded.[2,3]

Adherence to antiretroviral therapy (ART) is essential for achieving durable clinical outcomes in patients with HIV. Patients with inadequate adherence to ART are at an increased risk for incomplete viral suppression; and unless a new suppressive regimen is quickly constructed to reestablish virologic suppression, viremia is associated with an increased risk of disease progression, and death.[4-8] In the past several years, the availability of fixed-dose combinations and agents with prolonged half-lives have simplified pill burden and thus increased regimen adherence.[1,9] Several clinical trials and cohort studies support the conclusion that once-daily single tablet regimens (STR) can lead to significantly improved adherence, patient satisfaction, and virological outcomes.[10-13] For example, among homeless or marginally housed patients, those receiving an ART regimen composed of a single tablet per day had better virologic outcomes and a 26% increase in adherence than patients receiving other multi-pill regimens.[13] One recently published study analyzing a claims database noted that compared

with various multi-pill regimens, a STR was associated with increased adherence (as determined by pharmacy refill data). Furthermore, the increased likelihood of complete adherence was associated with a 25% decrease in the rate of hospitalization.[14]

In this study, we sought to assess how robust these findings were by analyzing similar metrics in a separate data set. The primary objective of this retrospective database analysis was to assess the effect of a single-tablet-per-day ART on adherence and hospitalization in a large population of Medicaid enrollees in the United States who received treatment for HIV infection.

METHODS

Data for this analysis were taken from the MarketScan Medicaid Multi-State Database, which contains health care claims from approximately 30 million Medicaid enrollees from 11 geographically dispersed states. The database includes patient-level demographics; periods of Medicaid enrollment; primary and secondary diagnoses; and detailed information about hospitalizations and therapeutic procedures, inpatient and outpatient physician services, and prescription drug use. In compliance with the Health Insurance and Portability and Accountability Act of 1996, all data were de-identified to protect the privacy of individual patients, physicians, and hospitals. Because the data were retrospective, pre-existing, and de-identified, RTI International's institutional review board determined that this study met all criteria for exemption.

Patients were selected for inclusion if they received at least one HIV or AIDS diagnosis (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code 042.xx) between June 1, 2006, and December 31, 2009. Patients also were required to have evidence of receipt of a complete ART regimen, defined as two nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent (i.e., another nucleoside/nucleotide reverse transcriptase inhibitor, a nonnucleoside/nucleotide reverse transcriptase inhibitor, a protease inhibitor [PI], a chemokine receptor R5 antagonist, or an integrase inhibitor). The first date of receipt of a complete regimen was termed the index date. ART agents were identified in the claims database by using National Drug Codes associated with relevant generic and brand names. Patients also were required to remain on the complete ART regimen for at least 60 days following their index dates and to have evidence of continuous enrollment in Medicaid during this period. To assess treatment-naïve versus experienced status and baseline comorbidities, patients were required to have at least 6 months of pre-index date Medicaid enrollment, with

enrollment information available from January 1, 2006 (i.e., 6 months before the earliest possible index date).

Patients were grouped into two mutually exclusive cohorts according to the daily pill count of their complete ART regimen. Patients were assigned to the STR cohort if they received an ART regimen consisting of a single tablet (i.e., an STR) at any point during the selection window, regardless of prior or subsequent use of other regimens. At the time of this study, only coformulated tenofovir/emtricitabine/efavirenz was available as an STR. Patients were assigned to the two-or-more-pills-per-day (2+PPD) cohort if they received a regimen consisting of two or more pills per day during the selection window and if they did not receive an STR at any point during that time.

Patients were followed from the start of their complete ART regimen (i.e., after June 1, 2006, the study index date) until the earliest date of regimen discontinuation, disenrollment from the health plan, or the end of the database (i.e., March 31, 2009). Furthermore, patients receiving 2+PPD were allowed to change medications, providing the patients continued to receive a complete regimen. Patients receiving STR were followed for as long as they remained on the STR. Discontinuation was defined as 60 consecutive days in which no refills were observed for any component of the regimen. Females with an ICD-9-CM diagnosis code indicating a pregnancy during the follow-up period were excluded from the analysis because the one available STR is not recommended for pregnant women, and hospitalizations for labor and delivery may have biased results in favor of the STR.

Patient characteristics measured at the index date included age, sex, and ART classes received (i.e., nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside/nucleotide reverse transcriptase inhibitors, PIs, ritonavir boosting therapy, or other therapies). The presence of comorbid medical conditions other than HIV or AIDS were assessed during the 6-month pre-

index period, using an established algorithm, the Charlson Comorbidity Index (CCI) score.[15] This score is made up of 17 comorbidities (defined by ICD-9-CM diagnosis and procedure codes), such as myocardial infarction and chronic pulmonary disease, which are weighted to correspond to the severity of the comorbid condition of interest. A higher comorbidity score represents a higher overall comorbidity burden during the pre-index period. Additionally, the incidence of other concomitant mental disorders (ICD-9-CM codes 306.xx through 319.xx) and drug and alcohol abuse (ICD-9-CM codes 292.xx and 303.xx through 305.xx) during the 6-month pre-index period also was assessed.

Medication adherence was assessed using the medication possession ratio (MPR), which has been shown to be the most widely adopted measure (57% of all studies) in published claims-based analyses of medication adherence [16] and has been used in studies of ART adherence among individuals with HIV.[17] The MPR, which is a proxy for refill compliance, generally measures the proportion of the ART exposure period in which supply was maintained for all ART components comprising the regimen. Specifically, MPR was calculated as the number of filled prescription days for all ART regimen components (using the days supplied in the pharmacy claims) divided by the number of days from the first observed prescription in the regimen through the earliest of either the exhaustion of the days supplied of the last observed prescription or the end of follow-up. For each patient in our study, the MPR was calculated over the period in which the patient remained on his or her ART regimen. For patients in the 2+PPD cohort, late refills and resulting days of missing supply for one or more ART components were all factored against their adherence measurements. For example, patients in the 2+PPD cohort with a supply for only one of the ART components on a given day were considered to have zero adherence for that day. In addition to reporting the mean (standard deviation [SD]) MPR achieved, we also reported the numbers and percentages of patients achieving various adherence

thresholds (i.e., MPRs of 1.0-0.95, 0.94-0.90, 0.89-0.85, and 0.84-0.80, corresponding to 100%-95%, 94%-90%, 89%-85%, and 84%-80% adherence, respectively).

To further understand adherence to ART regimens, for each patient in the 2+PPD cohort, complete (i.e., having a complete regimen), partial (i.e., receiving some but not all components of a complete regimen), and no medication days also were assessed. Specifically, we reported the percentage of days that each patient had complete, partial, and no medications available, along with the mean number of days that the patient had complete, partial and no medications. Additionally, we also reported the maximum number of consecutive days the patient had either an incomplete regimen or no medications available.

Hospitalizations were identified from the claims database using relevant place of service codes. Hospitalizations were observed from the index date until the earliest date of regimen discontinuation, end of enrollment in the health plan, or end of the database. The number and percentage of patients with at least one hospitalization were reported, along with the mean (SD) number of hospitalizations, and the mean (SD) number of inpatient days. Furthermore, we compared and reported the number of hospitalizations per 100 patient-years, along with the rate ratios and 95% confidence intervals, for both cohorts.

For each patient, overall health care utilization and associated costs were aggregated across all encounters, regardless of reason, that were observed during the follow-up period; we reported these costs by average and per-month amounts. The following categories of overall health care utilization and costs were evaluated and reported: inpatient, emergency department, office visit, home health visit, laboratory service, pharmacy, other outpatient care, and total. For each category of overall health care, the number and percentage of patients, the mean (SD) number of visits per month, and monthly per-patient costs were reported. Additionally, for patients with an

inpatient visit, the average number of inpatient days per month among patients with at least one stay during follow-up also was reported.

All analyses were carried out using SAS (version 9; Cary, North Carolina) statistical software. Descriptive analyses were conducted for all outcome measures and included means and SDs for continuous variables of interest (e.g., MPR) and frequency distributions of categorical variables of interest (e.g., geographic region). All descriptive analyses were stratified by cohort. Health care costs were updated to 2010 US dollars using the medical care component of the consumer price index.

A generalized linear model with a log link and a Poisson distribution was estimated to assess the relationship between the number of pills per day and the number of hospitalizations observed during follow-up. The dependent variable was a count of hospitalizations during exposure to the ART regimen. Additionally, a generalized linear model with a log link and a negative binomial distribution were estimated to assess monthly health care costs, adjusted for the patient and treatment characteristics. The dependent variables were monthly total costs and monthly total costs excluding costs pharmacy costs. For both models, independent variables included the following: treatment regimen received (i.e., STR vs. 2+PPD), age, sex, CCI score, treatment-naïve status, pre-index presence of mental health disorders, pre-index presence of alcohol or drug abuse disorders, length of follow-up (in days, hospital model only), and whether or not the patient met a 0.95 adherence threshold (cost model only). For the hospital model, incidence rate ratios (IRRs) were reported for all covariates, along with the mean predicted number of hospitalizations for patients receiving an STR versus patients receiving a 2+PPD. For the cost model, adjusted predicted mean costs were reported.

RESULTS

A total of 7,381 patients met the selection criteria (Figure 1). Of these, 5,584 patients (75.7%) received their ART regimen as 2+PPD; 1,797 patients (24.3%) received their ART regimen as a STR. On average, patients were approximately 42 years of age. Approximately 46% of patients were female (Table 1). Across both cohorts, the average CCI score was approximately the same (mean [SD]: 0.67 [1.38] among patients receiving an STR and 0.65 [1.36] among patients receiving 2+PPD). Furthermore, the incidence of concomitant mental disorders and drug and alcohol abuse diagnoses did not vary substantially by cohort. Patients receiving an STR had a mean regimen duration of 348 days; this was approximately 2.8 months shorter than the mean regimen duration of 433 days observed for patients receiving 2+PPD. Forty-seven percent of patients receiving an STR were treatment naïve, compared with 24.5% of patients receiving 2+PPD.

Table 1. Characteristics of the study sample, by cohort.

Characteristic	STR		2+PPD	
All Patients (N, %)	1,797	100.00%	5,584	100.00%
Age , mean (SD)	41.6	(10.56)	42.32	(11.37)
Age category (N, %)				
Aged less than 18 years	40	2.23%	271	4.85%
Aged 18 to 24 years	95	5.29%	139	2.49%
Aged 25 to 34 years	269	14.97%	661	11.84%
Aged 35 to 44 years	622	34.61%	1,975	35.37%
Aged 45 to 54 years	591	32.89%	1,875	33.58%
Aged 55 to 64 years	176	9.79%	638	11.43%
Aged 65+ years	4	0.22%	25	0.45%
Gender (N, %)				
Male	945	52.59%	3,063	54.85%
Female	852	47.41%	2,521	45.15%
Charlson comorbidity index score, mean (SD)	0.67	(1.38)	0.65	(1.36)
Charlson comorbidities (N, %)				
Myocardial infarction	11	0.61%	44	0.79%
Congestive heart failure	39	2.17%	141	2.53%

Characteristic	STR		2+PPD	
Peripheral vascular disease	14	0.78%	58	1.04%
Cardiovascular disease	52	2.89%	148	2.65%
Dementia	4	0.22%	10	0.18%
Chronic pulmonary disease	259	14.41%	704	12.61%
Rheumatological disease	11	0.61%	23	0.41%
Peptic ulcer disease	9	0.50%	25	0.45%
Mild liver disease	20	1.11%	49	0.88%
Severe liver disease	117	6.51%	333	5.96%
Diabetes mellitus without chronic complications	145	8.07%	445	7.97%
Diabetes mellitus with chronic complications	16	0.89%	89	1.59%
Paraplegia	6	0.33%	34	0.61%
Renal disease	11	0.61%	80	1.43%
Cancer	82	4.56%	221	3.96%
Metastatic cancer	11	0.61%	26	0.47%
Concomitant comorbidities (N, %)				
Mental disorders	382	21.26%	1,340	24.00%
Drug or alcohol abuse	338	18.81%	856	15.33%
Treatment naïve at index (N, %)	853	47.47%	1,366	24.46%
Mean (SD) regimen length	348.17	(259.32)	433.46	(351.50)
Index medications (N, %)				
NRTI	1,797	100.00%	5,584	100.00%
NNRTI	1,797	100.00%	1,500	26.86%
PI	0	0.00%	4,064	72.78%
Kaletra at index	---	---	1,633	40.18%
Boosted PI at index	---	---	1,664	40.94%
Non-boosted PI at index	---	---	767	18.87%
PE	0	0.00%	1,712	30.66%
Other	0	0.00%	87	1.56%

NOTE. 2+PPD = two or more pills per day; NNRTI = nonnucleoside/nucleotide reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PE = pharmacokinetic enhancer; PI = protease inhibitor; SD = standard deviation; STR = once-daily single-tablet regimen.

Patients receiving an STR had significantly better adherence than patients receiving 2+PPD (Table 2). Approximately 25.3% of patients receiving an STR achieved 95% adherence or greater, compared with 17.4% of patients receiving 2+PPD ($P \leq 0.0001$). Mean (SD) MPR was 0.84 (0.14) among patients receiving an STR and 0.80 (0.15) among patients receiving 2+PPD

(Table 2). Patients in the 2+PPD cohort received a complete regimen for 80.3% of the follow-up period (mean [SD]: 361.9 [315.0] days), a partial regimen for 5.6% of the follow-up period (mean [SD]: 22.2 [45.6] days), and no available medications for 14.1% of the follow-up period (mean [SD]: 49.4 [57.1] days) (Table 3). Alternatively, patients in the STR cohort received a complete regimen for 84.4% of the follow-up period (mean [SD]: 299.4 [234.6] days) and no available medications for 15.6% of the follow-up period (mean [SD]: 48.8 [54.2] days), which was a similar percentage of days as patients receiving 2+PPD. Patients receiving an STR had, on average, a maximum of 19.5 (SD: 15.9) consecutive days without a complete regimen (i.e., either a partial regimen or no medications available); patients receiving 2+PPD had, on average, a maximum of 23.9 (SD: 16.7) consecutive days without a complete regimen.

Table 2. Adherence to antiretroviral therapy, by cohort.

Cohort	Number of Patients	Mean (SD) MPR	MPR/Persistency Ratio (N, %)				
			<0.8	0.8 - <0.85	0.85 - <0.9	0.9 - <0.95	0.95 - 1
STR	1,797	0.84 (0.14)	537 29.88%	178 9.91%	243 13.52%	385 21.42%	454 25.26%
2+PPD	5,584	0.80 (0.15)	2,255 40.38%	621 11.12%	779 13.95%	957 17.14%	972 17.41%
Overall	7,381	0.81 (0.15)	2,792 37.83%	799 10.83%	1,022 13.85%	1,342 18.18%	1,426 19.32%
P-Value (1 vs. 2)		<.0001	<.0001	0.1491	0.6477	<.0001	<.0001

NOTE. 2+PPD = two or more pills per day; MPR = medication possession ratio; SD = standard deviation; STR = once-daily single-tablet regimen.

Table 3. Summary of incomplete adherence, by cohort.

Adherence Characteristic	STR	2+PPD
Percentage of days with complete adherence	84.42%	80.37%
Percentage of days with partial adherence	---	5.56%
Percentage of days with no ART medications	15.58%	14.07%
Complete adherence days, mean (SD)	299.36 (234.56)	361.87 (315.03)
Partial adherence days, mean (SD)	---	22.24 (45.58)
Days with no medication available, mean (SD)	48.81 (54.24)	49.35 (57.11)
Total follow-up duration, mean (SD)	348.17 (259.31)	433.46 (351.50)
Maximum consecutive gap in therapy,[a] mean (SD)	19.48 (15.89)	23.92 (16.67)

NOTE. 2+PPD = two or more pills per day; ART = antiretroviral therapy; SD = standard deviation; STR = once-daily single-tablet regimen.

[a] Represents either days with a partial regimen or days with no medications.

Among patients receiving an STR, 21.0% had at least one hospitalization, compared with 24.4% of patients receiving 2+PPD ($P = 0.003$) (Table 4). Among patients with a hospitalization, patients receiving an STR had numerically similar, although significantly fewer, hospitalizations over all available follow-up, when compared with patients receiving 2+PPD (mean [SD]: 1.9 [1.6] among patients receiving an STR vs. 2.1 [2.2] among patients receiving 2+PPD; $P = 0.001$).

Table 4. All-cause average monthly per patient health care utilization and costs, by cohort.

Resource Used	STR		2+PPD		P-Value
Hospitalizations					
Had ≥ 1 hospital admission (N, %)[a]	378	21.04%	1,365	24.44%	0.0031
Number of hospitalizations over all follow-up,[b] mean (SD)	1.88	(1.59)	2.1	(2.23)	0.0012
Inpatient days over all follow-up,[b] mean (SD)	9.99	(12.33)	12.33	(18.90)	0.0228
Number of admissions per month					
Mean (Std. Dev)	0.05	(0.00)	0.05	(0.15)	0.1429
Median	0		0		
Range (Min, Max)	0	2	0	1.97	
Days in hospital per month[c]					
Mean (SD)	1.32	(2.21)	1.45	(2.71)	0.3975
Median	0.58		0.5		
Range (Min, Max)	0.03	21.5	0.03	32.43	
Costs					
Mean (Std. Dev)	$834	($4,480)	$1,152	($5,212)	0.0203
Median	$0		$0		
Range (Min, Max)	$0	$143,530	$0	$97,626	
Emergency Room (ER)					
Had ≥ 1 ER visit (N, %)[a]	903	50.25%	2,749	49.23%	0.4517
Number of visits					
Mean (Std. Dev)	0.97	(3.00)	1.01	(2.99)	0.6107
Median	0.03		0		
Range (Min, Max)	0	67	0	89.91	
Costs					
Mean (Std. Dev)	$45	($160)	$46	($135)	0.873
Median	$0		$0		
Range (Min, Max)	$0	$3,063	$0	$4,161	
Office Visits (Primary Care) (N, %)					
Had ≥ 1 office visit (N, %)[a]	1,509	83.97%	4,699	84.15%	0.8576

Resource Used	STR	2+PPD	P-Value
Number of visits			
Mean (Std. Dev)	1.52 (3.00)	1.43 (2.19)	0.1669
Median	0.92	0.86	
Range (Min, Max)	0 61	0 40.30	
Costs			
Mean (Std. Dev)	$75 ($229)	$70 ($291)	0.5087
Median	$30	$26	
Range (Min, Max)	$0 $5,012	$0 $15,499	
Home Health (N, %)			
Had ≥ 1 home health visit (N, %)[a]	504 28.05%	1,861 33.33%	<.0001
Number of visits			
Mean (Std. Dev)	0.64 (3.00)	0.79 (3.16)	0.0625
Median	0	0	
Range (Min, Max)	0 45	0 43.06	
Costs			
Mean (Std. Dev)	$47 ($198)	$88 ($642)	0.007
Median	$0	$0	
Range (Min, Max)	$0 $4,142	$0 $36,653	
Laboratory (N, %)			
Had ≥ 1 lab order (N, %)[a]	1,168 65.00%	3,530 63.22%	0.1722
Number of claims			
Mean (Std. Dev)	1.24 (2.00)	1.19 (1.69)	0.2962
Median	0.66	0.57	
Range (Min, Max)	0 16	0 19.96	
Costs			
Mean (Std. Dev)	$52 ($94)	$46 ($120)	0.0401
Median	$20	$17	
Range (Min, Max)	$0 $1,689	$0 $7,246	
Pharmacy (N, %)			
Had ≥ 1 pharmacy claim (N, %)[a]	1,797 100.00%	5,584 100.00%	---
Number of claims			
Mean (Std. Dev)	4.99 (4.00)	6.73 (4.05)	<.0001
Median	3.96	5.76	
Range (Min, Max)	0.37 27	0.69 37.17	
Costs			
Mean (Std. Dev)	$1,593 ($1,105)	$1,779 ($1,307)	<.0001
Median	$1,494	$1,617	
Range (Min, Max)	$0 $27,034	$0 $54,232	
OP/ancillary (N, %)			
Had ≥ 1 other OP/ancillary (N, %)[a]	1,754 97.61%	5,469 97.94%	0.3957
Number of visits			
Mean (Std. Dev)	0.15 (0.00)	0.14 (0.13)	0.0078
Median	0.12	0.11	
Range (Min, Max)	0 1	0 0.52	
Costs			
Mean (Std. Dev)	$313 ($607)	$363 ($733)	0.0087
Median	$139	$159	
Range (Min, Max)	$0 $8,946	$0 $15,936	

Resource Used	STR		2+PPD		P-Value
Total Health Care Utilzation & Costs					
Had ≥ 1 medical visit/encounter (N, %)[a]	1,797	100.00%	5,584	100.00%	---
Number of total encounters					
Mean (Std. Dev)	14.69	(14.00)	16.97	(13.72)	<.0001
Median	11.34		13.13		
Range (Min, Max)	0.56	250	0.96	232.02	
Costs					
Mean (Std. Dev)	$2,959	($4,962)	$3,544	($5,811)	0.0001
Median	$1,916		$2,182		
Range (Min, Max)	$0	$146,367	$0	$103,103	

NOTE: SD = standard deviation.

[a]Estimated over all available follow-up.

[b]Among hospitalized patients.

[c]Among patients with at least one admission over all follow-up.

The multivariate Poisson regression model showed that receiving an STR was associated with a significantly lower risk of hospitalization than receiving the 2+PPD regimen (IRR = 0.8457; $P < 0.001$) (Table 5). When the received regimen type was controlled for, we found that patients were significantly more likely to be hospitalized if they had the following characteristics: a concomitant mental disorder diagnosis (vs. no concomitant mental disorder diagnosis; IRR = 1.2917; $P < 0.001$), a concomitant drug or alcohol abuse diagnosis (vs. no concomitant drug or alcohol abuse diagnosis; IRR = 2.0357; $P < 0.001$), a CCI score greater than 1 (IRR increased with increasing CCI score, from 2.3779 among patients with a CCI between 1 and 2 to 2.6432 among patients with a CCI greater than 3; all $P < 0.001$), were female (vs. male; IRR = 1.1069; $P = 0.003$), or were older than 35 years (vs. younger than 35 years; IRR increased with increasing age, up to 54 years, from 1.2482 among patients aged 35-44 years to 1.555 among patients aged 45-54 years; both $P < 0.1$). Additionally, the likelihood of a hospitalization increased with each additional day of follow-up (IRR = 1.0013; $P < 0.0001$).

Table 5. Predictors of hospitalization, using multivariate Poisson regression, and controlling for treatment cohort.

Specification: Adherence Covariate Excluded	Poisson Count Model		
	Parameter Estimate	Incidence Rate Ratio	P-Value
Received a STR (vs. 2+PPD regimen)	-0.1654	0.8475	0.0001
Female (vs. male)	0.1003	1.1069	0.003
Age (vs. less than 35)			
35 to 44 years	0.1016	1.2482	0.0669
45 to 54 years	0.2217	1.555	<.0001
55+ years	0.4415	1.1056	<.0001
Charlson comorbidity index score (vs. Charlson comorbidity index score less than 1)			
Between 1 and 2	0.8662	2.3779	<.0001
Greater than 2	0.972	2.6432	<.0001
Treatment naïve (vs. treatment experienced)	0.1196	1.127	0.0033
Had a mental disorder diagnosis (vs. no mental disorder diagnosis)	0.256	1.2917	<.0001
Had a drug or alcohol abuse diagnosis (vs. no drug or alcohol abuse diagnosis)	0.7109	2.0357	<.0001
Length of follow-up (in days)	0.0013	1.0013	<.0001

NOTE. 2+PPD = two or more pills per day; STR = once-daily single-tablet regimen.

From the Poisson regression analysis described above, we found the adjusted rate of hospitalization to be significantly lower for patients receiving an STR than for patients receiving 2+PPD (i.e., 39.5 hospitalizations per 100 patients receiving STR vs. 51.2 hospitalizations per 100 patients receiving 2+PPD) (Figure 2). These adjusted hospitalization rates translated to a 23% lower risk of hospitalization among patients receiving an STR, compared with patients receiving 2+PPD.

The percentage of patients with at least one home health visit was significantly lower among patients receiving STR than for patients receiving 2+PPD (Table 4). Between the two cohorts, no differences were observed in the percentage of patients with at least one emergency room, office visit, or laboratory claim. Similarly, no significant differences were found in the number of emergency room, office visits, home health visits, or laboratory claims per month. However, patients who received an STR had significantly lower costs per month associated with inpatient,

home health, laboratory, pharmacy, other, and total health care than patients receiving 2+PPD. Mean (SD) total health care costs per month were $2,959 ($4,962) among patients receiving an STR and $3,544 ($5,811) among patients receiving 2+PPD; thus, patients receiving an STR accrued, on average per month, $585 less than patients receiving 2+PPD ($P < 0.001$). The largest difference in costs between the two cohorts was observed for inpatient admissions ($317 more for patients receiving 2+PPD), followed by pharmacy costs ($187 more for patients receiving 2+PPD).

When monthly health care costs were adjusted for demographic, clinical, and treatment characteristics, patients receiving an STR had monthly total costs averaging $2,947; patients receiving 2+PPD had monthly total costs averaging $3,549 (Figure 3). Thus, patients receiving 2+PPD had $602 more in monthly heath care costs, which corresponded to a 17% reduction in costs associated with STR. Additionally, when monthly health care costs, excluding pharmacy costs, were adjusted for demographic, clinical, and treatment characteristics, patients receiving an STR had monthly total costs averaging $1,370; patients receiving 2+PPD had monthly total costs averaging $1,797. Thus, patients receiving 2+PPD had $427 more in adjusted monthly health care costs, which corresponded to a 23.8% reduction in costs associated with STR.

DISCUSSION

This retrospective database analysis examined adherence to ART regimens among patients with HIV infection, using pharmacy refill dates as the best available proxy for pill-taking behavior. One advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis of the timing in between refills, which also notes the amount of medication dispensed each time. The rate of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should the overall monthly health care utilization and costs.

This analysis largely confirms the previous report from Sax et al.[14]: we found that patients receiving an STR had significantly better adherence rates than patients receiving multiple pills per day. Our other finding was that higher rates of adherence were associated with similar or lower rates of hospitalization, regardless of the regimen; less-than-complete adherence was associated with higher rates of hospitalization and overall costs. Thus, multiple-pill regimens were associated both with lower rates of complete adherence and correspondingly higher overall health care costs. We observed a significantly higher rate of hospitalizations occurring in patients receiving multiple-pill regimens ($P < 0.001$) than in patients receiving an STR. The greater total health care costs were due to differences in both the pharmacy costs of the regimen components as well as the costs of hospitalizations and associated care. Therefore, one implication of our findings is that choosing a multiple-pill regimen for its cost alone might inadvertently result in little to no total health care cost-savings for a payer, given the potential risk of more frequent hospitalizations in patients receiving multiple-pill regimens.

Similar to previous studies [18,19], we found that patients who were adherent to therapy were less likely to be hospitalized. Our data demonstrated similar rates of hospitalizations among patients with the highest levels of complete adherence—at least 95%. This was consistent across

both treatment cohorts. This finding suggests that the differences observed in the rates of hospitalizations across regimens are primarily due to differences in adherence rates between the STR and 2+PPD regimens rather than any concerns for toxicities. This finding also may partially address the potential contribution of channeling bias, a concern with any observational data set. We found that adherent patients on any regimen have similar rates of hospitalization, which suggests that there may not have been a consistent bias to prescribe to more clinically immunosuppressed patients or to patients who were at greater risk for hospitalization due to other factors than a multiple-pill regimen. Furthermore, we found that the outcome of fewer hospitalizations for patients receiving an STR was consistent when we compared hospitalization risks for treatment-naïve patients with hospitalization risks for treatment-experienced patients. In the latter group, the impact of stage of illness prior to treatment would be lessened, given the impact of prior treatment on improving pretreatment immunosuppression, with an STR regimen. Of final note regarding channeling bias, previous analyses of Medicaid beneficiaries with HIV have shown that patients receiving ART are completely non-adherent (i.e., days with no ART supply/coverage on hand) for approximately 14% of their regimen duration regardless of the number of pills in the regimen [20]. This finding suggests that clinicians are not channeling more adherent patients to STRs. Together, these data support the observation that facilitating greater adherence to ART at any stage of illness may result in reducing hospitalization risk.

One follow-up question our study findings raises is whether the observed reduction in hospitalization risk and costs with STR was also due to less prevalent chronic comorbidities in patients prescribed STR. To assess this possibility, we replicated key descriptive analyses on hospitalization rates for patients with no baseline comorbidities as reported by the CCI. We found that the majority (~70%) of both STR and 2+PPD patients had no other CCI comorbidities. Among STR patients with no other comorbidities from the CCI, 13.9% had a

hospitalization compared with 18.3% of 2+PPD patients with no other comorbidities. Further, among STR patients with no comorbidities, 11.4% of adherent patients had a hospitalization compared with 14.7% of non-adherent patients. Similarly, among 2+PPD patients with no comorbidities, 12.4% of adherent patients had a hospitalization compared with 19.7% of non-adherent patients. Results of this sensitivity analysis, combined with the observation that the vast majority of patients in our study had no major comorbidities (from the CCI) requiring other chronic treatment, suggest that the observed association between poorer adherence and higher hospitalization was likely due to reduced ART adherence and not due to reduced adherence with other medications patients were taking.

There were several measurable differences present in the study population at baseline. Our study attempted to control for effects these differences may have had on rates of adherence and hospitalization. We used multivariate regressions to control for patient demographics, treatment characteristics (i.e., treatment naïve vs. experienced, type of ART received, year the ART was received), and clinical characteristics (i.e., CCI score, concomitant mental disorder, drug and alcohol abuse diagnoses). We found a number of factors were associated with an increased risk of poor adherence, including having a CCI score greater than 3; having a drug or alcohol abuse diagnosis; and being treatment experienced. Similarly, having a CCI score greater than 1, or having a concomitant mental disorder or drug or alcohol abuse diagnosis were associated with an increased risk of hospitalization. Nevertheless, after controlling for these factors, we still detected an independent effect of the regimen.

One hypothesis for a plausible mechanism by which these outcomes could occur stems from observations in the SMART study.[21] That study, comparing continuous antiviral treatment versus periodic treatment interruptions, demonstrated that HIV treatment interruptions that were of sufficient length of time to lead to recurrent HIV viremia were associated with a significantly

higher risk of all-cause morbidity and mortality. Our analysis was consistent with those findings: the mean maximum duration of nonadherence was about 3 weeks, which is a sufficient length of time to expect a return of HIV viremia. The SMART study noted that the higher risk of illness was not necessarily proximal to the time of the interruption but was observed for months afterwards. While there are differences between the SMART study design and population and our study population, our findings are consistent with SMART and with what might be expected in a population who periodically are without antivirals for an average time of more than 3 weeks. Of note, short cycle interruptions of 2 days were not associated with virologic rebound in patients receiving the STR that was used in the SMART study [22]. Therefore, our finding that the typical interruptions were much longer than this is supportive of a mechanism that could have resulted in increased patient morbidity.

It is also important to note that patients in this study generally were reasonably adherent to ART, with a mean adherence of just over 80% regardless of the number of pills received per day. This rate of adherence is consistent with other published reports of adherence, although other reports found even higher adherence rates to an STR.[11,12] Furthermore, the difference observed in our study between the STR and 2+PPD regimens (approximately 4%) is consistent with what was observed by Sax et al. of 2.2%.[14] This difference is also consistent with the differences in adherence rates reported when comparing average improvement between once-daily and twice-daily regimens (2.9%).[23] It is important to note that there also were highly nonadherent patients to both the STR and the 2+PPD regimes in this study population, supporting the generalizability of this population.

Of further note, the differences observed in our study were associated with factors that typically are not present during randomized clinical trials. Randomized trials typically actively work for patient adherence to study medications and use study coordinators to regularly monitor

patients to minimize missed doses. In our observational study, these typical adherence supports are not in place; thus, our data may reflect real-world lapses in patient behavior in refilling prescriptions, including partial regimen refills, which would not be observed in clinical trials. While there are concerns about the interpretation of observational data and the determination of causal relationships, it is not clear if a randomized study comparing an STR with a multiple-pill regimen would be able to detect the observed differences unless there was less patient support than is standard in clinical trials.

Our data do not suggest that all patients should be on an STR. There are many factors that weigh in the decision of which regimen is best for any given patient, including pre-existing virologic resistance and tolerability. In our study, the anticipated adherence benefits observed in association with a lower pill burden is relevant but should not be construed as a suggestion that an STR is the ideal choice for the entire population of patients with HIV. Nevertheless, our data do support the continued development of additional STR options, to broaden the number of patients for whom this is an option and the number of subsequent beneficial outcomes.

Our study has several limitations common to observational claims database analyses. Adherence was calculated by using pharmacy refill dates, and we have no measure of actual patient adherence to the prescriptions they filled. However, this measure has been found to be a useful proxy for actual medication adherence.[24] Because we did not randomize patients to the two different treatment regimens, we cannot exclude unmeasured confounding factors that may have influenced our outcomes. Among the most important of these factors in this study was that multiple trials have shown that medication resistance at the time of virologic failure is significantly less common in boosted PI treatments than on other regimens, including nonnucleoside/nucleotide reverse transcriptase inhibitor-based treatments.[25,26] Clinicians could have chosen to prescribe a boosted-PI–containing regimen (all of which contain three or

more pills per day) to their less-adherent patients. It cannot be determined from this data set that these patients would have been more adherent on an STR. Although we attempted to control for some of these variables through the use of multivariable models that included some of these factors (substance abuse and psychiatric diagnoses), residual confounding may remain. In addition, we had no laboratory results from patients and thus cannot confirm the degree of virologic suppression obtained across the regimens.

In our study, a large proportion of HIV-treated individuals (15% of the total HIV-treated population) were excluded from the analysis due to their having received incomplete ART regimens. We did not have sufficient data on these patients to explain why their regimens were incomplete. However, a previous study found that physician medication errors were somewhat common in individuals with HIV, with the most common error occurring with boosted PIs (estimated at 5.3% of patients); such errors may explain some of the incomplete regimens observed in our analysis.[27] Increased adoption of fixed-dose combinations as part of HIV treatment may help to alleviate the issue of incomplete regimens.

During our study period, the only available single-pill ART regimen was coformulated efavirenz/emtricitabine/tenofovir disoproxil fumarate. It is possible that these results would not be generalizable to other one- and multi-pill regimens if other treatments have different efficacy and toxicity profiles. With the recent approval by the Food and Drug Administration of two other STRs (i.e., tenofovir, emtricitabine, and rilpivirine and tenofovir, emtricitabine, elvitegravir and cobicistat), it may eventually be possible to explore the applicability of our observations to other STRs.

In summary, this study supported the results as reported by Sax et al.[14] We found that patients who received ART as a single pill per day were significantly more likely to be highly adherent to therapy than patients who received multiple-pill regimens. This difference in

adherence was associated with a lower risk of hospitalizations: patients with less-than-complete adherence were more likely to be hospitalized. While we acknowledge the limitations associated with any observational study, our data support our finding that the use of an STR may reduce health care costs as well as patient morbidity by decreasing hospitalization rates, which are higher in patients with less-than-complete medication adherence.

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FIGURE LEGENDS

Figure 1. Sample Selection Flow Chart

Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort

Figure 3. Adjusted Monthly Health Care Costs, by Cohort

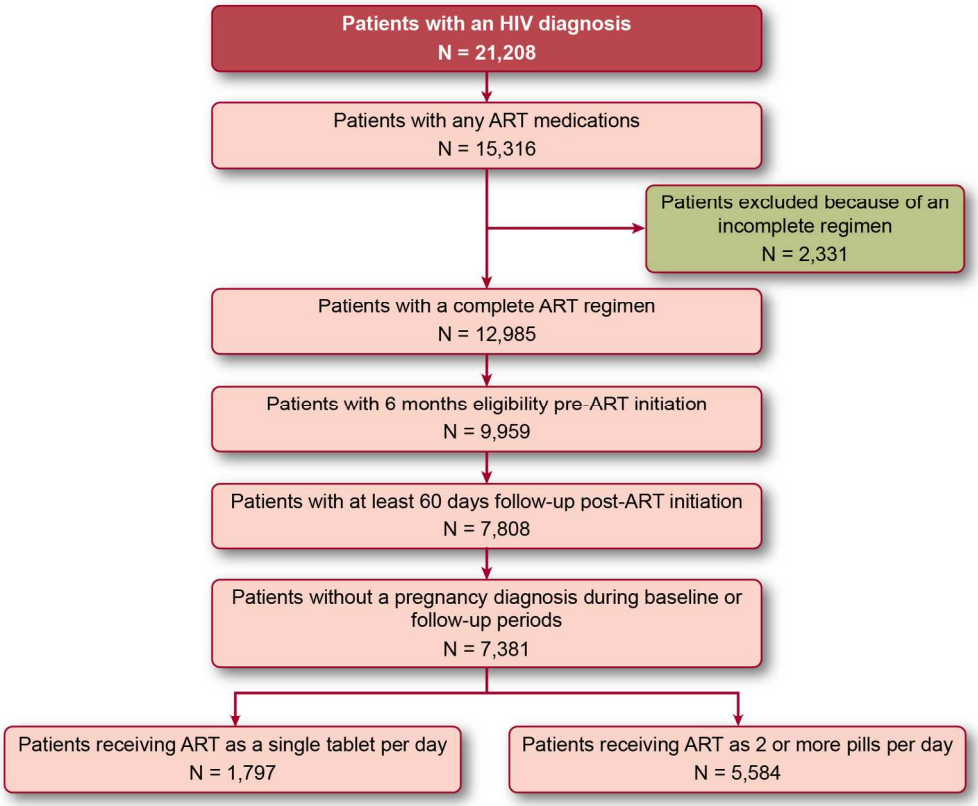

Figure 1. Sample Selection Flow Chart
159x131mm (300 x 300 DPI)

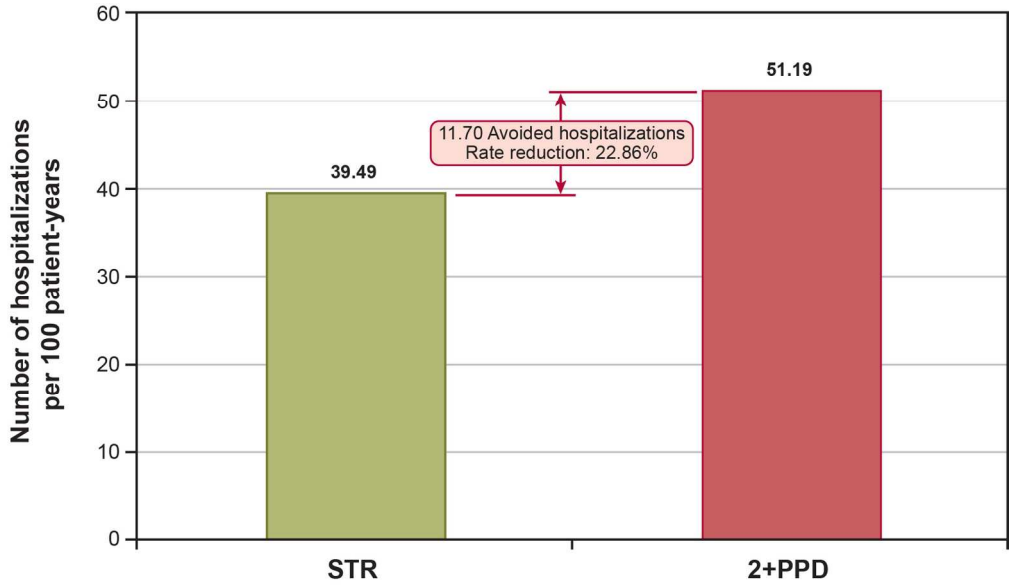

Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort
152x89mm (300 x 300 DPI)

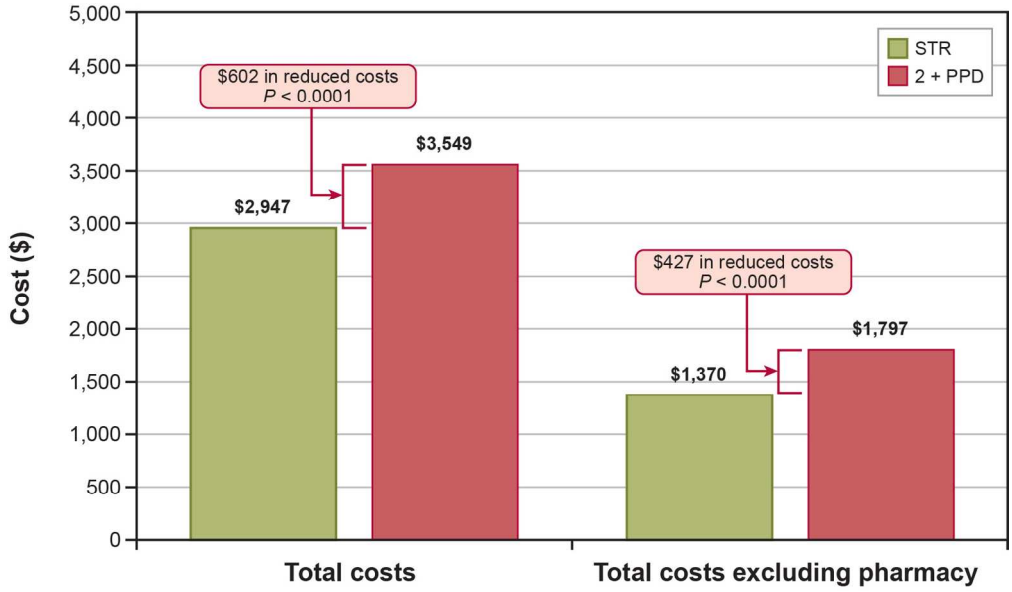

Figure 3. Adjusted Monthly Health Care Costs, by Cohort
152x89mm (300 x 300 DPI)

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Association between Daily Antiretroviral Pill Burden and Treatment Adherence, Hospitalization Risk, and Other Health Care Utilization and Costs in a United States Medicaid Population with HIV

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Association between Daily Antiretroviral Pill Burden and Treatment Adherence, Hospitalization Risk, and Other Health Care Utilization and Costs in a United States Medicaid Population with HIV

Short Title: Antiretroviral Pill Burden in Medicaid Patients

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ABSTRACT

Objectives: Lower pill burden leads to improved antiretroviral therapy (ART) adherence among human immunodeficiency virus (HIV) patients. Simpler dosing regimens have not been widely explored in real-world populations. We retrospectively assessed ART adherence, all-cause hospitalization risk and costs, and other health care utilization and costs in Medicaid enrollees with HIV treated with ART as a once-daily single-tablet regimen (STR) or two or more pills per day (2+PPD).

Design: Patients with an HIV diagnosis from 2005-2009 receiving complete ART (i.e., 2 nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent) for ≥60 days as STR or 2+PPD were selected and followed until the first of (1) discontinuation of the complete ART, (2) loss of enrollment, or (3) end of database. Adherence was measured using the medication possession ratio. Monthly all-cause health care utilization and costs were observed from regimen initiation until follow-up end.

Results: Of the 7,381 patients who met inclusion criteria, 1,797 were treated with STR and 5,584 with 2+PPD. STR patients were significantly more likely to reach 95% adherence and had fewer hospitalizations than 2+PPD patients (both $P<0.01$). STR patients had mean (SD) total monthly costs of $2,959 ($4,962); 2+PPD patients had $3,544 ($5,811) ($P<0.001$). Hospital costs accounted for 53.8% and pharmacy costs accounted for 32.5% of this difference. Multivariate analyses found that STR led to a 23% reduction in hospitalizations and a 17% reduction in overall health care costs. ART adherence appears to be a key mechanism mediating hospitalization risk, as patients with ≥95% adherence (regardless of regimen type) had a lower hospitalization rate compared with <95% adherence.

Conclusions: While it was expected that STR patients would have lower pharmacy costs, we also found that STR patients had fewer hospitalizations and lower hospital costs than 2+PPD patients, resulting in significantly lower total health care costs for STR patients.

ARTICLE SUMMARY

Article Focus

- To assess the association between a single-tablet-per-day ART regimen (STR) and treatment adherence, all-cause hospitalization risk, and other all-cause health care utilization and costs in a large population of Medicaid enrollees in the United States who received treatment for HIV infection

Key Messages

- Patients who received ART as a single pill per day were significantly more likely to be highly adherent (≥ 95%) to therapy than patients who received multiple-pill regimens.
- Improved adherence among patients treated with STR conferred a lower risk of hospitalization.
- The use of an STR may reduce health care costs as well as patient morbidity by decreasing hospitalization rates, which were higher in patients with less-than-complete medication adherence.

Strengths and Limitations of This Study

- This retrospective analysis used pharmacy refill dates as the best available proxy for pill-taking behavior; one advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis the timing in between refills, which also notes the amount of medication dispensed each time.
- Rates of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should measures of overall monthly health care utilization and costs.

- While our prescription claims-based measure of adherence has been found to be a valid proxy for actual medication-taking behavior, we had no measure of actual patient adherence (i.e., daily ingestion/consumption) to the prescriptions they filled.
- Because we did not randomize patients to the two different treatment regimens, we cannot exclude unmeasured confounding factors that may have influenced our outcomes; although we attempted to control for some of these variables through the use of multivariable models that included some of these factors (substance abuse and psychiatric diagnoses), residual confounding may remain.
- We had no laboratory results from patients and thus cannot confirm the degree of virologic suppression obtained across the regimens.

ADMINISTRATIVE STATEMENTS

Protection of Human Subjects

The research organization that conducted this study, RTI Health Solutions, a business unit of RTI International (RTI), holds a Federal-Wide Assurance (FWA #3331 effective until June 17, 2014) from the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) that allows us to review and approve human subjects protocols through our Institutional Review Board (IRB) committees. Since pre-existing, retrospective, de-identified patient data were analyzed for this study, which involved no patient contact or medical interventions and therefore no patient consent forms, the RTI IRB committee approved this study as exempt.

Author Contributions

Calvin Cohen assisted in development of the study design, evaluated and interpreted the study results, and drafted and critically revised the manuscript text. Juliana Meyers and Keith Davis assisted in development of the study design, obtained study funding, conducted all analytic programming and statistical analyses, assisted with evaluation and interpretation of the study

Funding Statement

This study was funded by Gilead Sciences, which is conducting clinical research in and markets current treatments for HIV/AIDS.

Data Sharing

Raw data used for this study are unavailable for public sharing (per terms of the private data use agreement governing original data acquisition).

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INTRODUCTION

The 2012 Department of Health and Human Services guidelines state that there are four preferred regimens for initiating human immunodeficiency virus (HIV) treatment in adults. Furthermore, there are multiple alternatives to these four regimens.[1] Patients and their treating physicians can choose from among these four preferred regimens, using the criteria of greatest efficacy, safety, and simplicity. The latter category is important because regimen simplicity is associated with greater long-term adherence. For example, all four preferred regimens are constructed with a relatively low pill burden (i.e., between one and four tablets per day), and three of the four regimens have once-daily dosing. While randomized trials have compared the components of some of these four regimens with each other, to date no studies compared the four regimens to each other as they are prescribed (i.e., in a real-world setting), given that these study trials have been blinded.[2,3]

Adherence to antiretroviral therapy (ART) is essential for achieving durable clinical outcomes in patients with HIV. Patients with inadequate adherence to ART are at an increased risk for incomplete viral suppression; and unless a new suppressive regimen is quickly constructed to reestablish virologic suppression, viremia is associated with an increased risk of disease progression and death.[4-8] It has been suggested that an ART adherence rate of at least 95% is required to achieve a lower risk of virologic failure, fewer hospital days, and reduced morbidity and mortality in patients with HIV[8-9], although one previous study indicated that viral suppression may be possible at less than 95% adherence.[10] In the past several years, the availability of fixed-dose combinations and agents with prolonged half-lives have simplified pill burden and thus increased regimen adherence.[1,11] Several clinical trials and cohort studies support the conclusion that once-daily single tablet regimens (STR) can lead to significantly improved adherence, patient satisfaction, and virological outcomes.[12-15] For example, among

homeless or marginally housed patients, those receiving an ART regimen composed of a single tablet per day had better virologic outcomes and a 26% increase in adherence than patients receiving other multi-pill regimens.[15] One recently published study analyzing a claims database noted that compared with various multi-pill regimens, a STR was associated with increased adherence (as determined by pharmacy refill data). Furthermore, the increased likelihood of complete adherence was associated with a 25% decrease in the rate of hospitalization.[16]

In this study, we sought to assess how robust these findings were by analyzing similar metrics in a separate data set. The primary objective of this retrospective database analysis was to assess the association between a single-tablet-per-day ART regimen and treatment adherence, all-cause hospitalization risk, and total all-cause health care costs in a large population of Medicaid enrollees in the United States (US) who received treatment for HIV infection. The secondary objective of this study was to examine the association between STR and other types of all-cause health care utilization (emergency department, pharmacy, outpatient, and other service types) and costs.

METHODS

Data for this analysis were taken from the MarketScan Medicaid Multi-State Database, which contains health care claims from approximately 30 million Medicaid enrollees from 11 geographically dispersed states. The database includes patient-level demographics; periods of Medicaid enrollment; primary and secondary diagnoses; and detailed information about hospitalizations and therapeutic procedures, inpatient and outpatient physician services, and prescription drug use. Each medical and pharmacy claim in the database also includes original cost information, which represents direct paid amounts (in US dollars) from Medicaid to providers for each service or prescription. In compliance with the Health Insurance and Portability and Accountability Act of 1996, all data were de-identified to protect the privacy of individual patients, physicians, and hospitals. Because the data were retrospective, pre-existing, and de-identified, RTI International's institutional review board determined that this study met all criteria for exemption from requirements of patient consent.

Patients were selected for inclusion if they received at least one HIV or AIDS diagnosis (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code 042.xx) between June 1, 2006, and December 31, 2009. Patients also were required to have evidence of receipt of a complete ART regimen, defined as two nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent (i.e., another nucleoside/nucleotide reverse transcriptase inhibitor, a nonnucleoside/nucleotide reverse transcriptase inhibitor, a protease inhibitor [PI], a chemokine receptor R5 antagonist, or an integrase inhibitor). The first date of receipt of a complete regimen was termed the index date. ART agents were identified in the claims database by using National Drug Codes associated with relevant generic and brand names. Patients also were required to remain on the complete ART regimen for at least 60 days following their index dates and to have evidence of continuous enrollment in Medicaid during

this period. To assess treatment-naïve versus experienced status and baseline comorbidities, patients were required to have at least 6 months of pre-index date Medicaid enrollment, with enrollment information available from January 1, 2006 (i.e., 6 months before the earliest possible index date).

Patients were grouped into two mutually exclusive cohorts according to the daily pill count of their complete ART regimen. Patients were assigned to the STR cohort if they received an ART regimen consisting of a single tablet (i.e., an STR) at any point during the selection window, regardless of prior or subsequent use of other regimens. At the time of this study, only coformulated tenofovir/emtricitabine/efavirenz was available as an STR. Patients were assigned to the two-or-more-pills-per-day (2+PPD) cohort if they received a regimen consisting of two or more pills per day during the selection window and if they did not receive an STR at any point during that time.

Patients were followed from the start of their complete ART regimen (i.e., after June 1, 2006, the study index date) until the earliest date of regimen discontinuation, disenrollment from the health plan, or the end of the database (i.e., March 31, 2009). Furthermore, patients receiving 2+PPD were allowed to change medications comprising the regimen, provided that the patients continued to receive a combination of agents that could still be classified as a complete 2+PPD regimen. Patients receiving STR were followed for as long as they remained on the STR. Discontinuation was defined as 60 consecutive days in which no refills were observed for any component of the regimen. Females with an ICD-9-CM diagnosis code indicating a pregnancy during the follow-up period were excluded from the analysis because the one available STR is not recommended for pregnant women, and hospitalizations for labor and delivery may have biased results in favor of the STR.

Patient characteristics measured at the index date included age, sex, and ART classes received (i.e., nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside/nucleotide reverse transcriptase inhibitors, PIs, ritonavir boosting therapy, or other therapies). The presence of comorbid medical conditions other than HIV or AIDS were assessed during the 6-month pre-index period, using an established algorithm, the Charlson Comorbidity Index (CCI) score.[17] This score is made up of 17 comorbidities (defined by ICD-9-CM diagnosis and procedure codes), such as myocardial infarction and chronic pulmonary disease, which are weighted to correspond to the severity of the comorbid condition of interest. A higher comorbidity score represents a higher overall comorbidity burden during the pre-index period. Additionally, the incidence of other concomitant mental disorders (ICD-9-CM codes 306.xx through 319.xx) and drug and alcohol abuse (ICD-9-CM codes 292.xx and 303.xx through 305.xx) during the 6-month pre-index period also was assessed.

Medication adherence was assessed using the medication possession ratio (MPR), which has been shown to be the most widely adopted measure (57% of all studies) in published claims-based analyses of medication adherence [18] and has been used in studies of ART adherence among individuals with HIV.[19] The MPR, which is a proxy for refill compliance, generally measures the proportion of the ART exposure period in which supply was maintained for all ART components comprising the regimen. Specifically, MPR was calculated as the number of filled prescription days for all ART regimen components (using the days supplied in the pharmacy claims) divided by the number of days from the first observed prescription in the regimen through the earliest of either the exhaustion of the days supplied of the last observed prescription or the end of follow-up. For each patient in our study, the MPR was calculated over the period in which the patient remained on his or her ART regimen. For patients in the 2+PPD cohort, late refills and resulting days of missing supply for one or more ART components were

all factored against their adherence measurements. For example, patients in the 2+PPD cohort with a supply for only one of the ART components on a given day were considered to have zero adherence for that day. In addition to reporting the mean (standard deviation [SD]) MPR achieved, we also reported the numbers and percentages of patients achieving various adherence thresholds (i.e., MPRs of 1.0-0.95, 0.94-0.90, 0.89-0.85, and 0.84-0.80, corresponding to 100%-95%, 94%-90%, 89%-85%, and 84%-80% adherence, respectively).

To further understand adherence to ART regimens, for each patient in the 2+PPD cohort, complete (i.e., having a complete regimen), partial (i.e., receiving some but not all components of a complete regimen), and no medication days also were assessed. Specifically, we reported the percentage of days that each patient had complete, partial, and no medications available, along with the mean number of days that the patient had complete, partial and no medications. Additionally, we also reported the maximum number of consecutive days the patient had either an incomplete regimen or no medications available.

Hospitalizations were identified from the claims database using relevant place of service codes. Hospitalizations were observed from the index date until the earliest date of regimen discontinuation, end of enrollment in the health plan, or end of the database. The number and percentage of patients with at least one hospitalization were reported, along with the mean (SD) number of hospitalizations, and the mean (SD) number of inpatient days. Furthermore, we compared and reported the number of hospitalizations per 100 patient-years, along with the rate ratios and 95% confidence intervals, for both cohorts as well as by adherence status (at least 95% vs. less than 95%).

For each patient, overall health care utilization and associated costs were aggregated across all encounters, regardless of reason, that were observed during the follow-up period; we reported these costs by average and per-month amounts. The following categories of overall health care

utilization and costs were evaluated and reported: inpatient, emergency department, office visit, home health visit, laboratory service, pharmacy, other outpatient care, and total. For each category of overall health care, the number and percentage of patients, the mean (SD) number of visits per month, and monthly per-patient costs were reported. Additionally, for patients with an inpatient visit, the average number of inpatient days per month among patients with at least one stay during follow-up also was reported. All cost data, which represented payments incurred by the Medicaid system, were standardized at the claim level to 2010 US dollars using the medical care component of the US Consumer Price Index.

All analyses were carried out using SAS (version 9; Cary, North Carolina) statistical software. Descriptive analyses were conducted for all outcome measures and included means and SDs for continuous variables of interest (e.g., MPR) and frequency distributions of categorical variables of interest (e.g., geographic region). All descriptive analyses were stratified by cohort. Health care costs were updated to 2010 US dollars using the medical care component of the consumer price index.

A generalized linear model with a log link and a Poisson distribution was estimated to assess the relationship between the number of pills per day and the number of hospitalizations observed during follow-up. The dependent variable was a count of hospitalizations during exposure to the ART regimen. Additionally, a generalized linear model with a log link and a negative binomial distribution were estimated to assess monthly health care costs, adjusted for the patient and treatment characteristics. The dependent variables were monthly total costs and monthly total costs excluding costs pharmacy costs. For both models, based on previous work by Sax et al. [16], independent variables included the following: treatment regimen received (i.e., STR vs. 2+PPD), age, sex, CCI score, treatment-naïve status, pre-index presence of mental health disorders, pre-index presence of alcohol or drug abuse disorders, length of follow-up (in days,

hospital model only), and whether or not the patient met a 0.95 adherence threshold (cost model only). For the hospital model, incidence rate ratios (IRRs) were reported for all covariates, along with the mean predicted number of hospitalizations for patients receiving an STR versus patients receiving a 2+PPD. For the cost model, adjusted predicted mean costs were reported.

RESULTS

A total of 7,381 patients met the selection criteria (Figure 1). Of these, 5,584 patients (75.7%) received their ART regimen as 2+PPD; 1,797 patients (24.3%) received their ART regimen as a STR. On average, patients were approximately 42 years of age. Approximately 46% of patients were female (Table 1). Across both cohorts, the average CCI score was approximately the same (mean [SD]: 0.67 [1.38] among patients receiving an STR and 0.65 [1.36] among patients receiving 2+PPD). Furthermore, the incidence of concomitant mental disorders and drug and alcohol abuse diagnoses did not vary substantially by cohort. Patients receiving an STR had a mean regimen duration of 348 days; this was approximately 2.8 months shorter than the mean regimen duration of 433 days observed for patients receiving 2+PPD. Forty-seven percent of patients receiving an STR were treatment naïve, compared with 24.5% of patients receiving 2+PPD.

Table 1. Characteristics of the study sample, by cohort.

Characteristic	STR (n = 1,797)		2+PPD (n = 5,584)		*P* Value
Age , mean (SD)	41.6	(10.56)	42.32	(11.37)	0.0137
Gender (N, %)					
Male	945	52.59%	3,063	54.85%	0.1123
Female	852	47.41%	2,521	45.15%	0.1439
Race (N, %)					
White	387	21.54%	1,221	21.87%	0.8893
Black	1,187	66.05%	3,658	65.51%	0.6877
Hispanic	18	1.00%	82	1.47%	0.7844
Other	204	11.35%	621	11.12%	0.7846
Unknown	1	0.06%	2	0.04%	0.8766
Basis of Medicaid Eligibility (N, %)					
Aged	1	0.06%	8	0.14%	0.5634
Disabled	1,089	60.60%	4,071	72.90%	<.0001
Income	583	32.44%	1,159	20.76%	<.0001
Other	58	3.23%	202	3.61%	0.8710
Unknown	65	3.62%	141	2.53%	0.0487
Medicare Eligibility (N, %)					

Characteristic	STR (n = 1,797)		2+PPD (n = 5,584)		*P* Value
Not dually eligible	1,791	99.67%	5,558	99.53%	0.9987
Dually eligible	5	0.28%	24	0.43%	0.6523
Unknown	1	0.05%	2	0.04%	0.9014
Charlson comorbidity index score, mean (SD)	0.67	(1.38)	0.65	(1.36)	0.5919
Concomitant mental health and substance abuse comorbidities (N, %)					
Mental disorders	382	21.26%	1,340	24.00%	0.0456
Drug or alcohol abuse	338	18.81%	856	15.33%	0.0323
Treatment naïve at index (N, %)	853	47.47%	1,366	24.46%	<.0001
Regimen length, mean (SD)	348.17	(259.32)	433.46	(351.50)	<.0001
Index medications (N, %)					
NRTI	1,797	100.00%	5,584	100.00%	---
NNRTI	1,797	100.00%	1,500	26.86%	<.0001
PI	---	---	4,064	72.78%	---
Kaletra at index	---	---	1,633	40.18%	---
Boosted PI at index	---	---	1,664	40.94%	---
Non-boosted PI at index	---	---	767	18.87%	---
PE	---	---	1,712	30.66%	---
Other	---	---	87	1.56%	---

NOTE. 2+PPD = two or more pills per day; NNRTI = nonnucleoside/nucleotide reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PE = pharmacokinetic enhancer; PI = protease inhibitor; SD = standard deviation; STR = once-daily single-tablet regimen.

Patients receiving an STR had significantly better adherence than patients receiving 2+PPD (Table 2). Approximately 25.3% of patients receiving an STR achieved 95% adherence or greater, compared with 17.4% of patients receiving 2+PPD ($P \leq 0.0001$). Mean (SD) MPR was 0.84 (0.14) among patients receiving an STR and 0.80 (0.15) among patients receiving 2+PPD (Table 2). Patients in the 2+PPD cohort received a complete regimen for 80.3% of the follow-up period (mean [SD]: 361.9 [315.0] days), a partial regimen for 5.6% of the follow-up period (mean [SD]: 22.2 [45.6] days), and no available medications for 14.1% of the follow-up period (mean [SD]: 49.4 [57.1] days) (Table 3). Alternatively, patients in the STR cohort received a complete regimen for 84.4% of the follow-up period (mean [SD]: 299.4 [234.6] days) and no available medications for 15.6% of the follow-up period (mean [SD]: 48.8 [54.2] days), which

was a similar percentage of days as patients receiving 2+PPD. Patients receiving an STR had, on average, a maximum of 19.5 (SD: 15.9) consecutive days without a complete regimen (i.e., either a partial regimen or no medications available); patients receiving 2+PPD had, on average, a maximum of 23.9 (SD: 16.7) consecutive days without a complete regimen.

Table 2. Adherence to antiretroviral therapy, by cohort.

Cohort	Number of Patients	Mean (SD) MPR	MPR/Persistency Ratio (N, %)				
			<0.8	0.8 - <0.85	0.85 - <0.9	0.9 - <0.95	0.95 - 1
STR	1,797	0.84 (0.14)	537 29.88%	178 9.91%	243 13.52%	385 21.42%	454 25.26%
2+PPD	5,584	0.80 (0.15)	2,255 40.38%	621 11.12%	779 13.95%	957 17.14%	972 17.41%
Overall	7,381	0.81 (0.15)	2,792 37.83%	799 10.83%	1,022 13.85%	1,342 18.18%	1,426 19.32%
P-Value (1 vs. 2)		<.0001	<.0001	0.1491	0.6477	<.0001	<.0001

NOTE. 2+PPD = two or more pills per day; MPR = medication possession ratio; SD = standard deviation; STR = once-daily single-tablet regimen.

Table 3. Summary of incomplete adherence, by cohort.

Adherence Characteristic	STR (n = 1,797)	2+PPD (n = 5,584)	*P* Value
Percentage of days with complete adherence	84.42%	80.37%	<.0001
Percentage of days with partial adherence	---	5.56%	---
Percentage of days with no ART medications	15.58%	14.07%	0.0356
Complete adherence days, mean (SD)	299.36 (234.56)	361.87 (315.03)	<.0001
Partial adherence days, mean (SD)	---	22.24 (45.58)	---
Days with no medication available, mean (SD)	48.81 (54.24)	49.35 (57.11)	0.0356
Total follow-up duration, mean (SD)	348.17 (259.31)	433.46 (351.50)	<.0001
Maximum consecutive gap in therapy,[a] mean (SD)	19.48 (15.89)	23.92 (16.67)	<.0001

NOTE. 2+PPD = two or more pills per day; ART = antiretroviral therapy; SD = standard deviation; STR = once-daily single-tablet regimen.

[a] Represents either days with a partial regimen or days with no medications.

Among patients receiving an STR, 21.0% had at least one hospitalization, compared with 24.4% of patients receiving 2+PPD (*P* = 0.003) (Table 4). Among patients with a hospitalization, patients receiving an STR had numerically similar, although significantly fewer, hospitalizations over all available follow-up, when compared with patients receiving 2+PPD (mean [SD]: 1.9

311 [1.6] among patients receiving an STR vs. 2.1 [2.2] among patients receiving 2+PPD;

312 $P = 0.001$).

313 **Table 4. All-cause average per patient health care utilization and costs, by cohort.**

Resource Used	STR (n = 1,797)		2+PPD (n = 5,584)		P-Value
Hospitalizations					
Had ≥ 1 hospital admission (N, %)[a]	378	21.04%	1,365	24.44%	0.0031
Number of hospitalizations (over all follow-up) [b] mean (SD)	1.88	(1.59)	2.1	(2.23)	0.0012
Inpatient days (over all follow-up)[b] mean (SD)	9.99	(12.33)	12.33	(18.90)	0.0228
Costs per month, mean (SD)	$834	($4,480)	$1,152	($5,212)	0.0203
Emergency Room (ER)					
Had ≥ 1 ER visit (N, %)[a]	903	50.25%	2,749	49.23%	0.4517
Number of visits per month, mean (SD)	0.97	(3.00)	1.01	(2.99)	0.6107
Costs per month, mean (SD)	$45	($160)	$46	($135)	0.873
Office Visits (Primary Care) (N, %)					
Had ≥ 1 office visit (N, %)[a]	1,509	83.97%	4,699	84.15%	0.8576
Number of visits per month, mean (SD)	1.52	(3.00)	1.43	(2.19)	0.1669
Costs per month, mean (SD)	$75	($229)	$70	($291)	0.5087
Home Health (N, %)					
Had ≥ 1 home health visit (N, %)[a]	504	28.05%	1,861	33.33%	<.0001
Number of visits per month, mean (SD)	0.64	(3.00)	0.79	(3.16)	0.0625
Costs per month, mean (SD)	$47	($198)	$88	($642)	0.007
Laboratory (N, %)					
Had ≥ 1 lab order (N, %)[a]	1,168	65.00%	3,530	63.22%	0.1722
Number of lab tests per month, mean (SD)	1.24	(2.00)	1.19	(1.69)	0.2962
Costs per month, mean (SD)	$52	($94)	$46	($120)	0.0401
Pharmacy (N, %)					
Had ≥ 1 pharmacy claim (N, %)[a]	1,797	100.00%	5,584	100.00%	---
Number of prescriptions per month, mean (SD)	4.99	(4.00)	6.73	(4.05)	<.0001
Costs per month, mean (SD)	$1,593	($1,105)	$1,779	($1,307)	<.0001
OP/ancillary (N, %)					
Had ≥ 1 other OP/ancillary (N, %)[a]	1,754	97.61%	5,469	97.94%	0.3957
Number of visits per month, mean (SD)	0.15	(0.00)	0.14	(0.13)	0.0078
Costs per month, mean (SD)	$313	($607)	$363	($733)	0.0087
Total Health Care Utilzation and Costs					
Had ≥ 1 medical visit/encounter (N, %)[a]	1,797	100.00%	5,584	100.00%	---
Number of total encounters per month, mean (SD)	14.69	(14.00)	16.97	(13.72)	<.0001
Costs per month, mean (SD)	$2,959	($4,962)	$3,544	($5,811)	0.0001

314 NOTE: SD = standard deviation.

[a]Estimated over all available follow-up.

[b]Among hospitalized patients.

The multivariate Poisson regression model showed that receiving an STR was associated with a significantly lower hospitalization rate than receiving the 2+PPD regimen (IRR = 0.8457; $P < 0.001$) (Table 5). When the received regimen type was controlled for, we found that patients were significantly more likely to be hospitalized if they had the following characteristics: a concomitant mental disorder diagnosis (vs. no concomitant mental disorder diagnosis; IRR = 1.2917; $P < 0.001$), a concomitant drug or alcohol abuse diagnosis (vs. no concomitant drug or alcohol abuse diagnosis; IRR = 2.0357; $P < 0.001$), a CCI score greater than 1 (IRR increased with increasing CCI score, from 2.3779 among patients with a CCI between 1 and 2 to 2.6432 among patients with a CCI greater than 3; all $P < 0.001$), were female (vs. male; IRR = 1.1069; $P = 0.003$), or were older than 35 years (vs. younger than 35 years; IRR increased with increasing age, up to 54 years, from 1.2482 among patients aged 35-44 years to 1.555 among patients aged 45-54 years; both $P < 0.1$). Additionally, the likelihood of a hospitalization increased slightly with each additional day of follow-up (IRR = 1.0013; $P < 0.0001$). Finally, being treatment naïve prior to index was predictive of an approximately 13% higher hospitalization rate as compared with being treatment experienced (IRR = 1.1270; $P = 0.0033$).

Table 5. Predictors of hospitalization, using multivariate Poisson regression, and controlling for treatment cohort.

	Poisson Count Model		
Specification: Adherence Covariate Excluded	**Parameter Estimate**	**Incidence Rate Ratio**	**P-Value**
Received a STR (vs. 2+PPD regimen)	-0.1654	0.8475	0.0001
Female (vs. male)	0.1003	1.1069	0.003
Age (vs. less than 35)			
35 to 44 years	0.1016	1.2482	0.0669

Specification: Adherence Covariate Excluded	Poisson Count Model		
	Parameter Estimate	Incidence Rate Ratio	P-Value
45 to 54 years	0.2217	1.5550	<.0001
55+ years	0.4415	1.1056	<.0001
Charlson comorbidity index score (vs. Charlson comorbidity index score less than 1)			
Between 1 and 2	0.8662	2.3779	<.0001
Greater than 2	0.972	2.6432	<.0001
Treatment naïve (vs. treatment experienced)	0.1196	1.1270	0.0033
Had a mental disorder diagnosis (vs. no mental disorder diagnosis)	0.256	1.2917	<.0001
Had a drug or alcohol abuse diagnosis (vs. no drug or alcohol abuse diagnosis)	0.7109	2.0357	<.0001
Length of follow-up (in days)	0.0013	1.0013	<.0001

NOTE. 2+PPD = two or more pills per day; STR = once-daily single-tablet regimen.

From the Poisson regression analysis described above, we found the adjusted rate of hospitalization to be significantly lower for patients receiving an STR than for patients receiving 2+PPD (i.e., 39.5 hospitalizations per 100 patient-years for patients receiving STR vs. 51.2 hospitalizations per 100 patient-years for those receiving 2+PPD) (Figure 2). These adjusted hospitalization rates translated to a 23% lower risk of hospitalization among patients receiving an STR, compared with patients receiving 2+PPD. As shown in Figure 3, adherence status seems to be a key mechanism mediating hospitalization risk as patients with at least 95% adherence (regardless of regimen type) had a statistically significant lower hospitalization rate compared to patients with less than 95% adherence. Improved adherence among patients treated with STR therefore appears to confer a lower risk of hospitalization and associated costs.

Examining other types of health care utilization, the percentage of patients with at least one home health visit was significantly lower among patients receiving STR than for patients receiving 2+PPD (Table 4). Between the two cohorts, no differences were observed in the percentage of patients with at least one emergency room, office visit, or laboratory claim.

Similarly, no significant differences were found in the number of emergency room, office visits, home health visits, or laboratory claims per month. However, patients who received an STR had significantly lower costs per month associated with inpatient, home health, laboratory, pharmacy, other, and total health care than patients receiving 2+PPD. Mean (SD) total health care costs per month were $2,959 ($4,962) among patients receiving an STR and $3,544 ($5,811) among patients receiving 2+PPD; thus, patients receiving an STR accrued, on average per month, $585 less than patients receiving 2+PPD ($P < 0.001$). The largest difference in costs between the two cohorts was observed for inpatient admissions ($317 more for patients receiving 2+PPD), followed by pharmacy costs ($187 more for patients receiving 2+PPD).

When monthly health care costs were adjusted for demographic, clinical, and treatment characteristics, patients receiving an STR had monthly total costs averaging $2,947; patients receiving 2+PPD had monthly total costs averaging $3,549 (Figure 4). Thus, patients receiving 2+PPD had $602 more in monthly heath care costs, which corresponded to a 17% reduction in costs associated with STR. Additionally, when monthly health care costs, excluding pharmacy costs, were adjusted for demographic, clinical, and treatment characteristics, patients receiving an STR had monthly total costs averaging $1,370; patients receiving 2+PPD had monthly total costs averaging $1,797. Thus, patients receiving 2+PPD had $427 more in adjusted monthly health care costs, which corresponded to a 23.8% reduction in costs associated with STR.

DISCUSSION

This retrospective database analysis examined adherence to ART regimens among patients with HIV infection, using pharmacy refill dates as the best available proxy for pill-taking behavior. One advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis of the timing in between refills, which also notes the amount of medication dispensed each time. The rate of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should the overall monthly health care utilization and costs.

This analysis largely confirms the previous report from Sax et al.[16]: we found that patients receiving an STR had significantly better adherence rates than patients receiving multiple pills per day. Our other finding was that higher rates of adherence were associated with similar or lower rates of hospitalization, regardless of the regimen; less-than-complete adherence was associated with higher rates of hospitalization and overall costs. Thus, multiple-pill regimens were associated both with lower rates of complete adherence and correspondingly higher overall health care costs. We observed a significantly higher rate of hospitalizations occurring in patients receiving multiple-pill regimens ($P < 0.001$) than in patients receiving an STR. The greater total health care costs were due to differences in both the pharmacy costs of the regimen components as well as the costs of hospitalizations and associated care. Therefore, one implication of our findings is that choosing a multiple-pill regimen for its cost alone might inadvertently result in little to no total health care cost-savings for a payer, given the potential risk of more frequent hospitalizations in patients receiving multiple-pill regimens.

Similar to previous studies [20,21], we found that patients who were adherent to therapy were less likely to be hospitalized. Our data demonstrated similar rates of hospitalizations among patients with the highest levels of complete adherence—at least 95%. This was consistent across

both treatment cohorts. This finding suggests that the differences observed in the rates of hospitalizations across regimens are primarily due to differences in adherence rates between the STR and 2+PPD regimens rather than any concerns for toxicities. This finding also may partially address the potential contribution of channeling bias, a concern with any observational data set. We found that adherent patients on any regimen have similar rates of hospitalization, which suggests that there may not have been a consistent bias to prescribe to more clinically immunosuppressed patients or to patients who were at greater risk for hospitalization due to other factors than a multiple-pill regimen. Furthermore, we found that the outcome of fewer hospitalizations for patients receiving an STR was consistent when we compared hospitalization risks for treatment-naïve patients with hospitalization risks for treatment-experienced patients. In the latter group, the impact of stage of illness prior to treatment would be lessened, given the impact of prior treatment on improving pretreatment immunosuppression, with an STR regimen. Of final note regarding channeling bias, previous analyses of Medicaid beneficiaries with HIV have shown that patients receiving ART are completely non-adherent (i.e., days with no ART supply/coverage on hand) for approximately 14% of their regimen duration regardless of the number of pills in the regimen [22]. This finding suggests that clinicians are not channeling more adherent patients to STRs. Together, these data support the observation that facilitating greater adherence to ART at any stage of illness may result in reducing hospitalization risk.

One follow-up question our study findings raises is whether the observed reduction in hospitalization risk and costs with STR was also due to less prevalent chronic comorbidities in patients prescribed STR. To assess this possibility, we replicated key descriptive analyses on hospitalization rates for patients with no baseline comorbidities as reported by the CCI. We found that the majority (~70%) of both STR and 2+PPD patients had no other CCI comorbidities. Among STR patients with no other comorbidities from the CCI, 13.9% had a

hospitalization compared with 18.3% of 2+PPD patients with no other comorbidities. Further, among STR patients with no comorbidities, 11.4% of adherent patients had a hospitalization compared with 14.7% of non-adherent patients. Similarly, among 2+PPD patients with no comorbidities, 12.4% of adherent patients had a hospitalization compared with 19.7% of non-adherent patients. Results of this sensitivity analysis, combined with the observation that the vast majority of patients in our study had no major comorbidities (from the CCI) requiring other chronic treatment, suggest that the observed association between poorer adherence and higher hospitalization was likely due to reduced ART adherence and not due to reduced adherence with other medications patients were taking.

There were several measurable differences present in the study population at baseline. Our study attempted to control for effects these differences may have had on rates of hospitalization between STR and 2+PPD patients. We used multivariate regressions to control for patient demographics, treatment characteristics (i.e., treatment naïve vs. experienced, type of ART received), and clinical characteristics (i.e., CCI score, concomitant mental disorder, drug and alcohol abuse diagnoses). We found that a number of factors were associated with an increased risk of hospitalization independent of treatment regimen, including having a CCI score greater than 1; having a concomitant drug or alcohol abuse diagnosis; having a concomitant mental health disorder; being female and of older age; and being treatment naive.

Even after controlling for the factors noted above, we still detected an independent association of regimen type with hospitalization rates and, in fact, observed an increase in the apparent protective effect of STR based on the predicted, adjusted hospitalization rate derived from the Poisson model (39.5 per 100 patients in the STR group vs. 51.2 per 100 patients in the 2+PPD group; see Figure 2). One possible explanation for this difference is that the Poisson model corrected a substantial imbalance in the proportion of patients who were treatment naïve

at index (47.5% of STR patients vs. 24.5% of 2+PPD patients). Lack of or naivety to ART exposure has been shown in some studies to be a positive predictor of hospitalization in HIV patients [23], perhaps because approximately one-third of HIV patients wait to seek care until their disease has progressed to the point that they need acute treatment. [24, 25] As noted in a recent study by Metsch et al. [26], these patients often obtain initial care in emergency departments and hospital inpatient wards, and they tend not to persistent with follow-up outpatient care. This pattern of treatment induction may further increase their risk of infection and re-hospitalization in the short-term. Because being treatment naïve was shown in our data to be predictive of hospitalization, the Poisson model's adjustment for the overrepresentation of treatment naivety in the STR group may therefore have resulted in the larger difference between STR and 2+PPD in hospitalizations than observed in the crude, unadjusted comparison.

One hypothesis for a plausible mechanism by which the outcomes observed in our study could occur stems from observations in the SMART study.[27] That study, comparing continuous antiviral treatment versus periodic treatment interruptions, demonstrated that HIV treatment interruptions that were of sufficient length of time to lead to recurrent HIV viremia were associated with a significantly higher risk of all-cause morbidity and mortality. Our analysis was consistent with those findings: the mean maximum duration of nonadherence was about 3 weeks, which is a sufficient length of time to expect a return of HIV viremia. The SMART study noted that the higher risk of illness was not necessarily proximal to the time of the interruption but was observed for months afterwards. While there are differences between the SMART study design and population and our study population, our findings are consistent with SMART and with what might be expected in a population who periodically are without antivirals for an average time of more than 3 weeks. Of note, short cycle interruptions of 2 days were not associated with virologic rebound in patients receiving the STR that was used in the SMART

study [28]. Therefore, our finding that the typical interruptions were much longer than this is supportive of a mechanism that could have resulted in increased patient morbidity.

It is also important to note that patients in this study generally were reasonably adherent to ART, with a mean adherence of just over 80% regardless of the number of pills received per day. This rate of adherence is consistent with other published reports of adherence, although other reports found even higher adherence rates to an STR.[13,14] Furthermore, the difference observed in our study between the STR and 2+PPD regimens (approximately 4%) is consistent with what was observed by Sax et al. of 2.2%.[16] This difference is also consistent with the differences in adherence rates reported when comparing average improvement between once-daily and twice-daily regimens (2.9%).[29] It is important to note that there also were highly nonadherent patients to both the STR and the 2+PPD regimes in this study population, supporting the generalizability of this population.

Of further note, the differences observed in our study were associated with factors that typically are not present during randomized clinical trials. Randomized trials typically actively work for patient adherence to study medications and use study coordinators to regularly monitor patients to minimize missed doses. In our observational study, these typical adherence supports are not in place; thus, our data may reflect real-world lapses in patient behavior in refilling prescriptions, including partial regimen refills, which would not be observed in clinical trials. While there are concerns about the interpretation of observational data and the determination of causal relationships, it is not clear if a randomized study comparing an STR with a multiple-pill regimen would be able to detect the observed differences unless there was less patient support than is standard in clinical trials.

Our data do not suggest that all patients should be on an STR. There are many factors that weigh in the decision of which regimen is best for any given patient, including pre-existing

virologic resistance and tolerability. In our study, the anticipated adherence benefits observed in association with a lower pill burden is relevant but should not be construed as a suggestion that an STR is the ideal choice for the entire population of patients with HIV. Nevertheless, our data do support the continued development of additional STR options, to broaden the number of patients for whom this is an option and the number of subsequent beneficial outcomes.

Our study has several limitations common to observational claims database analyses. Adherence was calculated by using pharmacy refill dates, and we have no measure of actual patient adherence to the prescriptions they filled. However, this measure has been found to be a useful proxy for actual medication adherence.[30] Because we did not randomize patients to the two different treatment regimens, we cannot exclude unmeasured confounding factors that may have influenced our outcomes. Among the most important of these factors in this study was that multiple trials have shown that medication resistance at the time of virologic failure is significantly less common in boosted PI treatments than on other regimens, including nonnucleoside/nucleotide reverse transcriptase inhibitor-based treatments.[31,32] Clinicians could have chosen to prescribe a boosted-PI–containing regimen (all of which contain three or more pills per day) to their less-adherent patients. It cannot be determined from this data set that these patients would have been more adherent on an STR. Although we attempted to control for some of these variables through the use of multivariable models that included some of these factors (substance abuse and psychiatric diagnoses), residual confounding may remain. In addition, we had no laboratory results from patients and thus cannot confirm the degree of virologic suppression obtained across the regimens. Finally, although our data include information from the Medicaid programs in 11 states, the authors were blinded (as per data privacy rules) as to which specific states are captured. Although the database's documentation

suggests that the states are geographically dispersed, we cannot assert that our findings would be fully representative of the general Medicaid population in the US.

In our study, a large proportion of HIV-treated individuals (15% of the total HIV-treated population) were excluded from the analysis due to their having received incomplete ART regimens. We did not have sufficient data on these patients to explain why their regimens were incomplete. However, a previous study found that physician medication errors were somewhat common in individuals with HIV, with the most common error occurring with boosted PIs (estimated at 5.3% of patients); such errors may explain some of the incomplete regimens observed in our analysis.[33] Increased adoption of fixed-dose combinations as part of HIV treatment may help to alleviate the issue of incomplete regimens.

During our study period, the only available single-pill ART regimen was coformulated efavirenz/emtricitabine/tenofovir disoproxil fumarate. It is possible that these results would not be generalizable to other one- and multi-pill regimens if other treatments have different efficacy and toxicity profiles. With the recent approval by the Food and Drug Administration of two other STRs (i.e., tenofovir, emtricitabine, and rilpivirine and tenofovir, emtricitabine, elvitegravir and cobicistat), it may eventually be possible to explore the applicability of our observations to other STRs.

In summary, this study supported the results as reported by Sax et al.[16] We found that patients who received ART as a single pill per day were significantly more likely to be highly adherent to therapy than patients who received multiple-pill regimens. This difference in adherence was associated with a lower risk of hospitalizations: patients with less-than-complete adherence were more likely to be hospitalized. While we acknowledge the limitations associated with any observational study, our data support our finding that the use of an STR may reduce

health care costs as well as patient morbidity by decreasing hospitalization rates, which are higher in patients with less-than-complete medication adherence.

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FIGURE LEGENDS

Figure 1. Sample Selection Flow Chart

Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort

Figure 3. Hospitalizations per 100 Patient-Years, by Cohort and Adherence

Figure 4. Adjusted Monthly Health Care Costs, by Cohort

Association between Daily Antiretroviral Pill Burden ~~Effects on~~and ~~Medication~~ Treatment Adherence, Hospitalization Risk, and Other Health Care Utilization and Costs in a United States Medicaid Population with HIV

Short Title: Antiretroviral Pill Burden in Medicaid Patients

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ABSTRACT

Objectives: Lower pill burden leads to improved ~~adherence to~~ antiretroviral therapy (ART) adherence among human immunodeficiency virus (HIV) patients. Simpler dosing regimens have not been widely explored in real-world populations. We retrospectively assessed ART adherence, all-cause hospitalization risk and costs, and other health care utilization and costs in Medicaid enrollees with HIV treated with ART as a once-daily single-tablet regimen (STR) or two or more pills per day (2+PPD).

Design: Patients with an HIV diagnosis from 2005-2009 receiving complete ART (i.e., 2 nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent) for ≥60 days ~~or more~~ as STR or 2+PPD were selected and followed until the first of (1) discontinuation of the complete ART, (2) loss of ~~continuous~~ enrollment, or (3) end of ~~the~~ database. Adherence was measured using the medication possession ratio. Monthly all-cause health care utilization and costs were observed from regimen initiation until ~~discontinuation~~ follow-up end ~~and reported overall and by care setting (inpatient, emergency department, office, pharmacy, other). To assess predictors of hospitalization, Poisson models, counting the number of hospitalizations and covariates for demographics, comorbidities, and ART-naïve status, were estimated.~~

Results: Of the 7,381 patients who met inclusion criteria, 1,797 were treated with STR and 5,584 with 2+PPD. STR patients were significantly more likely to reach ~~a~~ 95% adherence ~~threshold~~ and had fewer hospitalizations than 2+PPD patients (both~~:~~ P ~~<~~ 0.01). STR patients had mean (SD) total monthly costs of $2,959 ($4,962); 2+PPD patients had $3,544 ($5,811) (P ~~<~~ 0.001). Hospital costs accounted for 53.8% and pharmacy costs accounted for 32.5% of this difference. Multivariate analyses found that STR ~~treatment~~ led to a 23% reduction in hospitalizations and a 17% reduction in overall health care costs. ART adherence appears to be a

Comment [k1]: Text eliminated to stay within 300 word limit of abstract after requested changes/additions by reviewer. Other minor edits made throughout abstract to comply with word count.

key mechanism mediating hospitalization risk, as patients with ≥95% adherence (regardless of regimen type) had a lower hospitalization rate compared with <95% adherence.

Conclusions: While it was expected that STR patients would have lower pharmacy costs, we also found that STR patients had fewer hospitalizations and lower hospital costs than 2+PPD patients, resulting in significantly lower total health care costs for STR patients.

ARTICLE SUMMARY

Article Focus

- To assess the ~~effect of~~association between a single-tablet-per-day ART regimen (STR) ~~on~~ and treatment adherence ~~and~~ , all-cause hospitalization risk, and other all-cause health care utilization and costs in a large population of Medicaid enrollees in the United States who received treatment for HIV infection

Key Messages

- Patients who received ART as a single pill per day were significantly more likely to be highly adherent (≥ 95%) to therapy than patients who received multiple-pill regimens.
- Improved adherence among patients treated with STR conferred a lower risk of hospitalization.
- The use of an STR may reduce health care costs as well as patient morbidity by decreasing hospitalization rates, which were higher in patients with less-than-complete medication adherence.

Strengths and Limitations of This Study

- This retrospective analysis used pharmacy refill dates as the best available proxy for pill-taking behavior; one advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis the timing in between refills, which also notes the amount of medication dispensed each time.
- Rates of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should measures of overall monthly health care utilization and costs.

- While our prescription claims-based measure of adherence has been found to be a valid proxy for actual medication-taking behavior, we had no measure of actual patient adherence (i.e., daily ingestion/consumption) to the prescriptions they filled.
- Because we did not randomize patients to the two different treatment regimens, we cannot exclude unmeasured confounding factors that may have influenced our outcomes; although we attempted to control for some of these variables through the use of multivariable models that included some of these factors (substance abuse and psychiatric diagnoses), residual confounding may remain.
- We had no laboratory results from patients and thus cannot confirm the degree of virologic suppression obtained across the regimens.

ADMINISTRATIVE STATEMENTS

Protection of Human Subjects

The research organization that conducted this study, RTI Health Solutions, a business unit of RTI International (RTI), holds a Federal-Wide Assurance (FWA #3331 effective until June 17, 2014) from the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) that allows us to review and approve human subjects protocols through our Institutional Review Board (IRB) committees. Since pre-existing, retrospective, de-identified patient data were analyzed for this study, which involved no patient contact or medical interventions and therefore no patient consent forms, the RTI IRB committee approved this study as exempt.

Author Contributions

Calvin Cohen assisted in development of the study design, evaluated and interpreted the study results, and drafted and critically revised the manuscript text. Juliana Meyers and Keith Davis assisted in development of the study design, obtained study funding, conducted all analytic programming and statistical analyses, assisted with evaluation and interpretation of the study

Funding Statement

This study was funded by Gilead Sciences, which is conducting clinical research in and markets current treatments for HIV/AIDS.

Data Sharing

Raw data used for this study are unavailable for public sharing (per terms of the private data use agreement governing original data acquisition).

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INTRODUCTION

The 2012 Department of Health and Human Services guidelines state that there are four preferred regimens for initiating human immunodeficiency virus (HIV) treatment in adults. Furthermore, there are multiple alternatives to these four regimens.[1] Patients and their treating physicians can choose from among these four preferred regimens, using the criteria of greatest efficacy, safety, and simplicity. The latter category is important because regimen simplicity is associated with greater long-term adherence. For example, all four preferred regimens are constructed with a relatively low pill burden (i.e., between one and four tablets per day), and three of the four regimens have once-daily dosing. While randomized trials have compared the components of some of these four regimens with each other, to date no studies compared the four regimens to each other as they are prescribed (i.e., in a real-world setting), given that these study trials have been blinded.[2,3]

Adherence to antiretroviral therapy (ART) is essential for achieving durable clinical outcomes in patients with HIV. Patients with inadequate adherence to ART are at an increased risk for incomplete viral suppression; and unless a new suppressive regimen is quickly constructed to reestablish virologic suppression, viremia is associated with an increased risk of disease progression~~,~~ and death.[4-8] It has been suggested that an ART adherence rate of at least 95% is required to achieve a lower risk of virologic failure, fewer hospital days, and reduced morbidity and mortality in patients with HIV[8-9], although one previous study indicated that viral suppression may be possible at less than 95% adherence.[10] In the past several years, the availability of fixed-dose combinations and agents with prolonged half-lives have simplified pill burden and thus increased regimen adherence.[1,~~9~~11] Several clinical trials and cohort studies support the conclusion that once-daily single tablet regimens (STR) can lead to significantly improved adherence, patient satisfaction, and virological outcomes.[~~10-13~~12-15] For example,

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among homeless or marginally housed patients, those receiving an ART regimen composed of a single tablet per day had better virologic outcomes and a 26% increase in adherence than patients receiving other multi-pill regimens.[~~13~~15] One recently published study analyzing a claims database noted that compared with various multi-pill regimens, a STR was associated with increased adherence (as determined by pharmacy refill data). Furthermore, the increased likelihood of complete adherence was associated with a 25% decrease in the rate of hospitalization.[~~14~~16]

In this study, we sought to assess how robust these findings were by analyzing similar metrics in a separate data set. The primary objective of this retrospective database analysis was to assess the ~~effect~~ association between~~of~~ a single-tablet-per-day ART regimen and~~on~~ treatment adherence, ~~and~~ all-cause hospitalization risk, and total all-cause health care costs ~~-~~in a large population of Medicaid enrollees in the United States (US) who received treatment for HIV infection. The secondary objective of this study was to examine the association between STR and other types of all-cause health care utilization (emergency department, pharmacy, outpatient, and other service types) and costs.

METHODS

Data for this analysis were taken from the MarketScan Medicaid Multi-State Database, which contains health care claims from approximately 30 million Medicaid enrollees from 11 geographically dispersed states. The database includes patient-level demographics; periods of Medicaid enrollment; primary and secondary diagnoses; and detailed information about hospitalizations and therapeutic procedures, inpatient and outpatient physician services, and prescription drug use. Each medical and pharmacy claim in the database also includes original cost information, which represents direct paid amounts (in US dollars) from Medicaid to providers for each service or prescription. In compliance with the Health Insurance and Portability and Accountability Act of 1996, all data were de-identified to protect the privacy of individual patients, physicians, and hospitals. Because the data were retrospective, pre-existing, and de-identified, RTI International's institutional review board determined that this study met all criteria for exemption from requirements of patient consent.

Patients were selected for inclusion if they received at least one HIV or AIDS diagnosis (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code 042.xx) between June 1, 2006, and December 31, 2009. Patients also were required to have evidence of receipt of a complete ART regimen, defined as two nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent (i.e., another nucleoside/nucleotide reverse transcriptase inhibitor, a nonnucleoside/nucleotide reverse transcriptase inhibitor, a protease inhibitor [PI], a chemokine receptor R5 antagonist, or an integrase inhibitor). The first date of receipt of a complete regimen was termed the index date. ART agents were identified in the claims database by using National Drug Codes associated with relevant generic and brand names. Patients also were required to remain on the complete ART regimen for at least 60 days following their index dates and to have evidence of continuous enrollment in Medicaid during

this period. To assess treatment-naïve versus experienced status and baseline comorbidities, patients were required to have at least 6 months of pre-index date Medicaid enrollment, with enrollment information available from January 1, 2006 (i.e., 6 months before the earliest possible index date).

Patients were grouped into two mutually exclusive cohorts according to the daily pill count of their complete ART regimen. Patients were assigned to the STR cohort if they received an ART regimen consisting of a single tablet (i.e., an STR) at any point during the selection window, regardless of prior or subsequent use of other regimens. At the time of this study, only coformulated tenofovir/emtricitabine/efavirenz was available as an STR. Patients were assigned to the two-or-more-pills-per-day (2+PPD) cohort if they received a regimen consisting of two or more pills per day during the selection window and if they did not receive an STR at any point during that time.

Patients were followed from the start of their complete ART regimen (i.e., after June 1, 2006, the study index date) until the earliest date of regimen discontinuation, disenrollment from the health plan, or the end of the database (i.e., March 31, 2009). Furthermore, patients receiving 2+PPD were allowed to change medications comprising the regimen, ~~providing~~ provided that the patients continued to receive a combination of agents that could still be classified as a complete 2+PPD regimen. Patients receiving STR were followed for as long as they remained on the STR. Discontinuation was defined as 60 consecutive days in which no refills were observed for any component of the regimen. Females with an ICD-9-CM diagnosis code indicating a pregnancy during the follow-up period were excluded from the analysis because the one available STR is not recommended for pregnant women, and hospitalizations for labor and delivery may have biased results in favor of the STR.

Patient characteristics measured at the index date included age, sex, and ART classes received (i.e., nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside/nucleotide reverse transcriptase inhibitors, PIs, ritonavir boosting therapy, or other therapies). The presence of comorbid medical conditions other than HIV or AIDS were assessed during the 6-month pre-index period, using an established algorithm, the Charlson Comorbidity Index (CCI) score.[~~15~~17] This score is made up of 17 comorbidities (defined by ICD-9-CM diagnosis and procedure codes), such as myocardial infarction and chronic pulmonary disease, which are weighted to correspond to the severity of the comorbid condition of interest. A higher comorbidity score represents a higher overall comorbidity burden during the pre-index period. Additionally, the incidence of other concomitant mental disorders (ICD-9-CM codes 306.xx through 319.xx) and drug and alcohol abuse (ICD-9-CM codes 292.xx and 303.xx through 305.xx) during the 6-month pre-index period also was assessed.

Medication adherence was assessed using the medication possession ratio (MPR), which has been shown to be the most widely adopted measure (57% of all studies) in published claims-based analyses of medication adherence [~~16~~18] and has been used in studies of ART adherence among individuals with HIV.[~~17~~19] The MPR, which is a proxy for refill compliance, generally measures the proportion of the ART exposure period in which supply was maintained for all ART components comprising the regimen. Specifically, MPR was calculated as the number of filled prescription days for all ART regimen components (using the days supplied in the pharmacy claims) divided by the number of days from the first observed prescription in the regimen through the earliest of either the exhaustion of the days supplied of the last observed prescription or the end of follow-up. For each patient in our study, the MPR was calculated over the period in which the patient remained on his or her ART regimen. For patients in the 2+PPD cohort, late refills and resulting days of missing supply for one or more ART components were

all factored against their adherence measurements. For example, patients in the 2+PPD cohort with a supply for only one of the ART components on a given day were considered to have zero adherence for that day. In addition to reporting the mean (standard deviation [SD]) MPR achieved, we also reported the numbers and percentages of patients achieving various adherence thresholds (i.e., MPRs of 1.0-0.95, 0.94-0.90, 0.89-0.85, and 0.84-0.80, corresponding to 100%-95%, 94%-90%, 89%-85%, and 84%-80% adherence, respectively).

To further understand adherence to ART regimens, for each patient in the 2+PPD cohort, complete (i.e., having a complete regimen), partial (i.e., receiving some but not all components of a complete regimen), and no medication days also were assessed. Specifically, we reported the percentage of days that each patient had complete, partial, and no medications available, along with the mean number of days that the patient had complete, partial and no medications. Additionally, we also reported the maximum number of consecutive days the patient had either an incomplete regimen or no medications available.

Hospitalizations were identified from the claims database using relevant place of service codes. Hospitalizations were observed from the index date until the earliest date of regimen discontinuation, end of enrollment in the health plan, or end of the database. The number and percentage of patients with at least one hospitalization were reported, along with the mean (SD) number of hospitalizations, and the mean (SD) number of inpatient days. Furthermore, we compared and reported the number of hospitalizations per 100 patient-years, along with the rate ratios and 95% confidence intervals, for both cohorts as well as by adherence status (at least 95% vs. less than 95%).

For each patient, overall health care utilization and associated costs were aggregated across all encounters, regardless of reason, that were observed during the follow-up period; we reported these costs by average and per-month amounts. The following categories of overall health care

utilization and costs were evaluated and reported: inpatient, emergency department, office visit, home health visit, laboratory service, pharmacy, other outpatient care, and total. For each category of overall health care, the number and percentage of patients, the mean (SD) number of visits per month, and monthly per-patient costs were reported. Additionally, for patients with an inpatient visit, the average number of inpatient days per month among patients with at least one stay during follow-up also was reported. All cost data, which represented payments incurred by the Medicaid system, were standardized at the claim level to 2010 US dollars using the medical care component of the US Consumer Price Index.

All analyses were carried out using SAS (version 9; Cary, North Carolina) statistical software. Descriptive analyses were conducted for all outcome measures and included means and SDs for continuous variables of interest (e.g., MPR) and frequency distributions of categorical variables of interest (e.g., geographic region). All descriptive analyses were stratified by cohort. Health care costs were updated to 2010 US dollars using the medical care component of the consumer price index.

A generalized linear model with a log link and a Poisson distribution was estimated to assess the relationship between the number of pills per day and the number of hospitalizations observed during follow-up. The dependent variable was a count of hospitalizations during exposure to the ART regimen. Additionally, a generalized linear model with a log link and a negative binomial distribution were estimated to assess monthly health care costs, adjusted for the patient and treatment characteristics. The dependent variables were monthly total costs and monthly total costs excluding costs pharmacy costs. For both models, based on previous work by Sax et al. [16], independent variables included the following: treatment regimen received (i.e., STR vs. 2+PPD), age, sex, CCI score, treatment-naïve status, pre-index presence of mental health disorders, pre-index presence of alcohol or drug abuse disorders, length of follow-up (in days,

hospital model only), and whether or not the patient met a 0.95 adherence threshold (cost model only). For the hospital model, incidence rate ratios (IRRs) were reported for all covariates, along with the mean predicted number of hospitalizations for patients receiving an STR versus patients receiving a 2+PPD. For the cost model, adjusted predicted mean costs were reported.

RESULTS

A total of 7,381 patients met the selection criteria (Figure 1). Of these, 5,584 patients (75.7%) received their ART regimen as 2+PPD; 1,797 patients (24.3%) received their ART regimen as a STR. On average, patients were approximately 42 years of age. Approximately 46% of patients were female (Table 1). Across both cohorts, the average CCI score was approximately the same (mean [SD]: 0.67 [1.38] among patients receiving an STR and 0.65 [1.36] among patients receiving 2+PPD). Furthermore, the incidence of concomitant mental disorders and drug and alcohol abuse diagnoses did not vary substantially by cohort. Patients receiving an STR had a mean regimen duration of 348 days; this was approximately 2.8 months shorter than the mean regimen duration of 433 days observed for patients receiving 2+PPD. Forty-seven percent of patients receiving an STR were treatment naïve, compared with 24.5% of patients receiving 2+PPD.

Table 1. Characteristics of the study sample, by cohort.

Characteristic	STR (n = 1,797)		2+PPD (n = 5,584)		*P* Value
All Patients (N, %)	1,797	100.00%	5,584	100.00%	
Age , mean (SD)	41.6	(10.56)	42.32	(11.37)	0.0137
Age category (N, %)					
Aged less than 18 years	40	2.23%	271	4.85%	
Aged 18 to 24 years	95	5.29%	139	2.49%	
Aged 25 to 34 years	269	14.97%	661	11.84%	
Aged 35 to 44 years	622	34.61%	1,975	35.37%	
Aged 45 to 54 years	591	32.89%	1,875	33.58%	
Aged 55 to 64 years	176	9.79%	638	11.43%	
Aged 65+ years	4	0.22%	25	0.45%	
Gender (N, %)					
Male	945	52.59%	3,063	54.85%	0.1123
Female	852	47.41%	2,521	45.15%	0.1439
Race (N, %)					
White	387	21.54%	1,221	21.87%	0.8893
Black	1,187	66.05%	3,658	65.51%	0.6877
Hispanic	18	1.00%	82	1.47%	0.7844

Characteristic	STR (n = 1,797)		2+PPD (n = 5,584)		*P* Value
Other	204	11.35%	621	11.12%	0.7846
Unknown	1	0.06%	2	0.04%	0.8766
Basis of Medicaid Eligibility (N, %)					
Aged	1	0.06%	8	0.14%	0.5634
Disabled	1,089	60.60%	4,071	72.90%	<.0001
Income	583	32.44%	1,159	20.76%	<.0001
Other	58	3.23%	202	3.61%	0.8710
Unknown	65	3.62%	141	2.53%	0.0487
Medicare Eligibility (N, %)					
Not dually eligible	1,791	99.67%	5,558	99.53%	0.9987
Dually eligible	5	0.28%	24	0.43%	0.6523
Unknown	1	0.05%	2	0.04%	0.9014
Charlson comorbidity index score, mean (SD)	0.67	(1.38)	0.65	(1.36)	0.5919
~~Charlson comorbidities (N, %)~~	~~-~~	~~-~~	~~-~~	~~-~~	
~~Myocardial infarction~~	~~11~~	~~0.61%~~	~~44~~	~~0.79%~~	
~~Congestive heart failure~~	~~39~~	~~2.17%~~	~~141~~	~~2.53%~~	
~~Peripheral vascular disease~~	~~14~~	~~0.78%~~	~~58~~	~~1.04%~~	
~~Cardiovascular disease~~	~~52~~	~~2.89%~~	~~148~~	~~2.65%~~	
~~Dementia~~	~~4~~	~~0.22%~~	~~10~~	~~0.18%~~	
~~Chronic pulmonary disease~~	~~259~~	~~14.41%~~	~~704~~	~~12.61%~~	
~~Rheumatological disease~~	~~11~~	~~0.61%~~	~~23~~	~~0.41%~~	
~~Peptic ulcer disease~~	~~9~~	~~0.50%~~	~~25~~	~~0.45%~~	
~~Mild liver disease~~	~~20~~	~~1.11%~~	~~49~~	~~0.88%~~	
~~Severe liver disease~~	~~117~~	~~6.51%~~	~~333~~	~~5.96%~~	
~~Diabetes mellitus without chronic complications~~	~~145~~	~~8.07%~~	~~445~~	~~7.97%~~	
~~Diabetes mellitus with chronic complications~~	~~16~~	~~0.89%~~	~~89~~	~~1.59%~~	
~~Paraplegia~~	~~6~~	~~0.33%~~	~~34~~	~~0.61%~~	
~~Renal disease~~	~~11~~	~~0.61%~~	~~80~~	~~1.43%~~	
~~Cancer~~	~~82~~	~~4.56%~~	~~221~~	~~3.96%~~	
~~Metastatic cancer~~	~~11~~	~~0.61%~~	~~26~~	~~0.47%~~	
Concomitant mental health and substance abuse comorbidities (N, %)					
Mental disorders	382	21.26%	1,340	24.00%	0.0456
Drug or alcohol abuse	338	18.81%	856	15.33%	0.0323
Treatment naïve at index (N, %)	853	47.47%	1,366	24.46%	<.0001
~~Mean (SD) r~~Regimen length, mean (SD)	348.17	(259.32)	433.46	(351.50)	<.0001
Index medications (N, %)					
NRTI	1,797	100.00%	5,584	100.00%	---
NNRTI	1,797	100.00%	1,500	26.86%	<.0001
PI	---	---	4,064	72.78%	---

Characteristic	STR (n = 1,797)		2+PPD (n = 5,584)		*P* Value
Kaletra at index	---	---	1,633	40.18%	---
Boosted PI at index	---	---	1,664	40.94%	---
Non-boosted PI at index	---	---	767	18.87%	---
PE	---	---	1,712	30.66%	---
Other	---	---	87	1.56%	---

NOTE. 2+PPD = two or more pills per day; NNRTI = nonnucleoside/nucleotide reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PE = pharmacokinetic enhancer; PI = protease inhibitor; SD = standard deviation; STR = once-daily single-tablet regimen.

Patients receiving an STR had significantly better adherence than patients receiving 2+PPD (Table 2). Approximately 25.3% of patients receiving an STR achieved 95% adherence or greater, compared with 17.4% of patients receiving 2+PPD ($P \leq 0.0001$). Mean (SD) MPR was 0.84 (0.14) among patients receiving an STR and 0.80 (0.15) among patients receiving 2+PPD (Table 2). Patients in the 2+PPD cohort received a complete regimen for 80.3% of the follow-up period (mean [SD]: 361.9 [315.0] days), a partial regimen for 5.6% of the follow-up period (mean [SD]: 22.2 [45.6] days), and no available medications for 14.1% of the follow-up period (mean [SD]: 49.4 [57.1] days) (Table 3). Alternatively, patients in the STR cohort received a complete regimen for 84.4% of the follow-up period (mean [SD]: 299.4 [234.6] days) and no available medications for 15.6% of the follow-up period (mean [SD]: 48.8 [54.2] days), which was a similar percentage of days as patients receiving 2+PPD. Patients receiving an STR had, on average, a maximum of 19.5 (SD: 15.9) consecutive days without a complete regimen (i.e., either a partial regimen or no medications available); patients receiving 2+PPD had, on average, a maximum of 23.9 (SD: 16.7) consecutive days without a complete regimen.

Table 2. Adherence to antiretroviral therapy, by cohort.

Cohort	Number of Patients	Mean (SD) MPR	MPR/Persistency Ratio (N, %)									
			<0.8		0.8 - <0.85		0.85 - <0.9		0.9 - <0.95		0.95 - 1	
STR	1,797	0.84 (0.14)	537	29.88%	178	9.91%	243	13.52%	385	21.42%	454	25.26%
2+PPD	5,584	0.80 (0.15)	2,255	40.38%	621	11.12%	779	13.95%	957	17.14%	972	17.41%

Cohort	Number of Patients	Mean (SD) MPR	MPR/Persistency Ratio (N, %)				
			<0.8	0.8 - <0.85	0.85 - <0.9	0.9 - <0.95	0.95 - 1
Overall	7,381	0.81 (0.15)	2,792 37.83%	799 10.83%	1,022 13.85%	1,342 18.18%	1,426 19.32%
P-Value (1 vs. 2)		<.0001	<.0001	0.1491	0.6477	<.0001	<.0001

NOTE. 2+PPD = two or more pills per day; MPR = medication possession ratio; SD = standard deviation; STR = once-daily single-tablet regimen.

Table 3. Summary of incomplete adherence, by cohort.

Adherence Characteristic	STR (n = 1,797)	2+PPD (n = 5,584)	*P* Value
Percentage of days with complete adherence	84.42%	80.37%	<.0001
Percentage of days with partial adherence	---	5.56%	---
Percentage of days with no ART medications	15.58%	14.07%	0.0356
Complete adherence days, mean (SD)	299.36 (234.56)	361.87 (315.03)	<.0001
Partial adherence days, mean (SD)	---	22.24 (45.58)	---
Days with no medication available, mean (SD)	48.81 (54.24)	49.35 (57.11)	0.0356
Total follow-up duration, mean (SD)	348.17 (259.31)	433.46 (351.50)	<.0001
Maximum consecutive gap in therapy,[a] mean (SD)	19.48 (15.89)	23.92 (16.67)	<.0001

NOTE. 2+PPD = two or more pills per day; ART = antiretroviral therapy; SD = standard deviation; STR = once-daily single-tablet regimen.

[a] Represents either days with a partial regimen or days with no medications.

Among patients receiving an STR, 21.0% had at least one hospitalization, compared with 24.4% of patients receiving 2+PPD ($P = 0.003$) (Table 4). Among patients with a hospitalization, patients receiving an STR had numerically similar, although significantly fewer, hospitalizations over all available follow-up, when compared with patients receiving 2+PPD (mean [SD]: 1.9 [1.6] among patients receiving an STR vs. 2.1 [2.2] among patients receiving 2+PPD; $P = 0.001$).

Table 4. All-cause average ~~monthly~~ per patient health care utilization and costs, by cohort.

Comment [k3]: Removed this because hospitalization use (not cost) data are shown for all available follow-up.

Resource Used	STR (n = 1,797)	2+PPD (n = 5,584)	P-Value
Hospitalizations			

Resource Used	STR (n = 1,797)		2+PPD (n = 5,584)		P-Value
Had ≥ 1 hospital admission (N, %)[a]	378	21.04%	1,365	24.44%	0.0031
Number of hospitalizations (over all follow-up) [b] mean (SD)	1.88	(1.59)	2.1	(2.23)	0.0012
Inpatient days (over all follow-up) [b] mean (SD)	9.99	(12.33)	12.33	(18.90)	0.0228
Number of admissions per month	-	-	-	-	-
Mean (Std. Dev)	0.05	(0.00)	0.05	(0.15)	0.1429
Median	0	-	0	-	-
Range (Min, Max)	0	2	0	1.97	-
Days in hospital per month[e]	-	-	-	-	-
Mean (SD)	1.32	(2.21)	1.45	(2.71)	0.3975
Median	0.58	-	0.5	-	-
Range (Min, Max)	0.03	21.5	0.03	32.43	-
Costs per month, mean (SD)	$834	($4,480)	$1,152	($5,212)	0.0203
Mean (Std. Dev)	$834	($4,480)	$1,152	($5,212)	0.0203
Median	$0	-	$0	-	-
Range (Min, Max)	$0	$143,530	$0	$97,626	-
Emergency Room (ER)					
Had ≥ 1 ER visit (N, %)[a]	903	50.25%	2,749	49.23%	0.4517
Number of visits per month, mean (SD)	0.97	(3.00)	1.01	(2.99)	0.6107
Mean (Std. Dev)	0.97	(3.00)	1.01	(2.99)	0.6107
Median	0.03	-	0	-	-
Range (Min, Max)	0	67	0	89.91	-
Costs per month, mean (SD)	$45	($160)	$46	($135)	0.873
Mean (Std. Dev)	$45	($160)	$46	($135)	0.873
Median	$0	-	$0	-	-
Range (Min, Max)	$0	$3,063	$0	$4,161	-
Office Visits (Primary Care) (N, %)					
Had ≥ 1 office visit (N, %)[a]	1,509	83.97%	4,699	84.15%	0.8576
Number of visits per month, mean (SD)	1.52	(3.00)	1.43	(2.19)	0.1669
Mean (Std. Dev)	1.52	(3.00)	1.43	(2.19)	0.1669
Median	0.92	-	0.86	-	-
Range (Min, Max)	0	61	0	40.30	-
Costs per month, mean (SD)	$75	($229)	$70	($291)	0.5087
Mean (Std. Dev)	$75	($229)	$70	($291)	0.5087
Median	$30	-	$26	-	-
Range (Min, Max)	$0	$5,012	$0	$15,499	-
Home Health (N, %)					
Had ≥ 1 home health visit (N, %)[a]	504	28.05%	1,861	33.33%	<.0001
Number of visits per month, mean (SD)	0.64	(3.00)	0.79	(3.16)	0.0625
Mean (Std. Dev)	0.64	(3.00)	0.79	(3.16)	0.0625
Median	0	-	0	-	-

Resource Used	STR (n = 1,797)		2+PPD (n = 5,584)		P-Value
Range (Min, Max)	0	45	0	43.06	-
Costs per month, mean (SD)	$47	($198)	$88	($642)	0.007
Mean (Std. Dev)	$47	($198)	$88	($642)	0.007
Median	$0	-	$0	-	-
Range (Min, Max)	$0	$4,142	$0	$36,653	-
Laboratory (N, %)					
Had ≥ 1 lab order (N, %)[a]	1,168	65.00%	3,530	63.22%	0.1722
Number of claimslab tests per month, mean (SD)	1.24	(2.00)	1.19	(1.69)	0.2962
Mean (Std. Dev)	1.24	(2.00)	1.19	(1.69)	0.2962
Median	0.66	-	0.57	-	-
Range (Min, Max)	0	16	0	19.96	-
Costs per month, mean (SD)	$52	($94)	$46	($120)	0.0401
Mean (Std. Dev)	$52	($94)	$46	($120)	0.0401
Median	$20	-	$17	-	-
Range (Min, Max)	$0	$1,689	$0	$7,246	-
Pharmacy (N, %)					
Had ≥ 1 pharmacy claim (N, %)[a]	1,797	100.00%	5,584	100.00%	---
Number of claimsprescriptions per month, mean (SD)	4.99	(4.00)	6.73	(4.05)	<.0001
Mean (Std. Dev)	4.99	(4.00)	6.73	(4.05)	<.0001
Median	3.96	-	5.76	-	-
Range (Min, Max)	0.37	27	0.69	37.17	-
Costs per month, mean (SD)	$1,593	($1,105)	$1,779	($1,307)	<.0001
Mean (Std. Dev)	$1,593	($1,105)	$1,779	($1,307)	<.0001
Median	$1,494	-	$1,617	-	-
Range (Min, Max)	$0	$27,034	$0	$54,232	-
OP/ancillary (N, %)					
Had ≥ 1 other OP/ancillary (N, %)[a]	1,754	97.61%	5,469	97.94%	0.3957
Number of visits per month, mean (SD)	0.15	(0.00)	0.14	(0.13)	0.0078
Mean (Std. Dev)	0.15	(0.00)	0.14	(0.13)	0.0078
Median	0.12	-	0.11	-	-
Range (Min, Max)	0	1	0	0.52	-
Costs per month, mean (SD)	$313	($607)	$363	($733)	0.0087
Mean (Std. Dev)	$313	($607)	$363	($733)	0.0087
Median	$139	-	$159	-	-
Range (Min, Max)	$0	$8,946	$0	$15,936	-
Total Health Care Utilzation & and Costs					
Had ≥ 1 medical visit/encounter (N, %)[a]	1,797	100.00%	5,584	100.00%	---
Number of total encounters per month, mean (SD)	14.69	(14.00)	16.97	(13.72)	<.0001
Mean (Std. Dev)	14.69	(14.00)	16.97	(13.72)	<.0001
Median	11.34	-	13.13	-	-

Resource Used	STR (n = 1,797)		2+PPD (n = 5,584)		P-Value
Range (Min, Max)	0.56	250	0.96	232.02	-
Costs per month, mean (SD)	$2,959	($4,962)	$3,544	($5,811)	0.0001
Mean (Std. Dev)	$2,959	($4,962)	$3,544	($5,811)	0.0001
Median	$1,916	-	$2,182	-	-
Range (Min, Max)	$0	$146,367	$0	$103,103	-

NOTE: SD = standard deviation.

[a]Estimated over all available follow-up.

[b]Among hospitalized patients.

[c]Among patients with at least one admission over all follow-up.

The multivariate Poisson regression model showed that receiving an STR was associated with a significantly lower risk of hospitalization rate than receiving the 2+PPD regimen (IRR = 0.8457; $P < 0.001$) (Table 5). When the received regimen type was controlled for, we found that patients were significantly more likely to be hospitalized if they had the following characteristics: a concomitant mental disorder diagnosis (vs. no concomitant mental disorder diagnosis; IRR = 1.2917; $P < 0.001$), a concomitant drug or alcohol abuse diagnosis (vs. no concomitant drug or alcohol abuse diagnosis; IRR = 2.0357; $P < 0.001$), a CCI score greater than 1 (IRR increased with increasing CCI score, from 2.3779 among patients with a CCI between 1 and 2 to 2.6432 among patients with a CCI greater than 3; all $P < 0.001$), were female (vs. male; IRR = 1.1069; $P = 0.003$), or were older than 35 years (vs. younger than 35 years; IRR increased with increasing age, up to 54 years, from 1.2482 among patients aged 35-44 years to 1.555 among patients aged 45-54 years; both $P < 0.1$). Additionally, the likelihood of a hospitalization increased slightly with each additional day of follow-up (IRR = 1.0013; $P < 0.0001$). Finally, being treatment naïve prior to index was predictive of an approximately 13% higher hospitalization rate as compared with being treatment experienced (IRR = 1.1270; $P = 0.0033$).

Table 5. Predictors of hospitalization, using multivariate Poisson regression, and controlling for treatment cohort.

Specification: Adherence Covariate Excluded	Poisson Count Model		
	Parameter Estimate	Incidence Rate Ratio	P-Value
Received a STR (vs. 2+PPD regimen)	-0.1654	0.8475	0.0001
Female (vs. male)	0.1003	1.1069	0.003
Age (vs. less than 35)			
35 to 44 years	0.1016	1.2482	0.0669
45 to 54 years	0.2217	1.5550	<.0001
55+ years	0.4415	1.1056	<.0001
Charlson comorbidity index score (vs. Charlson comorbidity index score less than 1)			
Between 1 and 2	0.8662	2.3779	<.0001
Greater than 2	0.972	2.6432	<.0001
Treatment naïve (vs. treatment experienced)	0.1196	1.1270	0.0033
Had a mental disorder diagnosis (vs. no mental disorder diagnosis)	0.256	1.2917	<.0001
Had a drug or alcohol abuse diagnosis (vs. no drug or alcohol abuse diagnosis)	0.7109	2.0357	<.0001
Length of follow-up (in days)	0.0013	1.0013	<.0001

NOTE. 2+PPD = two or more pills per day; STR = once-daily single-tablet regimen.

From the Poisson regression analysis described above, we found the adjusted rate of hospitalization to be significantly lower for patients receiving an STR than for patients receiving 2+PPD (i.e., 39.5 hospitalizations per 100 patient-years ~~receiving~~ for patients receiving STR vs. 51.2 hospitalizations per 100 patient-years~~s~~ for those receiving 2+PPD) (Figure 2). These adjusted hospitalization rates translated to a 23% lower risk of hospitalization among patients receiving an STR, compared with patients receiving 2+PPD. As shown in Figure 3, adherence status seems to be a key mechanism mediating hospitalization risk as patients with at least 95% adherence (regardless of regimen type) had a statistically significant lower hospitalization rate

compared to patients with less than 95% adherence. Improved adherence among patients treated with STR therefore appears to confer a lower risk of hospitalization and associated costs.

Examining other types of health care utilization, ~~T~~the percentage of patients with at least one home health visit was significantly lower among patients receiving STR than for patients receiving 2+PPD (Table 4). Between the two cohorts, no differences were observed in the percentage of patients with at least one emergency room, office visit, or laboratory claim. Similarly, no significant differences were found in the number of emergency room, office visits, home health visits, or laboratory claims per month. However, patients who received an STR had significantly lower costs per month associated with inpatient, home health, laboratory, pharmacy, other, and total health care than patients receiving 2+PPD. Mean (SD) total health care costs per month were $2,959 ($4,962) among patients receiving an STR and $3,544 ($5,811) among patients receiving 2+PPD; thus, patients receiving an STR accrued, on average per month, $585 less than patients receiving 2+PPD ($P < 0.001$). The largest difference in costs between the two cohorts was observed for inpatient admissions ($317 more for patients receiving 2+PPD), followed by pharmacy costs ($187 more for patients receiving 2+PPD).

When monthly health care costs were adjusted for demographic, clinical, and treatment characteristics, patients receiving an STR had monthly total costs averaging $2,947; patients receiving 2+PPD had monthly total costs averaging $3,549 (Figure ~~3~~4). Thus, patients receiving 2+PPD had $602 more in monthly heath care costs, which corresponded to a 17% reduction in costs associated with STR. Additionally, when monthly health care costs, excluding pharmacy costs, were adjusted for demographic, clinical, and treatment characteristics, patients receiving an STR had monthly total costs averaging $1,370; patients receiving 2+PPD had monthly total costs averaging $1,797. Thus, patients receiving 2+PPD had $427 more in adjusted monthly health care costs, which corresponded to a 23.8% reduction in costs associated with STR.

DISCUSSION

This retrospective database analysis examined adherence to ART regimens among patients with HIV infection, using pharmacy refill dates as the best available proxy for pill-taking behavior. One advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis of the timing in between refills, which also notes the amount of medication dispensed each time. The rate of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should the overall monthly health care utilization and costs.

This analysis largely confirms the previous report from Sax et al.[~~14~~16]: we found that patients receiving an STR had significantly better adherence rates than patients receiving multiple pills per day. Our other finding was that higher rates of adherence were associated with similar or lower rates of hospitalization, regardless of the regimen; less-than-complete adherence was associated with higher rates of hospitalization and overall costs. Thus, multiple-pill regimens were associated both with lower rates of complete adherence and correspondingly higher overall health care costs. We observed a significantly higher rate of hospitalizations occurring in patients receiving multiple-pill regimens ($P < 0.001$) than in patients receiving an STR. The greater total health care costs were due to differences in both the pharmacy costs of the regimen components as well as the costs of hospitalizations and associated care. Therefore, one implication of our findings is that choosing a multiple-pill regimen for its cost alone might inadvertently result in little to no total health care cost-savings for a payer, given the potential risk of more frequent hospitalizations in patients receiving multiple-pill regimens.

Similar to previous studies [~~18~~20,~~19~~21], we found that patients who were adherent to therapy were less likely to be hospitalized. Our data demonstrated similar rates of hospitalizations among patients with the highest levels of complete adherence—at least 95%. This was consistent across

both treatment cohorts. This finding suggests that the differences observed in the rates of hospitalizations across regimens are primarily due to differences in adherence rates between the STR and 2+PPD regimens rather than any concerns for toxicities. This finding also may partially address the potential contribution of channeling bias, a concern with any observational data set. We found that adherent patients on any regimen have similar rates of hospitalization, which suggests that there may not have been a consistent bias to prescribe to more clinically immunosuppressed patients or to patients who were at greater risk for hospitalization due to other factors than a multiple-pill regimen. Furthermore, we found that the outcome of fewer hospitalizations for patients receiving an STR was consistent when we compared hospitalization risks for treatment-naïve patients with hospitalization risks for treatment-experienced patients. In the latter group, the impact of stage of illness prior to treatment would be lessened, given the impact of prior treatment on improving pretreatment immunosuppression, with an STR regimen. Of final note regarding channeling bias, previous analyses of Medicaid beneficiaries with HIV have shown that patients receiving ART are completely non-adherent (i.e., days with no ART supply/coverage on hand) for approximately 14% of their regimen duration regardless of the number of pills in the regimen [22~~20~~]. This finding suggests that clinicians are not channeling more adherent patients to STRs. Together, these data support the observation that facilitating greater adherence to ART at any stage of illness may result in reducing hospitalization risk.

One follow-up question our study findings raises is whether the observed reduction in hospitalization risk and costs with STR was also due to less prevalent chronic comorbidities in patients prescribed STR. To assess this possibility, we replicated key descriptive analyses on hospitalization rates for patients with no baseline comorbidities as reported by the CCI. We found that the majority (~70%) of both STR and 2+PPD patients had no other CCI comorbidities. Among STR patients with no other comorbidities from the CCI, 13.9% had a

hospitalization compared with 18.3% of 2+PPD patients with no other comorbidities. Further, among STR patients with no comorbidities, 11.4% of adherent patients had a hospitalization compared with 14.7% of non-adherent patients. Similarly, among 2+PPD patients with no comorbidities, 12.4% of adherent patients had a hospitalization compared with 19.7% of non-adherent patients. Results of this sensitivity analysis, combined with the observation that the vast majority of patients in our study had no major comorbidities (from the CCI) requiring other chronic treatment, suggest that the observed association between poorer adherence and higher hospitalization was likely due to reduced ART adherence and not due to reduced adherence with other medications patients were taking.

There were several measurable differences present in the study population at baseline. Our study attempted to control for effects these differences may have had on rates of ~~adherence and~~ hospitalization between STR and 2+PPD patients. We used multivariate regressions to control for patient demographics, treatment characteristics (i.e., treatment naïve vs. experienced, type of ART received~~, year the ART was received~~), and clinical characteristics (i.e., CCI score, concomitant mental disorder, drug and alcohol abuse diagnoses). We found that a number of factors were associated with an increased risk of ~~poor adherence~~hospitalization independent of treatment regimen, including having a CCI score greater than ~~3~~1; having a concomitant drug or alcohol abuse diagnosis; having a concomitant mental health disorder; being female and of older age; and being treatment ~~experienced~~naive. ~~Similarly, having a CCI score greater than 1, or having a concomitant mental disorder or drug or alcohol abuse diagnosis were associated with an increased risk of hospitalization.~~

~~Nevertheless,~~Even after controlling for the~~se~~ factors noted above, we still detected an independent ~~effect~~ association of ~~the~~ regimen type with hospitalization rates and, in fact, observed an increase in the apparent protective effect of STR based on the predicted, adjusted

Comment [k4]: Did not notice this typo in earlier drafts. This should have said "hospitalization."

hospitalization rate derived from the Poisson model (39.5 per 100 patients in the STR group vs. 51.2 per 100 patients in the 2+PPD group; see Figure 2). One possible explanation for this difference is that the Poisson model corrected a substantial imbalance in the proportion of patients who were treatment naïve at index (47.5% of STR patients vs. 24.5% of 2+PPD patients). Lack of or naivety to ART exposure has been shown in some studies to be a positive predictor of hospitalization in HIV patients [23], perhaps because approximately one-third of HIV patients wait to seek care until their disease has progressed to the point that they need acute treatment. [24, 25] As noted in a recent study by Metsch et al. [26], these patients often obtain initial care in emergency departments and hospital inpatient wards, and they tend not to persistent with follow-up outpatient care. This pattern of treatment induction may further increase their risk of infection and re-hospitalization in the short-term. Because being treatment naïve was shown in our data to be predictive of hospitalization, the Poisson model's adjustment for the overrepresentation of treatment naivety in the STR group may therefore have resulted in the larger difference between STR and 2+PPD in hospitalizations than observed in the crude, unadjusted comparison.

One hypothesis for a plausible mechanism by which the~~se~~ outcomes observed in our study could occur stems from observations in the SMART study.[~~21~~27] That study, comparing continuous antiviral treatment versus periodic treatment interruptions, demonstrated that HIV treatment interruptions that were of sufficient length of time to lead to recurrent HIV viremia were associated with a significantly higher risk of all-cause morbidity and mortality. Our analysis was consistent with those findings: the mean maximum duration of nonadherence was about 3 weeks, which is a sufficient length of time to expect a return of HIV viremia. The SMART study noted that the higher risk of illness was not necessarily proximal to the time of the interruption but was observed for months afterwards. While there are differences between the

SMART study design and population and our study population, our findings are consistent with SMART and with what might be expected in a population who periodically are without antivirals for an average time of more than 3 weeks. Of note, short cycle interruptions of 2 days were not associated with virologic rebound in patients receiving the STR that was used in the SMART study [~~22~~28]. Therefore, our finding that the typical interruptions were much longer than this is supportive of a mechanism that could have resulted in increased patient morbidity.

It is also important to note that patients in this study generally were reasonably adherent to ART, with a mean adherence of just over 80% regardless of the number of pills received per day. This rate of adherence is consistent with other published reports of adherence, although other reports found even higher adherence rates to an STR.[~~11~~13,~~12~~14] Furthermore, the difference observed in our study between the STR and 2+PPD regimens (approximately 4%) is consistent with what was observed by Sax et al. of 2.2%.[~~14~~16] This difference is also consistent with the differences in adherence rates reported when comparing average improvement between once-daily and twice-daily regimens (2.9%).[~~23~~29] It is important to note that there also were highly nonadherent patients to both the STR and the 2+PPD regimes in this study population, supporting the generalizability of this population.

Of further note, the differences observed in our study were associated with factors that typically are not present during randomized clinical trials. Randomized trials typically actively work for patient adherence to study medications and use study coordinators to regularly monitor patients to minimize missed doses. In our observational study, these typical adherence supports are not in place; thus, our data may reflect real-world lapses in patient behavior in refilling prescriptions, including partial regimen refills, which would not be observed in clinical trials. While there are concerns about the interpretation of observational data and the determination of causal relationships, it is not clear if a randomized study comparing an STR with a multiple-pill

regimen would be able to detect the observed differences unless there was less patient support than is standard in clinical trials.

Our data do not suggest that all patients should be on an STR. There are many factors that weigh in the decision of which regimen is best for any given patient, including pre-existing virologic resistance and tolerability. In our study, the anticipated adherence benefits observed in association with a lower pill burden is relevant but should not be construed as a suggestion that an STR is the ideal choice for the entire population of patients with HIV. Nevertheless, our data do support the continued development of additional STR options, to broaden the number of patients for whom this is an option and the number of subsequent beneficial outcomes.

Our study has several limitations common to observational claims database analyses. Adherence was calculated by using pharmacy refill dates, and we have no measure of actual patient adherence to the prescriptions they filled. However, this measure has been found to be a useful proxy for actual medication adherence.[~~24~~30] Because we did not randomize patients to the two different treatment regimens, we cannot exclude unmeasured confounding factors that may have influenced our outcomes. Among the most important of these factors in this study was that multiple trials have shown that medication resistance at the time of virologic failure is significantly less common in boosted PI treatments than on other regimens, including nonnucleoside/nucleotide reverse transcriptase inhibitor-based treatments.[~~25~~31,~~26~~32] Clinicians could have chosen to prescribe a boosted-PI–containing regimen (all of which contain three or more pills per day) to their less-adherent patients. It cannot be determined from this data set that these patients would have been more adherent on an STR. Although we attempted to control for some of these variables through the use of multivariable models that included some of these factors (substance abuse and psychiatric diagnoses), residual confounding may remain. In addition, we had no laboratory results from patients and thus cannot confirm the degree of

virologic suppression obtained across the regimens. Finally, although our data include information from the Medicaid programs in 11 states, the authors were blinded (as per data privacy rules) as to which specific states are captured. Although the database's documentation suggests that the states are geographically dispersed, we cannot assert that our findings would be fully representative of the general Medicaid population in the US.

In our study, a large proportion of HIV-treated individuals (15% of the total HIV-treated population) were excluded from the analysis due to their having received incomplete ART regimens. We did not have sufficient data on these patients to explain why their regimens were incomplete. However, a previous study found that physician medication errors were somewhat common in individuals with HIV, with the most common error occurring with boosted PIs (estimated at 5.3% of patients); such errors may explain some of the incomplete regimens observed in our analysis.[~~27~~33] Increased adoption of fixed-dose combinations as part of HIV treatment may help to alleviate the issue of incomplete regimens.

During our study period, the only available single-pill ART regimen was coformulated efavirenz/emtricitabine/tenofovir disoproxil fumarate. It is possible that these results would not be generalizable to other one- and multi-pill regimens if other treatments have different efficacy and toxicity profiles. With the recent approval by the Food and Drug Administration of two other STRs (i.e., tenofovir, emtricitabine, and rilpivirine and tenofovir, emtricitabine, elvitegravir and cobicistat), it may eventually be possible to explore the applicability of our observations to other STRs.

In summary, this study supported the results as reported by Sax et al.[~~14~~16] We found that patients who received ART as a single pill per day were significantly more likely to be highly adherent to therapy than patients who received multiple-pill regimens. This difference in adherence was associated with a lower risk of hospitalizations: patients with less-than-complete

adherence were more likely to be hospitalized. While we acknowledge the limitations associated with any observational study, our data support our finding that the use of an STR may reduce health care costs as well as patient morbidity by decreasing hospitalization rates, which are higher in patients with less-than-complete medication adherence.

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FIGURE LEGENDS

Figure 1. Sample Selection Flow Chart

Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort

Figure 3. Hospitalizations per 100 Patient-Years, by Cohort and Adherence

Figure 43. Adjusted Monthly Health Care Costs, by Cohort

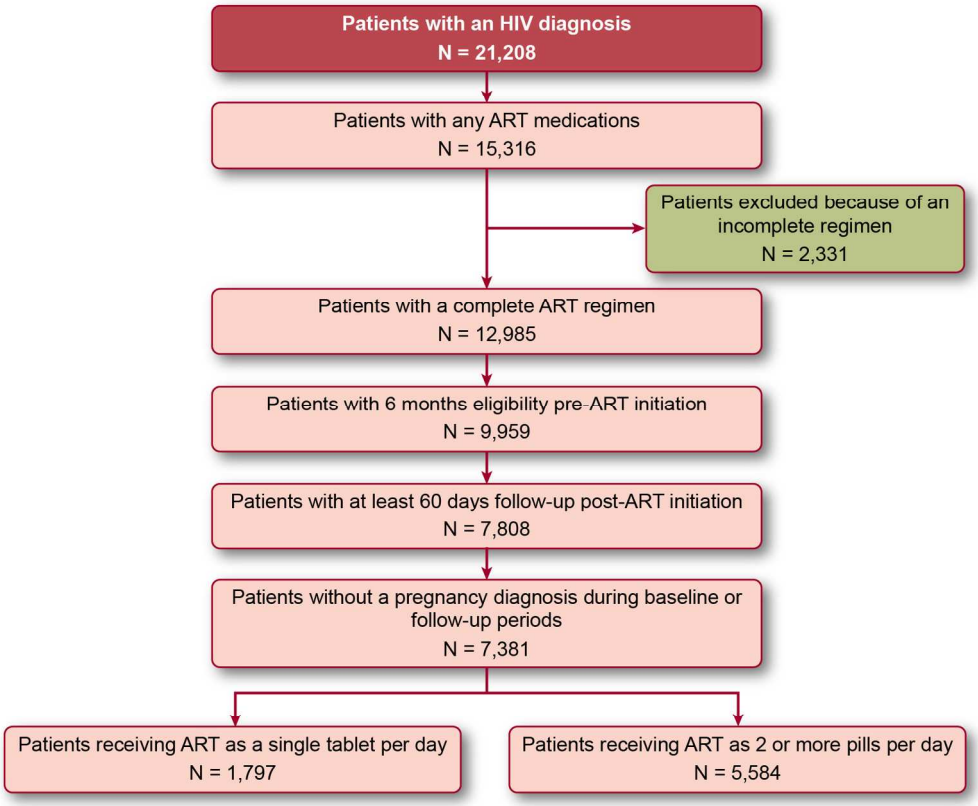

Figure 1. Sample Selection Flow Chart
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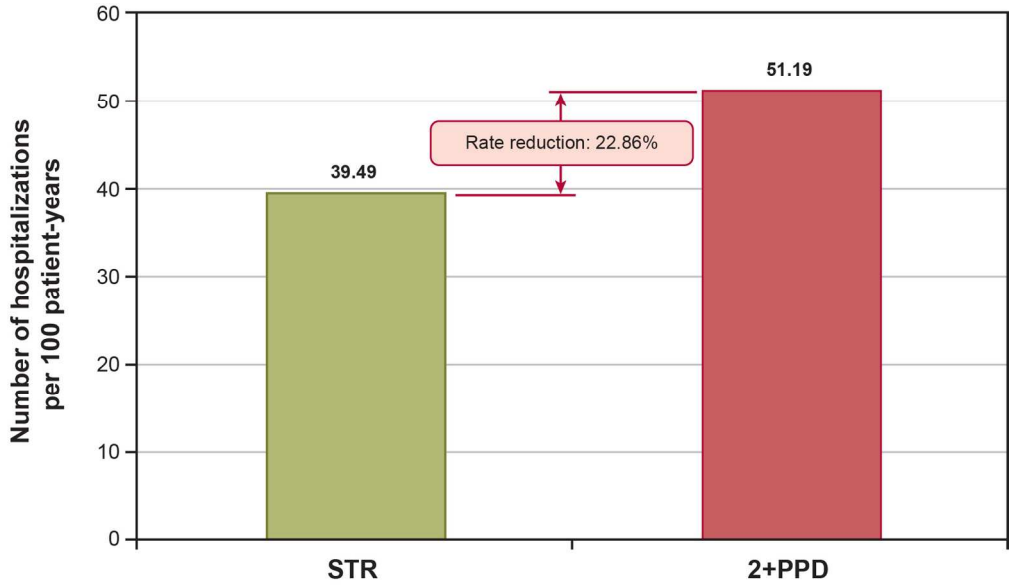

Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort
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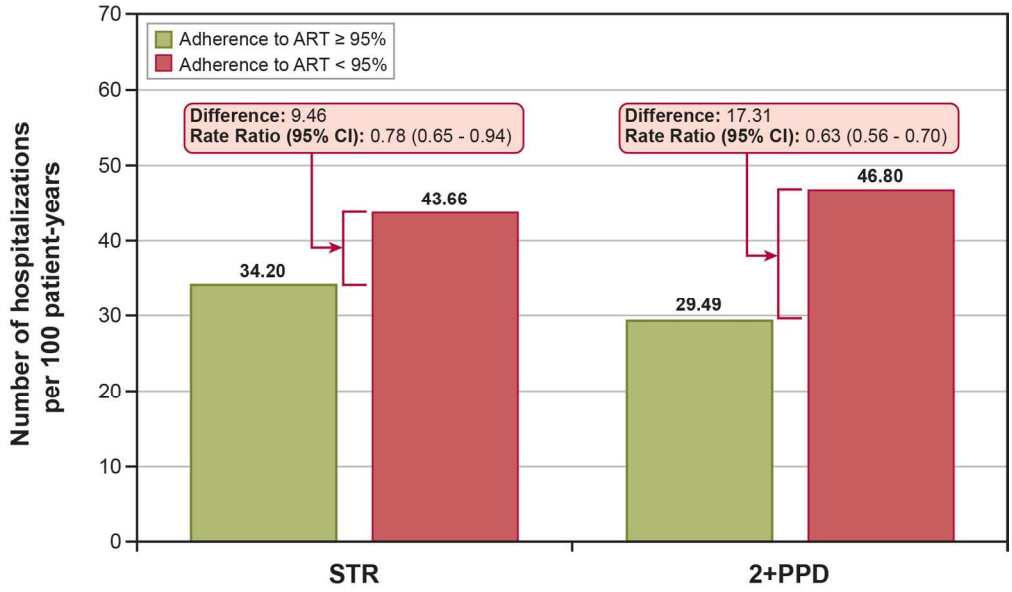

Figure 3. Hospitalizations per 100 Patient-Years, by Cohort and Adherence
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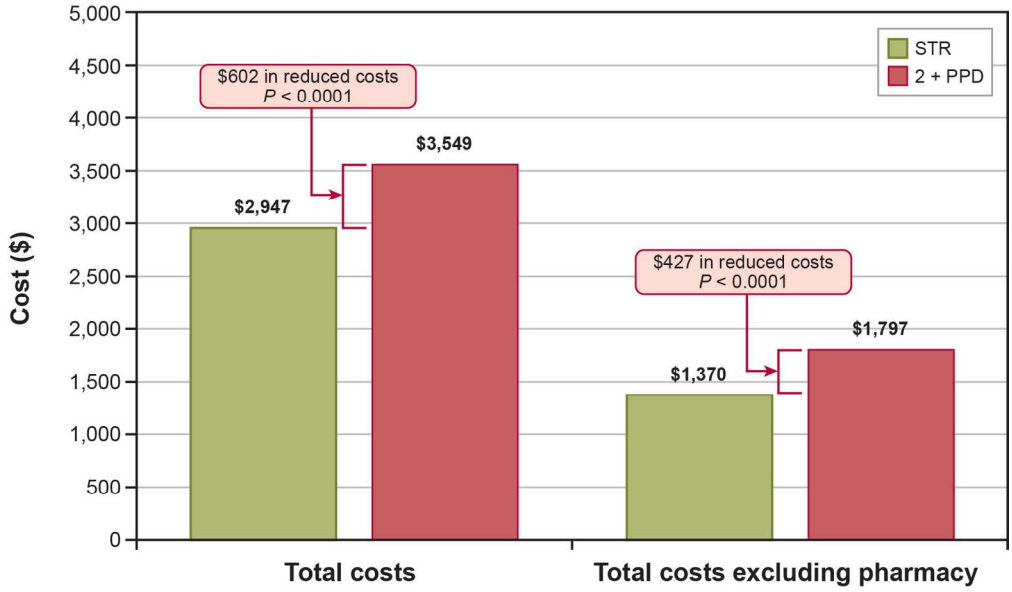

Figure 4. Adjusted Monthly Health Care Costs, by Cohort
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