Real-World Health Plan Data Analysis: Key Trends in Medication Adherence and Overall Costs in Patients with HIV

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ABSTRACT

BACKGROUND: Adherence to effective antiretroviral therapy (ART) is essential to achieve long-term viral suppression in patients with HIV-1. Single-tablet regimens (STRs) have improved adherence and decreased health care costs and hospitalizations, but previous study results suggest that the relationship between ART adherence and health care costs and utilization is complex.

OBJECTIVE: To assess ART adherence trends in patients with HIV-1 to determine if differences in utilization, demographics, and overall costs exist among patients with varying levels of medication adherence.

METHODS: This retrospective study analyzed medical and pharmacy claims data from an administrative claims database between January 1, 2007, and June 30, 2016, for Medicaid or commercially insured patients continuously enrolled for ≥ 6 months before and ≥ 15 months after the index date (date of first medical claim with an HIV diagnosis or pharmacy claim for HIV ART medication between July 1, 2007, and June 30, 2014). Qualifying patients were aged ≥ 18 years with a diagnosis of HIV-1 infection or at least 1 pharmacy claim for HIV ART at index and at least 2 pharmacy claims during the follow-up period. Patients were categorized on the basis of adherence as measured by proportion of days covered (PDC; ≥ 95%, highly adherent; < 95%, less adherent) and treatment with an STR or multiple-tablet regimen (MTR). Commercially insured patients were stratified by duration of follow-up data (< 3 or ≥ 3 years). There were not enough Medicaid patients for follow-up analysis. Outcomes of interest were ART adherence and annual medical and pharmacy utilization and costs. Descriptive statistics were generated, and health care resource utilization and costs were reported as annual averages. Chi-square and t-tests were used to examine differences between the cohorts.

RESULTS: A total of 332 Medicaid patients and 1,698 patients insured commercially met inclusion criteria. Adherence to ART medication (mean PDC) during the first 15 months was lower in Medicaid patients (65%) versus commercial patients (79%; *P* < 0.0001). Patients treated with STRs comprised 47% and 37% of patients in the < 3-year and ≥ 3-year follow-up cohorts, respectively. More STR patients achieved ≥ 95% adherence than MTR patients (< 3-year follow-up, 53% vs. 39%; ≥ 3-year follow-up, 61% vs. 45%; *P* < 0.001). In both follow-up cohorts, less adherent patients had higher mean annual medical costs, and results were significant for patients with ≥ 3-year follow-up ($8,224 vs. $3,097; *P* = 0.0007). These results were largely driven by savings in mean annual inpatient costs among the highly adherent patients in both cohorts (< 3-year follow-up, −$2,525 [*P* = 0.0003]; ≥ 3-year follow-up, −$815 [*P* < 0.001]).

CONCLUSIONS: Patients on STRs were more adherent than patients on MTRs regardless of length of follow-up. Better adherence was associated with significant inpatient cost savings. The relationship between adherence and total medical costs is nuanced depending on the duration of follow-up.

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What is already known about this subject

- Strict adherence to antiretroviral therapy (ART) is essential to achieve durable clinical outcomes in patients with HIV-1 and minimize drug resistance and virologic failure.
- According to previous studies in real-world settings, which had mean follow-up of approximately 1 year, the introduction of single-tablet regimens (STRs) to reduce pill burden resulted in improved ART adherence and decreased health care costs and hospitalizations for patients with HIV-1 compared with multiple-tablet regimens (MTRs).
- The relationship between adherence and health care costs may be more complex than these studies suggest, as demonstrated by 1 analysis that showed higher total health care costs over a 24-month period for asymptomatic HIV-positive patients who were at least 90% adherent compared with those who were < 90% adherent to ART.

What this study adds

- This study provides insight into the longer-term relationship between ART adherence and health care costs, demonstrating that, after ≥ 3 years of ART, highly adherent patients incurred lower mean annual medical costs, driven primarily by savings in inpatient costs, compared with less adherent patients.
- The study results add to the growing body of literature demonstrating that STRs are associated with higher adherence to ART than MTRs.
- Compared with commercially insured patients, patients with Medicaid insurance had a lower ART adherence rate and a greater number of comorbidities.

The Centers for Disease Control and Prevention estimate that more than 1.1 million people in the United States are living with human immunodeficiency virus (HIV)-1, with approximately 39,782 new HIV diagnoses in 2016 and 6,721 deaths attributed directly to HIV in 2014.[1] Deaths from HIV infection have declined across the United States since the introduction of highly active antiretroviral therapy (ART).[2]

Adherence to ART is essential to achieve durable virologic suppression and minimize drug resistance.[3,4] An adherence rate of 95%, widely cited as the minimum rate necessary to maintain HIV-1 viral load suppression of < 400 copies/mL, has

been associated with fewer days in the hospital and reduced morbidity and mortality compared with lower adherence rates.[5,6]

A variety of factors can negatively affect medication adherence among people living with HIV (PLWH), such as complexity of the regimen (e.g., pill burden and dosing frequency), concerns about side effects, overall mental or physical health, and other patient-related and sociodemographic variables.[7-9] The introduction of single-tablet regimens (STRs) to reduce pill burden has resulted in improved adherence and decreased health care costs and hospitalizations for PLWH compared with multiple-tablet regimens (MTRs) in real-world settings.[6,10-13] However, the relationship between adherence and health care costs may be more complicated than previously thought. For example, Pruitt et al. (2015) found that, over a 24-month period, total health care costs were significantly higher for ART-adherent (≥ 90%), asymptomatic HIV-positive patients compared with nonadherent (< 90%), asymptomatic HIV-positive patients.[14] These investigators called for further research to examine the long-term association of ART adherence with total health care costs.

This study assessed ART adherence trends in PLWH and determined if differences in utilization, demographics, and overall costs exist among patients with varying levels of medication adherence.

■ Methods

Study Design and Data Source

A retrospective cohort design was implemented using data from a medical and pharmacy administrative claims database (Magellan Rx Management, Middletown, RI) from multiple regional health plans (Medicaid and commercial) in the United States between January 1, 2007, and June 30, 2016. The index date was the date of the first medical claim with an HIV diagnosis code or pharmacy claim for an HIV medication during the index period (July 1, 2007-June 30, 2014). Baseline metrics were measured in the 6-month period before the index date, and patients were followed for at least 15 months after the index date. ART adherence and health care costs and utilization were assessed annually following the index date.

Inclusion Criteria

Patients who met all of the following criteria were included: (a) HIV diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 042 or *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM] code B20) or asymptomatic HIV infection (ICD-9-CM code V08 or ICD-10-CM code Z21) in the index period or at least 1 pharmacy claim for HIV ART at index; (b) at least 2 pharmacy claims for HIV medication during the follow-up period; (c) aged ≥ 18 years on the index date; and (d) continuous eligibility for medical and pharmacy

TABLE 1	Comparison of Baseline Characteristics and Adherence of Commercially Insured and Medicaid Populations		
	Commercial Insurance (n = 1,698)	**Medicaid (n = 332)**	**P Value**
Age, years, mean (SD) [median]	46.5 (10.6) [47.2]	43.4 (11.2) [44.5]	< 0.0001
Age range, n (%)			
18-29	150 (8.8)	48 (14.5)	
30-39	255 (15.0)	64 (19.3)	
40-49	597 (35.2)	109 (32.8)	0.0011a
50-59	536 (31.6)	95 (28.6)	
60-69	151 (8.9)	15 (4.5)	
70+	9 (0.5)	1 (0.3)	
Sex, n (%)			
Female	349 (20.6)	203 (61.1)	< 0.0001
Male	1,349 (79.4)	129 (38.9)	
CCI score, n (%)			
0	1,228 (72.3)	157 (47.3)	
1	266 (15.7)	91 (27.4)	< 0.0001b
2	120 (7.1)	38 (11.4)	
≥ 3	84 (4.9)	46 (13.9)	
CCI, mean (SD) [median]	0.5 (1.1) [0.0]	1.1 (1.6) [1.0]	< 0.0001
Comorbidities of interest, n (%)			
HCV	84 (4.9)	58 (17.5)	< 0.0001
MDD	134 (7.9)	73 (22.0)	< 0.0001
Adherence, mean (SD) [median], %			
PDC	79 (26) [88]	65 (29) [70]	< 0.0001
Regimen, n (%)			
MTR	999 (58.8)	247 (74.4)	< 0.0001
STR	699 (41.2)	85 (25.6)	< 0.0001

aP value represents the difference in the percentage of younger patients in the Medicaid population compared with the commercial insurance population.
bP value represents the difference in the percentage of Medicaid patients with ≥ 2 comorbidities at baseline compared with the commercial insurance population.
CCI = Deyo-Charlson Comorbidity Index; HCV = hepatitis C virus; MDD = major depressive disorder; MTR = multiple-tablet regimen; PDC = proportion of days covered; SD = standard deviation; STR = single-tablet regimen.

coverage from 6 months before the index date through at least 15 months after the index date. For patients using STR tenofovir disoproxil fumarate/emtricitabine, an additional HIV diagnosis was required for inclusion.

Study Outcomes

The study outcomes of interest were ART adherence and annual medical and pharmacy utilization and costs. Adherence was measured by proportion of days covered (PDC), calculated by the available days of supply of a dispensed medication from pharmacy claims data relative to the follow-up time for each individual patient.[15] PDC was calculated for each patient's individual antiretroviral product. For patients classified as using MTR, the average PDC was used to characterize the adherence.

	< 3-Year Data				**≥ 3-Year Data**			
	All (N = 686)	**STR (n = 322)**	**MTR (n = 364)**	**P Value**	**All (N = 1,012)**	**STR (n = 377)**	**MTR (n = 635)**	**P Value**
Age, years, mean (SD)	45.10 (11.21)	42.52 (11.81)	47.38 (10.13)	<0.0001	47.49 (10.12)	45.15 (10.99)	48.88 (9.30)	<0.0001
Female sex, n (%)	124 (18.1)	37 (11.5)	87 (23.9)	<0.0001	225 (22.2)	72 (19.1)	153 (24.1)	0.0721
CCI, mean (SD)	0.60 (1.20)	0.52 (0.97)	0.68 (1.37)	0.0699	0.43 (0.99)	0.35 (0.81)	0.48 (1.08)	0.0247
ART class, n (%)								
NRTI	664 (96.8)	322 (100.0)	342 (94.0)	<0.0001	987 (97.5)	377 (100.0)	610 (96.1)	<0.0001
NNRTI	371 (54.1)	249 (77.3)	122 (33.5)	<0.0001	636 (92.7)	354 (93.9)	282 (44.4)	<0.0001
PI	229 (33.4)	0 (0.0)	229 (62.9)	<0.0001	405 (40.0)	0 (0.0)	405 (63.8)	<0.0001
INSTI	252 (36.7)	94 (29.2)	158 (43.4)	0.0001	304 (44.3)	46 (12.2)	258 (40.6)	<0.0001

TABLE 2 Baseline Characteristics of Commercially Insured Patients, Stratified by Duration of Follow-up

ART = antiretroviral therapy; CCI = pre-index Deyo-Charlson Comorbidity Index (HIV diagnosis not included); INSTI = integrase strand transfer inhibitor; MTR = multiple-tablet regimen; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SD = standard deviation; STR = single-tablet regimen.

Adherence was assessed at PDC ≥ 95%. Near perfect adherence (95% or greater) has been demonstrated to have greater optimized virologic outcome for patients with HIV infection.[5]

Annual medical utilization and costs were assessed by patient count; visit count; total costs; cost per patient; and patient count by procedure codes of interest, segregated by site of care identifed by place of service code, as well as relevant procedure codes (i.e., hospital, emergency department, and office) and classified as medical costs, pharmacy costs, and total costs.

Baseline patient characteristics were assessed, including age; sex; comorbidities (Deyo-Charlson Comorbidity Index [CCI score]); hepatitis C virus (HCV) coinfection; severe and persistent mental health disorders (i.e., schizophrenia, bipolar disorder, and major depressive disorder); and concomitant medications (by class).

Cohort Assignment

Each patient was categorized on the basis of ART regimen pill burden (STR or MTR). In the health care cost analyses, commercially insured patients were further divided into 2 cohorts on the basis of length of available follow-up data (< 3 or ≥ 3 years).

Statistical Analysis

Descriptive statistics were calculated to describe all baseline variables. Mean, median, and standard deviation (SD) were calculated for continuous variables, and categorical variables were characterized by count and percentage. Health care utlization and costs, reported as annual averages, were analyzed using only the commercial population because of the low number of patients in the Medicaid group in the ≥ 3-year follow-up cohort (n = 24). For medical and pharmacy data, cost information was based on allowed amounts for claims. Costs were segregated by site of care, classified as medical costs and pharmacy costs, and aggregated as total costs. Utilization metrics included number of visits to various sites of care and number of prescription fills. To determine differences in categorical variables, the chi-square test was used. Differences in continuous variables were examined by using the t-test. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

■ Results

The analysis included 332 patients with Medicaid insurance and 1,698 patients with commercial insurance. The Medicaid group had a higher comorbidity burden, determined by the mean (SD) CCI, compared with the commercial group (1.1 [1.6] vs. 0.5 [1.1], respectively; $P < 0.0001$) and a higher incidence of HCV (17.5% vs. 4.9% respectively; $P < 0.0001$) and major depressive disorder (22.0% vs. 7.9%, respectively; $P < 0.0001$; Table 1). Adherence to ART, as determined by PDC mean (SD), over the first 15 months was lower in the Medicaid group (65% [29%]) compared with the commercial group (79% [26%]; $P < 0.0001$).

Among the patients with commercial insurance, 686 had < 3 years, and 1,012 had ≥ 3 years of follow-up data (mean follow-up time, 2.1 vs. 4.7 years, respectively; Table 2). Patients receiving STRs represented 47% of patients with < 3 years and 37% of patients with ≥ 3 years of follow-up. Mean overall ART adherence was significantly higher among STR patients compared with MTR patients in both follow-up cohorts (< 3-year, 53% vs. 39%, respectively; ≥ 3-year, 61% vs. 45%, respectively; $P < 0.0001$ for both comparisons). Similarly, a greater proportion of STR patients in the < 3-year and ≥ 3-year follow-up groups achieved ≥ 95% adherence (14% and 20%, respectively) compared with MTR patients (6% and 5%, respectively; Table 3).

Less adherent patients in both cohorts had numerically lower pharmacy costs compared with highly adherent patients (Table 4). This difference was significant for the cohort with ≥ 3 years of follow-up data (PDC < 95%, $18,794; PDC ≥ 95%, $26,771; $P < 0.0001$).

TABLE 3	Overall Adherence			
Patients with <3-year data (n = 686)				
Cohort	n	Overall PDC	Standard Deviation	P Value
MTR	364	39%	26	<0.0001
STR	322	53%	28	
Adherence	n		Proportion of Patients	
PDC<95%	620			
MTR			94%	
STR			86%	
PDC≥95%	66			
MTR			6%	
STR			14%	
Patients with ≥3-year data (n = 1,012)				
Cohort	n	Overall PDC	Standard Deviation	P Value
MTR	635	45%	28	<0.0001
STR	377	61%	31	
Adherence	n		Proportion of Patients	
PDC<95%	906			
MTR			95%	
STR			80%	
PDC≥95%	106			
MTR			5%	
STR			20%	

MTR = multiple-tablet regimen; PDC = proportion of days covered; STR = single-tablet regimen.

In both follow-up cohorts, less adherent patients had numerically higher mean annual medical costs (excluding pharmacy costs) compared with highly adherent patients, and this difference was statistically significant for the ≥3-year follow-up cohort (less adherent patients, $8,224; highly adherent patients, $3,097; $P = 0.0007$). In addition, statistically significant cost savings were realized in mean annual inpatient costs among highly adherent patients in both cohorts: −$2,525 in the <3-year follow-up cohort ($P = 0.0003$ vs. nonadherent patients); −$815 in the ≥3-year follow-up cohort ($P < 0.001$). However, there was no statistical differences observed in the total costs between the highly adherent and nonadherent patients.

■ Discussion

This study assessed ART adherence in patients with HIV-1 and its potential association with health care utilization and costs. Patients with Medicaid insurance were less adherent to ART and had a greater number of comorbidities than patients with commercial insurance (Table 1). These findings are not surprising given the socioeconomic challenges typically faced by patients with Medicaid insurance, including lower income, lower literacy rates, poorer nutrition, and less access to transportation and stable housing.[7-9,16] Many of these challenges intersect with or affect known barriers to medication adher-

ence, such as regimen complexity (e.g., pill burden and dosing frequency), concerns about medication side effects, overall mental or physical health, beliefs about ART utility, stigma associated with having HIV, and other patient-related and sociodemographic variables.[7-9,17]

Comparisons between STRs and MTRs among patients with commercial insurance demonstrated significantly higher ART adherence with STRs. These findings are consistent with previous studies that demonstrated superior ART adherence with a single pill per day compared with multiple pills per day.[6,10-13] In several of these studies, the superior adherence associated with STRs was also associated with a lower risk of hospitalization compared with MTRs.[6,11,13] For example, an analysis of Medicaid claims data in which 1,797 of 7,381 included patients were treated with an STR showed that STR patients had fewer hospitalizations ($P < 0.0012$) than MTR patients and lower total monthly health care costs than MTR patients ($2,959 vs. $3,544, respectively; $P < 0.0001$; mean follow-up duration, 348 days for STRs, 433 days for MTRs).[6]

Compared with highly adherent patients, less adherent patients in both follow-up cohorts in our study had numerically lower pharmacy costs. Patients in the <3-year follow-up cohort had higher medical costs at lower adherence levels compared with the ≥3-year follow-up cohort, but the difference was not significant. However, inpatient costs were significantly higher for less adherent patients in this cohort ($P = 0.0003$). This is likely attributable to the longer average hospital stays in this cohort because there was no difference in the number of inpatient visits between highly adherent and less adherent patients. In the ≥3-year follow-up cohort, patients with high adherence had significantly lower medical costs (excluding pharmacy costs) compared with less adherent patients (PDC <95%, $8,224; PDC≥95%, $3,097; $P = 0.0007$). This cost difference may be the result of the higher average number of inpatient visits and longer hospital stays for less adherent patients compared with highly adherent patients.

Statistically significant effect of ART adherence on medical costs in our study did not manifest until after 3 years of follow-up. However, similarly to Pruitt et al,[14] our study indicates that although not statistically significant, the total costs (medical and pharmacy) are higher for patients who are highly adherent compared with patients who are less adherent. This result may be attributed to higher pharmacy costs for the adherent patients in both cohorts.

This health care cost analysis examined the complex relationship between ART adherence and health care costs and utilization over time for commercially insured patients with HIV-1. Patients on STRs were shown to be more adherent than patients on MTRs regardless of the follow-up duration. The lower proportion of Medicaid patients on STRs compared with commercial patients in this analysis may reflect difficulty accessing these medications in the Medicaid population.

| TABLE 4 | Annual Health Care Utilization and Costs |

Measure		Patients with < 3-Year Data				Patients with ≥ 3-Year Data			
		All (N = 686)	PDC < 95% (n = 620)	PDC ≥ 95% (n = 66)	P Value	All (N = 1,012)	PDC < 95% (n = 906)	PDC ≥ 95% (n = 106)	P Value
Utilization,[a] mean (SD)	Number of inpatient visits	0.35 (1.75)	0.33 (1.70)	0.50 (2.14)	0.5535	0.28 (1.00)	0.30 (1.05)	0.08 (0.40)	< 0.0001
	Average length of stay	2.98 (4.79)	3.07 (5.00)	2.34 (2.68)	0.0054	1.32 (1.43)	1.35 (1.44)	0.77 (1.10)	< 0.0001
	Outpatient visits	5.80 (4.53)	5.86 (4.61)	5.26 (3.72)	0.2266	4.87 (4.12)	4.88 (4.25)	4.77 (2.85)	0.726
	Laboratory visits	3.05 (4.61)	3.23 (4.79)	1.40 (1.59)	< 0.0001	1.66 (5.15)	1.80 (5.42)	0.44 (0.68)	< 0.0001
	Emergency room visits	0.38 (0.86)	0.38 (0.88)	0.29 (0.65)	0.2972	0.26 (0.45)	0.26 (0.46)	0.19 (0.34)	0.0406
Costs, mean (SD), $[b]	Inpatient	2,690 (15,156)	2,933 (15,908)	408 (2,237)	0.0003	773 (5,775)	859 (6,098)	44 (192)	< 0.0001
	Outpatient	860 (1,316)	868 (1,368)	785 (654)	0.3971	781 (2,804)	798 (2,959)	631 (480)	0.1241
	Laboratory	1,641 (10,740)	1,712 (11,281)	976 (1,832)	0.1465	1,062 (4,583)	1,148 (4,829)	325 (794)	< 0.0001
	Emergency department	319 (907)	299 (740)	505 (1,849)	0.3731	246 (561)	250 (573)	215 (445)	0.4663
	Other costs	4,956 (20,238)	4,759 (17,643)	6,799 (36,715)	0.6571	4,824 (28,787)	5,169 (30,199)	1,883 (10,425)	0.0217
	Medical	10,467 (32,722)	10,572 (32,231)	9,474 (37,280)	0.8185	7,687 (31,219)	8,224 (32,758)	3,097 (10,559)	0.0007
	Pharmacy	23,706 (19,689)	23,385 (20,049)	26,727 (15,728)	0.1145	19,630 (16,746)	18,794 (16,551)	26,772 (16,777)	< 0.0001
	Total	34,173 (39,096)	33,957 (38,280)	36,201 (46,356)	0.7053	27,317 (36,850)	27,018 (38,324)	29,869 (20,209)	0.2244

[a]Utilization was calculated for the entire cohort
[b]Rounded to the nearest dollar.
PDC = proportion of days covered; SD = standard deviation.

Medicaid patients may encounter formulary restrictions (e.g., prior authorizations requirements) that may delay access to required regimens,[18] and they ultimately may not be considered in favor of less costly alternatives.

In the commercial population, overall adherence was low regardless of follow-up period, and the proportion of patients attaining 95% adherence ranged between 5%-20%, depending on regimen (STR or MTR; Table 3). Given the multifactorial nature of medication adherence, access to STRs and other strategies to enhance adherence among patients are critical.

While measurement of medication adherence rates at the population level based on pharmacy claims data is of value for epidemiologic and policy-making purposes, these population-based measures provide minimal information about individual patients. It is important to promote near-perfect adherence at the individual patient level because of its effect on individual ART effectiveness and on public health issues such as preventing the emergence of treatment resistance and minimizing the risk of HIV transmission.

Limitations

There are several limitations to consider in interpreting the results of this analysis. First, the analysis is based on real-world claims data, and services performed but not billed are not included in the study (e.g., physician samples for pharmaceutical products and services performed pro bono). Also, although the data assessed were representative of an array of geographic regions, the results may not be generalizable to all regions of the United States. Finally, the relationship between adherence and total medical costs is more nuanced than previously reported and may be affected by the duration of follow-up. Therefore, our results suggest further examination of the effect of improved adherence over a longer period of time on clinical and cost outcomes.

■ Conclusions

In this study, overall adherence was less than optimal for patients living with HIV. However, patients on STRs were more adherent than patients on MTRs. The relationship between adherence and total medical costs is more nuanced than previously reported, depending on the length of follow-up. Results suggest further examination of the time dependency of improved adherence to improved clinical and cost outcomes.

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