Risk Factors, Health Care Resource Utilization, and Costs Associated with Nonadherence to Antiretrovirals in Medicaid-Insured Patients with HIV

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ABSTRACT

BACKGROUND: Adherence to antiretrovirals (ARVs) is critical to achieving durable virologic suppression.

OBJECTIVE: To investigate risk factors of poor adherence and the effect of suboptimal adherence on health care resource utilization (HCRU) and costs in Medicaid patients.

METHODS: A retrospective longitudinal study was conducted using Medicaid data. Adults (aged ≥ 18 years) with human immunodeficiency virus (HIV)-1 initiating selected ARVs (index date) were identified. Adherence was measured using medication possession ratio (MPR) and proportion of days covered (PDC) at 6 and 12 months post-index. Risk factors of poor adherence ($PDC < 80\%$) were assessed using a logistic regression. HCRU and costs were compared between suboptimal ($80\% \leq PDC < 95\%$) and optimal ($PDC \geq 95\%$) adherence groups using Poisson and ordinary least square models, respectively.

RESULTS: In total, 3,477 patients were identified. Using MPR, 1,282 (39.0%) of the evaluable patients had poor adherence; 667 (20.2%) had suboptimal adherence; and 1,342 (40.8%) had optimal adherence versus 1,342 (51.1%), 509 (19.0%), and 804 (30.0%), respectively, using PDC at 6 months. PDC at 12 months was even lower. Younger age ($OR = 1.58$; 95% $CI = 1.18-2.11$; $P = 0.002$), noncapitated coverage ($OR = 1.40$; 95% $CI = 1.16-1.69$; $P < 0.001$), dual Medicaid/Medicare coverage ($OR = 5.98$; 95% $CI = 4.39-8.16$; $P < 0.001$), no baseline ARV treatment ($OR = 1.98$; 95% $CI = 1.62-2.41$; $P < 0.001$), and baseline asymptomatic HIV ($OR = 1.37$; 95% $CI = 1.13-1.68$; $P = 0.002$) were associated with higher risk of poor adherence. Suboptimal adherence patients had higher total number of days spent in a hospital (incidence rate ratio [IRR] = 1.62; 95% $CI = 1.13-2.19$; $P = 0.008$), total number of long-term care admissions (IRR = 3.11; 95% $CI = 1.26-7.39$; $P = 0.008$), total medical costs (mean monthly cost difference = \$339; 95% $CI = \$153-\536 ; $P < 0.001$), and inpatient costs (mean monthly cost difference = \$259; 95% $CI = \$122-\418 ; $P < 0.001$) compared with patients with optimal adherence.

CONCLUSIONS: Nonadherence to ARVs was observed in 60%-80% of Medicaid patients, depending on the adherence measure used, and was associated with incremental HCRU and costs. Age, insurance type and coverage, previous ARV treatment, and HIV symptoms were predictors of adherence. Treatment options that enhance adherence and prevent developing virologic failure with drug resistance should be considered for HIV patients.

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What is already known about this subject

- For people with human immunodeficiency virus (HIV), optimal adherence to antiretroviral therapy is critical in maintaining virologic suppression.
- Some studies have suggested that adherence to antiretroviral therapy is particularly challenging in low-income populations.

What this study adds

- Nonadherence to antiretrovirals was found in a large proportion of Medicaid patients with HIV and was associated with incremental health care resource utilization and costs.
- Predictors of adherence included age, insurance type and coverage, previous antiretroviral treatment, and HIV symptoms.

In the United States, the Centers for Disease Control and Prevention estimates that more than 1.2 million people had human immunodeficiency virus (HIV) infection in 2016.¹ HIV is treated using antiretroviral (ARV) therapy, which typically combines 3 or more ARVs to prevent HIV replication and disease progression and reduce the risk of transmission. ARV therapy does not cure HIV infection but can increase patients' survival and improve quality of life.^{2,3} With the success of highly active ARV therapy in decreasing mortality and morbidity, HIV has transitioned from being a terminal condition to a chronic condition that is managed over a longer period of time. This has resulted in an increase in the number of patients with HIV in the United States and, recently, a decrease in the number of new cases.⁴

In some patients with HIV, ARV therapy does not lead to sustained suppression of HIV replication. This situation is called virologic failure and usually results, if mutations develop, in a switch to a second-line therapy.^{5,6} Several factors may be responsible for virologic failure, such as drugs' barrier to resistance,^{7,8} drug-food interactions, and drug-drug interactions with concomitant medications.⁹ Optimal adherence to ARVs is also critical to achieving and maintaining virologic suppression and preventing the development of resistance and, thus, to improving overall health, quality of life, and survival.

in patients with HIV.⁸⁻¹⁰ While in many disease areas an adherence level of 80% is considered a reasonable cut-off point that stratifies adherent and nonadherent patients, in patients with HIV, adherence to ARV therapy $\geq 95\%$ is usually considered necessary for optimal ARV efficacy.¹¹⁻¹³

Some studies have suggested adherence to ARV therapy varies in different patient populations and is particularly challenging in low-income populations.¹⁴⁻¹⁶ The purpose of this study was to evaluate adherence to ARV treatment, assess the risk factors of poor adherence, and compare health care resource utilization (HCRU) and health care costs between patients with suboptimal versus optimal adherence among Medicaid-insured patients with HIV initiating commonly used ARVs.

Methods

Data Sources

Medicaid databases from 6 states (Iowa: 2Q 2012-1Q 2015; Kansas: 2Q 2012-1Q 2015; New Jersey: 2Q 2012-1Q 2014; Missouri: 2Q 2012-1Q 2015; Mississippi: 2Q 2012-1Q 2015; and Wisconsin: 2Q 2012-4Q 2013) were available for use in this study. Medicaid databases contain information on medical claims (e.g., type of service; service unit; date; *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]; Current Procedural Terminology, 4th Edition, codes; physician specialty; and type of provider); prescription drug claims (e.g., days supply, service date, and National Drug Code numbers); and eligibility (e.g., age, gender, enrollment start/end dates, and date/year of death). All data collected were de-identified in compliance with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act.¹⁷

Study Design and Patient Selection

A retrospective longitudinal study was conducted to achieve the study objectives. For the purpose of this study, the most commonly used ARVs at the beginning of the study period (November 2012) were considered: darunavir 800 mg, atazanavir 300 mg, elvitegravir 150 mg, and efavirenz 600 mg (all once-daily), and raltegravir 400 mg twice-daily. The index date was defined as the date of the first claim of one of the ARVs of interest during the study period. Agents had to be taken as part of an ARV regimen. Darunavir 800 mg and atazanavir 300 mg had to be administered in combination with ≥ 1 boosting agent (ritonavir or cobicistat). All ARV regimens had to be administered with ≥ 2 different nucleoside reverse transcriptase inhibitors (NRTIs) within 14 days; elvitegravir 150 mg had to be administered as part of the 1-pill combination elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild), which includes 2 NRTIs and 1 boosting agent.

Patients included in this study were aged ≥ 18 years, had ≥ 6 months of continuous enrollment pre-index, and had ≥ 1 diagnosis for HIV-1 (ICD-9-CM codes 042 and V08) with no other dosage of the index ARV during the 6-month pre-index

(baseline) period. These patients could have been naive to ARVs or treatment experienced. Patients diagnosed with HIV-2 during the baseline period were excluded.

Patients were observed from the index date to either the end of eligibility (e.g., disenrollment, loss of follow-up, or death) or the end of data availability (March 2015), whichever occurred first.

Outcome Measures and Statistical Analysis

Demographic and clinical characteristics were assessed during the baseline period and included age, gender, race, region characteristics, insurance eligibility, year of index date, ARV medication use (excluding boosting agents), HIV symptoms (ICD-9-CM code 042), and Charlson Comorbidity Index (CCI),¹⁸ as well as most prevalent comorbidities (any mental comorbidity excluding substance-related and addictive disorders, hypertension, substance-related and addictive disorders, psychoses, chronic pulmonary disease, and diabetes).^{19,20} Baseline total all-cause medical costs and all-cause medical costs for each type of visit (outpatient, inpatient, emergency room, long-term care, home care, and other visits) were reported.

Treatment patterns assessed during the observation period included the number of claims for any ARV (not limited to the agents used in the population selection, excluding boosting agents); the proportion of patients with ≥ 2 claims for any ARV; and time on ARV treatment, defined as the period between the first observed pharmacy claim for any ARV and the end of the last observed pharmacy claim (based on the days supply) for any ARV.

The proportion of patients with ≥ 1 or ≥ 2 observed gaps of ≥ 30 and ≥ 60 days in treatment with any ARV (not limited to the agents used in the population selection, excluding boosting agents) was assessed during the observation period and reported along with the average gap length per patient. A gap was defined as the period between the end of a pharmacy claim and the start of the following pharmacy claim for any ARV. It was calculated for patients with ≥ 2 claims for any ARV.

Adherence to any ARV (not limited to the agents used in the population selections, excluding boosting agents) was assessed during the observation period and included medication possession ratio (MPR) and proportion of days covered (PDC) at 6 and 12 months post-index, calculated among patients with ≥ 6 and ≥ 12 months of observation period, respectively. MPR was defined as the number of nonoverlapping days supply of any ARV post-index, divided by the time on treatment (in days). PDC was defined as the sum of nonoverlapping days supply of any ARV during a fixed period of time, divided by the length of the period. MPR was calculated for patients with ≥ 2 claims of any ARV. Patients were classified into 3 adherence groups based on MPR and on PDC independently: poor adherence (adherence $< 80\%$), suboptimal adherence (adherence between 80% and 95%), and optimal adherence (adherence $\geq 95\%$).^{11,21} Patients were considered to be adherent to ARV treatment even if they changed ARV regimen.

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TABLE 1 Baseline Demographic and Clinical Characteristics

	ARV Patients (N = 3,477)		ARV Patients (N = 3,477)
Demographic characteristics^a		Clinical characteristics^b	
Age, years, mean ± SD [median]	44.9 ± 10.9 [46.3]	Year of index date, n (%)	
Age categories, years, n (%)		2012	206 (5.9)
18-24	185 (5.3)	2013	2,353 (67.7)
25-34	533 (15.3)	2014	778 (22.4)
35-44	862 (24.8)	2015	140 (4.0)
45-54	1,281 (36.8)	ARV agent taken on the index date, n (%)	
≥ 55	616 (17.7)	Efavirenz	1,101 (31.7)
Male, n (%)	2,055 (59.1)	Elvitegravir	664 (19.1)
Race, n (%)		Atazanavir	596 (17.1)
White	998 (28.7)	Raltegravir	587 (16.9)
Black	1,938 (55.7)	Darunavir	580 (16.7)
Hispanic	28 (0.8)	No baseline ARV medication use, ^c n (%)	2,557 (73.5)
Other	300 (8.6)	HIV symptoms ^d	2,182 (62.8)
Unknown	213 (6.1)	CCI (excluding HIV symptoms), mean ± SD [median]	0.6 ± 1.2 [0.0]
State, n (%)		Comorbidities	
Iowa	283 (8.1)	Any mental comorbidity excluding substance-related and addictive disorders	1,050 (30.2)
Kansas	99 (2.8)	Hypertension	742 (21.3)
Mississippi	393 (11.3)	Substance-related and addictive disorders	622 (17.9)
Missouri	1,205 (34.7)	Psychoses	537 (15.4)
New Jersey	1,316 (37.8)	Chronic pulmonary disease	510 (14.7)
Wisconsin	181 (5.2)	Diabetes	305 (8.8)
Region characteristics, n (%)		Health care costs^b	
Urban	2,275 (65.4)	Monthly all-cause medical costs, ^e mean ± SD [median]	706 ± 2,106 [46]
Suburban	767 (22.1)	Outpatient visits	124 ± 318 [15]
Rural	435 (12.5)	Emergency room visits	15 ± 54 [0]
Insurance eligibility, n (%)		Inpatient visits	380 ± 1,806 [0]
Capitated or dual Medicaid/Medicare coverage	2,136 (61.4)	Long-term care admission	25 ± 415 [0]
Capitated	1,755 (50.5)	Home care	67 ± 392 [0]
Dual Medicaid/Medicare coverage	553 (15.9)	Other	96 ± 414 [0]

^aAssessed at the index date.

^bAssessed within the 6-month baseline period.

^cThe count excluded the boosting agents (ritonavir and cobicistat).

^dPresence of HIV symptoms was identified using the ICD-9-CM code 042.

^e2015 U.S. dollars.

ARV = antiretroviral; CCI = Charlson Comorbidity Index; HIV = human immunodeficiency virus; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; SD = standard deviation.

Descriptive statistics were used to report baseline characteristics, treatment patterns, and adherence outcomes. Means, standard deviations (SDs), and medians were reported for continuous variables and frequencies and percentages for categorical variables.

First, univariable logistic regression models were used to assess risk factors of poor adherence according to PDC at 6 and 12 months using odds ratios (ORs). The following potential risk factors of poor adherence were considered: age, gender, race, region, year of index date, no capitated insurance eligibility (plans where providers are paid a fixed amount per enrollee to cover a defined scope of services), and dual Medicaid/

Medicare coverage eligibility, each evaluated at index; and CCI score, baseline ARV medication use (excluding boosting agents), the most prevalent comorbidities, and HIV symptoms, each evaluated during the baseline period. Second, a multivariable regression model including all the considered risk factors was performed and ORs were reported.

Monthly HCRU and health care costs were evaluated over the observation period and reported for each type of visit (outpatient, emergency room, inpatient, long-term care, home care, and other visits). All costs represent the amount paid by Medicaid and were expressed in constant 2015 U.S. dollars using the medical care component of the Consumer Price

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Index.²² Monthly HCRU and health care costs were compared between patients with optimal (PDC $\geq$ 95%) and suboptimal (80% $\leq$ PDC<95%) adherence using PDC at 6 and 12 months. Patients with PDC<80% were excluded from this analysis due to likely different HCRU patterns and baseline characteristics than patients with suboptimal adherence.

To minimize the effect of potential confounding factors without reducing the size of the study population, inverse probability of treatment weighting (IPTW), which controls for differences in baseline characteristics between the 2 cohorts, was used. The IPTW was defined as the inverse of the probability of having suboptimal or optimal adherence, based on a multivariable logistic regression model conditional on the baseline covariates. After weighting, the baseline characteristics were compared between the 2 groups using standardized differences. Characteristics with standardized differences <10% were considered balanced.²³

HCRU incidence rate ratios (IRRs) and the mean monthly cost differences (MMCDs) between the 2 weighted groups were estimated using Poisson and ordinary least square models, respectively. Given the nonnormal distribution of the HCRU and costs, comparison tests were conducted for the IRRs and MMCDs using 95% confidence intervals (CIs) and *P* values, both estimated using a nonparametric bootstrap resampling method with 499 replications.²⁴ *P* values <0.05 were considered statistically significant. Only patients with an observation period of $\geq$ 6 and $\geq$ 12 months were considered for the analysis using PDC at 6 and 12 months, respectively.

Results

Baseline Characteristics

A total of 3,477 patients was included in the study (darunavir [n=580], atazanavir [n=596], raltegravir [n=587], elvitegravir [n=664], efavirenz [n=1,101]). Of note, drug subgroups were not mutually exclusive because a patient could be initiated on 2 or more of these drugs simultaneously.

Baseline characteristics are presented in Table 1. The mean age was 44.9 years (SD=10.9; median=46.3). Among the selected patients, 59.1% were male, 55.7% were black, 65.4% were living in an urban area, 62.8% had HIV symptoms, and 26.5% were previously treated with ARVs during the baseline period. At baseline, the most prevalent comorbidity noted was any mental comorbidity (excluding substance-related and addictive disorders), present in 30.2% of the study population. Additionally, other frequently observed baseline comorbidities included hypertension (21.3%), substance-related and addictive disorders (17.9%), psychoses (15.4%), chronic pulmonary disease (14.7%), and diabetes (8.8%). The mean monthly health care medical cost during the baseline period was \$706 (SD=\$2,106; median=\$46), mainly driven by inpatient visit costs (mean=\$380; SD=\$1,806; median=\$0).

TABLE 2 Treatment Patterns and Adherence During the Observation Period^a

	ARV Patients (N = 3,477)	
Observation period, days, mean ± SD [median]	386.5 ± 235.0 [366.0]	
≥ 6 months, n (%)	2,683	(77.2)
≥ 12 months, n (%)	1,780	(51.2)
Number of claims of any ARV, mean ± SD [median]	14.2 ± 14.2 [10.0]	
Patients with ≥ 2 claims of any ARV, n (%)	3,291	(94.7)
Time on treatment ^b for any ARV, days, mean ± SD [median]	324.5 ± 236.7 [296.0]	
Observed gaps ^c of ≥ 30 days (n = 3,291)		
≥ 1 gap, n (%)	1,348	(41.0)
≥ 2 gaps, n (%)	555	(16.9)
Average length of gap per patient, mean ± SD [median]	154.4 ± 118.0 [114.0]	
Observed gaps ^c of ≥ 60 days (n = 3,291)		
≥ 1 gap, n (%)	1,014	(30.8)
≥ 2 gaps, n (%)	364	(11.1)
Average length of gap per patient, mean ± SD [median]	199.9 ± 110.7 [188.5]	
MPR, ^d mean ± SD [median] (n = 3,291)	0.78 ± 0.26 [0.90]	
Poor adherence (MPR < 80%), n (%)	1,282	(39.0)
Suboptimal adherence (80% ≤ MPR < 95%), n (%)	667	(20.2)
Optimal adherence (MPR ≥ 95%), n (%)	1,342	(40.8)
PDC ^{e,f} at 6 months, mean ± SD [median] (n = 2,683)	0.71 ± 0.27 [0.79]	
Poor adherence (PDC < 80%), n (%)	1,370	(51.0)
Suboptimal adherence (80% ≤ PDC < 95%), n (%)	509	(19.0)
Optimal adherence (PDC ≥ 95%), n (%)	804	(30.0)
PDC ^{e,g} at 12 months, mean ± SD [median] (n = 1,780)	0.58 ± 0.31 [0.58]	
Poor adherence (PDC < 80%), n (%)	1,176	(66.1)
Suboptimal adherence (80% ≤ PDC < 95%), n (%)	298	(16.7)
Optimal adherence (PDC ≥ 95%), n (%)	306	(17.2)

^aAll counts excluded boosting agents (ritonavir and cobicistat).

^bTime on treatment was defined as the number of days between the first fill and the last refill plus the days supply of the last refill.

^cA gap was defined as a period of time between the end of a prescription and the following claim of any ARV and was calculated over the entire observation period for patients with $\geq$ 2 ARV claims.

^dMPR was defined as the number of nonoverlapping days supply of any ARV during the follow-up period divided by the time on treatment. It was calculated for patients with $\geq$ 2 ARV claims.

^ePDC was defined as the sum of nonoverlapping days supply of any ARV during a fixed period of time divided by the length of the period.

^fCalculated for patients with $\geq$ 6 months of observation period.

^gCalculated for patients with $\geq$ 12 months of observation period.

ARV = antiretroviral; PDC = proportion of days covered; MPR = medication possession ratio; SD = standard deviation.

Treatment Patterns

Table 2 presents the treatment patterns and adherence during the observation period. The mean length of the observation period post-index was 386.5 days (SD=235.0; median=366.0), and 2,683 (77.2%) and 1,780 (51.2%) patients had $\geq$ 6 and $\geq$ 12 months of observation period, respectively. The mean number of claims for any ARV was 14.2 (SD=14.2; median=10.0). Mean time on treatment was 324.5 (SD=236.7; median=296.0) days with 1,348 (41.0%) patients with $\geq$ 1 gap of $\geq$ 30 days in ARV treatment and 1,014 (30.8%) with $\geq$ 1 gap of $\geq$ 60 days.

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TABLE 3 Risk Factors of Poor Adherence (Based on the PDC at 6 Months) Using a Logistic Regression Model

Potential Risk Factors of Poor Adherence	Poor Adherence Based on PDC at 6 Months PDC < 80% ^a (n = 2,683)							
	PDC < 80% (n = 1,370)	PDC ≥ 80% (n = 1,313)	Univariable Logistic Model			Multivariable Logistic Model ^b		
	n (%)	n (%)	OR	(95% CI)	P Value	OR	(95% CI)	P Value
Age categories, years (reference: ≥ 50 years)								
18-29	172 (12.6)	131 (10.0)	1.27	(0.98-1.65)	0.074	1.58	(1.18-2.11)	0.002 ^c
30-49	722 (52.7)	722 (55.0)	0.97	(0.82-1.14)	0.684	0.96	(0.80-1.16)	0.690
≥ 50	476 (34.7)	460 (35.0)	1.00	—	—	1.00	—	—
Female (reference: male)	495 (36.1)	564 (43.0)	0.75	(0.64-0.88)	<0.001 ^c	1.10	(0.92-1.32)	0.291
Race (reference: black)								
White	476 (34.7)	318 (24.2)	1.57	(1.32-1.87)	<0.001 ^c	1.14	(0.93-1.40)	0.212
Black	723 (52.8)	758 (57.7)	1.00	—	—	1.00	—	—
Other ^d	171 (12.5)	237 (18.1)	0.76	(0.61-0.94)	0.014 ^c	1.00	(0.78-1.28)	0.976
Region characteristics (reference: suburban/rural)								
Suburban/rural	547 (39.9)	394 (30.0)	1.00	—	—	1.00	—	—
Urban	823 (60.1)	919 (70.0)	0.65	(0.55-0.76)	<0.001 ^c	1.00	(0.81-1.24)	0.995
No capitated insurance eligibility	795 (58.0)	582 (44.3)	1.74	(1.49-2.02)	<0.001 ^c	1.40	(1.16-1.69)	<0.001 ^c
Dual coverage insurance eligibility^e	392 (28.6)	69 (5.3)	7.22	(5.52-9.46)	<0.001 ^c	5.98	(4.39-8.16)	<0.001 ^c
Year of index date (reference: 2014 or after)								
Before 2014	1,071 (78.2)	1,067 (81.3)	0.83	(0.68-1.00)	0.047 ^c	1.20	(0.96-1.51)	0.117
2014 or after	299 (21.8)	246 (18.7)	1.00	—	—	1.00	(1.00-1.00)	—
No prior ARV medication use^{f,g}	1,129 (82.4)	862 (65.7)	2.45	(2.05-2.93)	<0.001 ^c	1.98	(1.62-2.41)	<0.001 ^c
CCI score (excluding HIV symptoms)^f								
0	948 (69.2)	863 (65.7)	1.33	(0.98-1.80)	0.063	1.12	(0.71-1.78)	0.624
1	238 (17.4)	219 (16.7)	1.32	(0.94-1.85)	0.113	1.03	(0.68-1.55)	0.887
2	99 (7.2)	128 (9.7)	0.94	(0.64-1.38)	0.744	0.76	(0.48-1.20)	0.240
≥ 3	85 (6.2)	103 (7.8)	1.00	—	—	1.00	—	—
Comorbidities								
Chronic pulmonary disease	191 (13.9)	217 (16.5)	0.82	(0.66-1.01)	0.063	1.17	(0.86-1.61)	0.323
Diabetes	124 (9.1)	122 (9.3)	0.97	(0.75-1.26)	0.829	1.18	(0.83-1.68)	0.358
Hypertension	274 (20.0)	297 (22.6)	0.86	(0.71-1.03)	0.098	1.02	(0.80-1.30)	0.877
Psychoses	216 (15.8)	210 (16.0)	0.98	(0.80-1.21)	0.872	0.96	(0.72-1.28)	0.768
Substance-related and addictive disorders	219 (16.0)	259 (19.7)	0.77	(0.64-0.94)	0.012 ^c	1.12	(0.89-1.43)	0.336
Any mental comorbidity excluding substance-related and addictive disorders	384 (28.0)	413 (31.5)	0.85	(0.72-1.00)	0.052	0.92	(0.72-1.17)	0.485
No HIV symptoms^{f,h}	493 (36.0)	433 (33.0)	1.14	(0.97-1.34)	0.102	1.37	(1.13-1.68)	0.002 ^c

^aIncludes patients with ≥ 6 months of observation period.

^bThe states were included in the model as a controlling factor.

^cIndicates that P < 0.05.

^dIncludes Hispanic, other, and unknown races.

^eRefers to insurance coverage by both Medicaid and Medicare.

^fAssessed within the 6-month baseline period.

^gThe count excluded boosting agents (ritonavir and cobicistat).

^hPatients with no diagnosis code for HIV with symptoms, identified using ICD-9-CM diagnosis code 042. Of note, asymptomatic HIV corresponds to the ICD-9-CM code V08. ARV=antiretroviral; CCI=Charlson Comorbidity Index; CI=confidence interval; HIV=human immunodeficiency virus; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; OR=odds ratio; PDC=proportion of days covered.

Mean MPR was 0.78 (SD=0.26; median=0.90; n=3,291). Based on MPR, 39.0%, 20.2%, and 40.8% of patients had poor, suboptimal, and optimal adherence to ARVs, respectively. Average PDC was 0.71 (SD=0.27; median=0.79; n=2,683) at 6 months and 0.58 (SD=0.31; median=0.58; n=1,780) at 12 months. Using PDC at 6 months, 51.0%, 19.0%, and 30.0% of patients had poor,

suboptimal, and optimal adherence to ARVs, respectively, versus 66.1%, 16.7%, and 17.2%, respectively, using PDC at 12 months.

Risk Factors of Poor Adherence

Assessing adherence using PDC at 6 months, the following factors were found to be associated with significantly higher

FIGURE 1 Comparison of Monthly HCRU and Associated Costs During the Observation Period Between Patients with Suboptimal Versus Optimal Adherence Based on PDC at 6 Months^a (n=2,683)

^aSuboptimal adherence is 80% ≤ PDC < 95%; optimal adherence is PDC ≥ 95%.

^bObtained from Poisson regression models with bootstrap procedure.

^cIndicates that $P < 0.05$.

^dObtained from ordinary least square regression models with bootstrap procedure.

^e2015 U.S. dollars.

CI = confidence interval; HCRU = health care resource utilization; IRR = incident rate ratio; PDC = proportion of days covered.

risk of poor adherence in the univariable analysis: white race (vs. black; OR=1.57; $P < 0.001$), noncapitated insurance coverage (OR=1.74; $P < 0.001$), dual Medicaid/Medicare coverage (OR=7.22; $P < 0.001$), and no baseline ARV treatment (OR=2.45; $P < 0.001$; Table 3). Female (OR=0.75; $P < 0.001$), other races (vs. black; OR=0.76; $P = 0.014$), urban regions (vs. suburban/urban; OR=0.65; $P < 0.001$), and earlier index dates (2012-2013 vs. 2014-2015; OR=0.83; $P = 0.047$) were associated with significantly lower risk of poor adherence (Table 3). However, in the multivariable analysis, only younger age (18-29 years vs. ≥ 50 years; OR=1.58; $P = 0.002$), noncapitated insurance coverage (OR=1.40; $P < 0.001$), dual Medicaid/Medicare coverage (OR=5.98; $P < 0.001$), no baseline ARV treatment (OR=1.98; $P < 0.001$), and baseline asymptomatic HIV (OR=1.37; $P = 0.002$) were associated with significantly higher risk of poor adherence.

Using PDC at 12 months to assess adherence (Appendix A, available in online article), white race (vs. black; OR=1.48; $P < 0.001$), noncapitated insurance coverage (OR=1.26;

$P = 0.021$), dual Medicaid/Medicare coverage (OR=13.42; $P < 0.001$), no prior ARV treatment during baseline period (OR=2.20; $P < 0.001$), and lower CCI scores (0 and 1 vs. 3 or more; OR=1.69 and $P = 0.010$ for CCI score 0; OR=1.57 and $P = 0.046$ for CCI score 1) were found to be associated with significantly higher risk of poor adherence in the univariable analysis. Females (OR=0.73; $P = 0.002$) and substance-related and addictive disorders (OR=0.75; $P = 0.031$) were associated with decreased risk of poor adherence. In the multivariable analysis, only dual Medicaid/Medicare coverage (OR=14.35; $P < 0.001$), no baseline ARV treatment (OR=1.73; $P < 0.001$), and baseline asymptomatic HIV (OR=1.48; $P = 0.003$) were associated with a significantly higher risk of poor adherence.

Comparison of HCRU and Health Care Costs Between Patients with Suboptimal Versus Optimal Adherence

To control for potential differences in baseline characteristics between patients with optimal and suboptimal adherence, IPTW was used. After weighting, most characteristics for

the 2 groups were well balanced. Post-IPTW, the effective sample sizes for the optimally ($PDC \geq 95\%$) and suboptimally ($80\% \leq PDC < 95\%$) adherent patients were 661 and 652, respectively, at 6 months, and 299 and 305, respectively, at 12 months. Using PDC at 6 months, patients with suboptimal adherence had a significantly higher total number of days spent in a hospital (0.417 days/month) compared with patients with optimal adherence (0.276 days/month) with $IRR=1.62$ (95% $CI=1.13-2.19$; $P=0.008$; Figure 1), and more long-term care admissions on average (0.003 vs. 0.001 per month) with $IRR=3.11$ (95% $CI=1.26-7.39$; $P=0.008$; Figure 1). Patients with suboptimal adherence also had significantly higher mean medical costs (\$763 monthly) compared with patients with optimal adherence (\$424 monthly) with $MMCD=\$339$ (95% $CI=\$153-\536 ; $P<0.001$; Figure 1). This difference was mainly driven by inpatient visit costs ($MMCD=\$259$; 95% $CI=\$122-\418 ; $P<0.001$; Figure 1).

Using PDC at 12 months to define the adherence groups (Appendix B, available in online article) gave similar results: significantly higher total number of days spent in a hospital ($IRR=1.79$; 95% $CI=1.17-2.70$; $P=0.004$) and significantly higher mean medical costs ($MMCD=\$341$; 95% $CI=\$70-\584 ; $P=0.008$), also mainly driven by inpatient visits ($MMCD=\$231$; 95% $CI=\$45-\411 ; $P=0.016$).

Discussion

This study revealed nonadherence rates of 60% (MPR) to 80% (PDC), as well as 30%-40% of patients with gaps in ARV treatment among Medicaid-insured patients with HIV initiated on commonly used ARVs, suggesting a large proportion of patients were nonadherent to ARVs.

These findings seem to be more pronounced in this study of Medicaid patients than in other studies of commercially insured patients with HIV. For instance, a study of a commercially insured population revealed that about 75% of patients with HIV had PDC at 6 months $\geq 80\%$, and 80% and 69% had $MPR \geq 80\%$ and $\geq 90\%$, respectively,¹⁵ versus only 49% with PDC at 6 months $\geq 80\%$, and 61% and 50% with $MPR \geq 80\%$ and $\geq 90\%$, respectively, in the current study. Our results were, nevertheless, consistent with most reports using Medicaid data.

A previous study on Medicaid patients with HIV showed that mean PDC at 12 months was 0.64 (vs. 0.58 for the current study), with 32% of patients having $PDC \geq 90\%$ (vs. 24% for the current study).²⁵ In another study using multistate Medicaid data on HIV-infected adults aged 50-64 years, 32% of patients had a PDC by combination ARV therapies at 11 months $\geq 95\%$.²⁶ Using a slightly different adherence definition, the current study found that 17.2% of patients had $PDC \geq 95\%$ at 12 months. To our knowledge, only 1 study (by Juday et al., 2013) appears to conflict with our findings on adherence levels, reporting higher optimal adherence rates in different ARV groups using Medicaid data (around 50% of patients had $PDC \geq 95\%$ over the entire observation period).²⁷

However, in the Juday et al. study, the follow-up period ended when a gap of ≥ 30 days was observed in the initial therapy. Consequently, no gaps of ≥ 30 days were included in the period used to assess adherence, potentially inflating it artificially. In contrast, our study identified a significant proportion of patients who experienced gaps of ≥ 30 days and ≥ 60 days. These large gaps in treatment are important to consider, as they may more accurately depict real-world adherence to treatment and identify sporadic treatment patterns that could increase the risk of HIV-1 drug resistance.

In the current study, adherence appeared to be higher at 6 months than at 12 months. The proportion of patients with poor adherence was 51.1% and 66.1% using PDC at 6 and 12 months, respectively. Risk factors associated with poor adherence also varied based on whether the PDC was evaluated at 6 or at 12 months. While younger age (18-29 vs. ≥ 50 years), noncapitated insurance coverage, dual Medicaid/Medicare coverage, no baseline ARV use, and baseline asymptomatic HIV were found to be significantly associated with poor adherence using PDC at 6 months, only dual Medicaid/Medicare coverage, no baseline ARV use, and baseline asymptomatic HIV were significantly associated with poor adherence at 12 months. These findings suggest that predicting adherence to ARVs at different time points of treatment could be challenging, and adherence assessments should be conducted continuously throughout treatment.

Our findings confirm some previously documented factors associated with poor adherence.^{28,29} Becker et al. (2002) measured adherence using PDC at 12 months and found that younger HIV-infected adults are at greater risk of poor adherence.³⁰ While we could not demonstrate age as a significant predictor of poor adherence using PDC at 12 months, we did note younger age as a significant predictor of poor adherence using PDC at 6 months. This could be attributed to the different analytical methods they used. For example, instead of defining adherence groups as was done in our study, the investigators used continuous PDC and tested the effect of age using an analysis of variance model.

Additionally, our study confirmed the findings of Kong et al. (2012), who studied Medicaid-insured patients with HIV from 2003 to 2007.²⁵ These investigators found that depression was not associated with decreasing adherence. Conversely, our findings differ slightly from previous research demonstrating that black race was significantly associated with nonadherence. While we were able to identify black race as a significant predictor of poor adherence in the univariable analysis, this was not the case in the multivariable analysis. This could be partially because of the difference in the study period and the population. Additionally, the ARV regimens examined in Kong's study (lamivudine-, abacavir-, zidovudine-, emtricitabine-, efavirenz-, and lopinavir-based regimens) are very different from those used in the current study. In addition, the variables included in our logistic regression model were different.

Our study also showed that patients with suboptimal adherence had a higher total number of days spent in a hospital, more long-term care admissions, and higher medical costs compared with patients with optimal adherence. These results are consistent with other studies. For instance, Gardner et al. (2008) found that higher adherence to ARVs was associated with decreased HCRU and costs.³¹ Nachega et al. (2010) further found that higher adherence to ARVs was associated with lower health care costs, in particular, reduced hospitalization costs.³²

While this study did not examine the relationship between nonadherence and the development of drug resistance, according to DHHS guidelines as well as previous literature,^{9,12,13,33,34} one of the most common causes of virologic failure and development of ARV resistance is suboptimal adherence. Our study showed increased HCRUs and costs associated with nonadherence mainly driven by inpatient visits; however, it was not able to distinctly describe the clinical drivers of these incremental costs. A previous study has shown that ARV-experienced patients with HIV who developed secondary resistance had 22% higher mean monthly costs than those without resistance (1,291 vs. 1,083 Canadian dollars), leading the authors to hypothesize that increased costs associated with nonadherence may be driven by the development of ARV resistance.³⁵

While further research is needed to directly associate nonadherence with added costs attributed to resistance, there are several options available for clinicians that may improve adherence or help prevent the development of resistance. Today, multiple ARVs are being coformulated to allow for convenience and, in many cases, once-daily dosing. Additionally, regimens with higher barriers to resistance should be considered for patients with HIV with high risk of nonadherence.⁷

Limitations

This study has some limitations. As with all real-world data sources, the Medicaid data used may contain inaccuracies or omissions in diagnoses, billing, and other variables, although this is not expected to be differential between groups. Data from the 6 states may not be generalizable to the overall Medicaid population, other states, or non-Medicaid patients.

In addition, ARV claims were assumed to indicate their use. However, patients might not have adhered to treatment as prescribed. Thus, the adherence assessed in this study may differ from self-reported adherence or actual adherence. Social factors that could affect adherence, such as stigma and family support, are not available in claims data and were not considered as potential risk factors for poor adherence. Moreover, while our current analysis was able to identify some significant predictors of poor adherence, information on the reasons for nonadherence was not available. Additional work should be performed to examine predictors or reasons for the large gaps in treatment that were reported.

Population selection was based on a list of most commonly prescribed ARVs at the beginning of the study period. However, this list could change over time and may not reflect the current practice. Our study was not designed to assess adherence to individual components of ARV regimens, since the treatment guidelines advocate for the combination of ARVs from different classes.⁹ Also, since boosting agents taken alone do not contribute to an effective ARV regimen, and to not artificially inflate the adherence to ARVs, calculation of gaps, MPR, and PDC excluded boosting agents, even though they were part of the ARV regimens used to identify the study population. Nevertheless, regimens that involve boosting agents that are not part of coformulations represent an adherence issue that could compromise the regimen effectiveness if boosting agents were omitted. Therefore, there is risk of overestimating adherence, assuming some patients took some regimens without the accompanied boosting agents.

In this study, an adherence level of 95% was considered in the definition of optimal adherence. However, some studies, such as FOTO,³⁶ allowed 1 group of patients to skip ARV doses over the weekend and revealed noninferior success compared with constant ARV dosing. Given improvements in ARV therapy, including agents with longer half-lives and higher barriers to resistance, consideration may be given to whether previously defined adherence thresholds are still relevant or need to be reexamined.

Conclusions

Nonadherence to ARVs was observed in a large proportion of Medicaid patients and was associated with incremental HCRU and costs. These findings are of concern, as nonadherence to ARVs remains a significant cause of virologic failure. In addition, age, insurance type and coverage, prior ARV treatment, and symptomatic HIV disease were revealed as predictors of adherence. Clinicians may consider treatment options that may improve adherence and reduce the risk of drug resistance in patients at risk of virologic failure.

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Risk Factors, Health Care Resource Utilization, and Costs Associated with Nonadherence to Antiretrovirals in Medicaid-Insured Patients with HIV

DISCLOSURES

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**Risk Factors, Health Care Resource Utilization, and Costs Associated
with Nonadherence to Antiretrovirals in Medicaid-Insured Patients with HIV**

APPENDIX A Risk Factors of Poor Adherence (Based on the PDC at 12 Months) Using a Logistic Regression Model

Potential Risk Factors of Low Adherence	Low Adherence Based on PDC at 12 Months PDC < 80% ^a (n = 1,780)							
	PDC < 80% (n = 1,176)	PDC ≥ 80% (n = 604)	Univariable Logistic Model			Multivariable Logistic Model ^b		
	n (%)	n (%)	OR	(95% CI)	P Value	OR	(95% CI)	P Value
Age categories, years (reference: ≥ 50 years)								
18-29	123 (10.5)	63 (10.4)	1.00	(0.71-1.42)	0.990	1.45	(0.99-2.11)	0.057
30-49	640 (54.4)	329 (54.5)	1.00	(0.81-1.23)	0.989	1.09	(0.86-1.39)	0.483
≥ 50	413 (35.1)	212 (35.1)	1.00	—	—	1.00	—	—
Female (reference: male)	392 (33.3)	246 (40.7)	0.73	(0.59-0.89)	0.002 ^c	1.04	(0.83-1.31)	0.744
Race (reference: black)								
White	438 (37.2)	167 (27.6)	1.48	(1.18-1.85)	<0.001 ^c	1.05	(0.81-1.38)	0.697
Black	599 (50.9)	338 (56.0)	1.00	—	—	1.00	(1.00-1.00)	—
Other ^d	139 (11.8)	99 (16.4)	0.79	(0.59-1.06)	0.116	1.00	(0.72-1.39)	0.978
Region characteristics (reference: suburban/rural)								
Suburban/rural	472 (40.1)	222 (36.8)	1.00	—	—	1.00	—	—
Urban	704 (59.9)	382 (63.2)	0.87	(0.71-1.06)	0.166	1.15	(0.88-1.51)	0.300
No capitated insurance eligibility^e	671 (57.1)	310 (51.3)	1.26	(1.03-1.53)	0.021 ^c	0.90	(0.70-1.16)	0.402
Dual Medicaid/Medicare coverage insurance eligibility	396 (33.7)	22 (3.6)	13.42	(8.62-20.90)	<0.001 ^c	14.35	(8.90-23.16)	<0.001 ^c
Year of index date (reference: 2014 or after)								
Before 2014	956 (81.3)	501 (82.9)	0.89	(0.69-1.16)	0.391	1.06	(0.77-1.47)	0.720
2014 or after	220 (18.7)	103 (17.1)	1.00	—	—	1.00	—	—
No prior ARV medication use^{f,g}	973 (82.7)	414 (68.5)	2.20	(1.75-2.77)	<0.001 ^c	1.73	(1.34-2.23)	<0.001 ^c
CCI score (excluding HIV symptoms)^f								
0	813 (69.1)	394 (65.2)	1.69	(1.13-2.50)	0.010 ^c	1.41	(0.78-2.55)	0.258
1	204 (17.3)	106 (17.5)	1.57	(1.01-2.45)	0.046 ^c	1.22	(0.71-2.10)	0.469
2	99 (8.4)	55 (9.1)	1.47	(0.89-2.43)	0.132	1.22	(0.67-2.22)	0.507
≥ 3	60 (5.1)	49 (8.1)	1.00	—	—	1.00	—	—
Comorbidities								
Chronic pulmonary disease	151 (12.8)	96 (15.9)	0.78	(0.59-1.03)	0.078	1.05	(0.70-1.56)	0.827
Diabetes	100 (8.5)	60 (9.9)	0.84	(0.60-1.18)	0.318	0.90	(0.57-1.43)	0.663
Hypertension	227 (19.3)	130 (21.5)	0.87	(0.68-1.11)	0.268	0.95	(0.69-1.30)	0.730
Psychoses	173 (14.7)	99 (16.4)	0.88	(0.67-1.15)	0.351	0.81	(0.55-1.18)	0.269
Substance-related and addictive disorders	182 (15.5)	118 (19.5)	0.75	(0.58-0.97)	0.031 ^c	1.04	(0.76-1.41)	0.824
Any mental comorbidity excluding substance-related and addictive disorders	313 (26.6)	181 (30.0)	0.85	(0.68-1.05)	0.135	0.93	(0.68-1.27)	0.652
No HIV symptoms^h	409 (34.8)	198 (32.8)	1.09	(0.89-1.35)	0.400	1.48	(1.14-1.91)	0.003 ^c

^aIncludes patients with ≥ 6 months of observation period.

^bThe states were included in the model as a controlling factor.

^cIndicates that $P < 0.05$.

^dIncludes Hispanic, other, and unknown races.

^eRefers to insurance coverage by both Medicaid and Medicare.

^fAssessed within the 6-month baseline period.

^gThe count excluded the boosting agents (ritonavir and cobicistat).

^hPatients with no diagnosis code for HIV with symptoms, identified using ICD-9-CM diagnosis code 042. Of note, asymptomatic HIV corresponds to the ICD-9-CM code V08.

ARV = antiretroviral; CCI = Charlson Comorbidity Index; CI = confidence interval; HIV = human immunodeficiency virus; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; OR = odds ratio; PDC = proportion of days covered.

Risk Factors, Health Care Resource Utilization, and Costs Associated with Nonadherence to Antiretrovirals in Medicaid-Insured Patients with HIV

APPENDIX B Comparison of Monthly HCRU and Associated Costs During the Observation Period Between Patients with Suboptimal Versus Optimal Adherence Based on PDC at 12 Months^a (n = 1,780)

^aSuboptimal adherence is 80% ≤ PDC < 95%; optimal adherence is PDC ≥ 95%.

^bObtained from Poisson regression models with bootstrap procedure.

^cIndicates that P < 0.05.

^dThese values could not be estimated because of insufficient sample size.

^eObtained from ordinary least square regression models with bootstrap procedure.

^f2015 U.S. dollars.

CI = confidence interval; HCRU = health care resource utilization; IRR = incident rate ratio; PDC = proportion of days covered.