RESEARCH

Adherence to Antiretroviral Therapy in Managed Care Members in the United States: A Retrospective Claims Analysis

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ABSTRACT

BACKGROUND: Antiretroviral therapy (ART) extends life for patients with human immunodeficiency virus (HIV) infection. However, HIV treatment is lifelong, and adherence presents a special challenge. Suboptimal adherence to ART may lead to disease progression and virologic failure. Earlier studies with combination ART demonstrated that as much as 90%-95% adherence was needed to prevent disease progression.

OBJECTIVE: To measure adherence to ART regimens in commercially insured patients with HIV infection and analyze the clinical and demographic factors associated with ≥90% adherence.

METHODS: This study used retrospective claims data from a Mid-Atlantic states MCO. Members 18 years and older with an HIV diagnosis identified by medical claims were included in the cohort, and pharmacy claims were retrieved for these members. An ART regimen was established for each patient within a 120-day period after the last physician's visit occurring between January 1, 2010, and August 31, 2010. For patients who received an ART regimen recommended by the U.S. Department of Health and Human Services (HHS) 2011 Antiretroviral Guidelines, adherence, as measured by medication possession ratio (MPR), was calculated based on pharmacy claims for 12 months after the end of the 120-day period. Logistic regression was used to examine the association between MPR ≥ 90% and age, sex, type of health plan, use of single-tablet regimens (STR), inpatient and outpatient utilization, and direct health care costs.

RESULTS: Of the 4,547 adults with HIV diagnosis, 3,528 (77.6%) had received at least 1 antiretroviral. An HHS-recommended ART regimen was identified in 2,377 patients with 1,136 (47.8%) receiving STR. Mean MPR for patients on an HHS-recommended ART regimen was 91.5% ± 14.0 with 73.1% of patients having achieved MPR ≥ 90%. In univariate analyses, sex, number of outpatient visits, cost of inpatient care, and use of STR were significantly associated with MPR ≥ 90%. In multivariate analysis, only male sex ($P = 0.027$) and the use of STR ($P = 0.009$) were positively associated with MPR ≥ 90%. Patients on STR were 1.3 times more likely to achieve at least 90% adherence.

CONCLUSIONS: Adherence is a challenge for patients with HIV, and more than a quarter of patients who were on an HHS-recommended ART regimen failed to achieve an accepted adherence MPR threshold of ≥ 90%. Use of STR was associated with an increased likelihood of achieving adherence of at least 90%. Interventions to improve ART adherence are needed, and STR may be an effective strategy as it decreases pill burden.

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What is already known about this subject

- Higher adherence to antiretroviral therapy (ART) for patients with human immunodeficiency virus (HIV) is associated with improved clinical outcomes, including decreased viral load, delayed progression to acquired immune deficiency syndrome (AIDS) and even decreased mortality.
- Previously reported rates of adherence to ART vary widely depending on study methodology, geographic location, and patient population.
- In a worldwide meta-analysis of 84 observational studies, only 62% of adults with HIV achieved adherence of at least 90% to ART.

What this study adds

- This study adds to the current understanding of real-world antiretroviral regimens as well as patient adherence to ART in more recent years (2010-2011).
- Only 67.4% of patients on ART were on U.S. Department of Health and Human Services (HHS)-recommended antiretroviral combinations, while 1.2% of patients were on contraindicated therapies and 31.4% of patients were on other regimens that were not listed as recommended or contraindicated.
- Mean adherence to HHS-recommended ART regimens, as calculated by medication possession ratio (MPR), was 91.5% ± 14.0, with 73.1% of patients having achieved MPR ≥ 90%.
- Patients on a single-tablet regimen (STR) were 1.3 times more likely to achieve adherence of at least 90%, as measured by MPR.

Antiretroviral therapy (ART) is the cornerstone of treatment for patients with human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS) and has been credited with extending life.[1-4] Adherence rates as high as 90%-95% were found necessary to prevent or delay therapeutic failure and progression to AIDS in studies published in the early 2000s.[5-7] This high adherence threshold, coupled with the fact that HIV treatment is lifelong, poses a special challenge in managing HIV.[1] Recently published ART adherence research is concerning: in the United States, 16% of patients with HIV admitted to missing at least 1 dose in the past 3 days,[8] and 84% of patients reported nonadherence to dose, schedule, or instructions in the last 2 days.[9]

Pharmacy claims data have been used successfully to measure adherence to ART, and the results have been shown to correlate with clinical outcomes.[6,10,11] Lower adherence, as

measured by medication possession ratio (MPR), has been found to be associated with lower CD4 counts, increased viral load, and decreased mortality. This study assesses real-world adherence to ART in recent years in the United States using retrospective pharmacy claims from a managed care organization (MCO). Medication adherence, as measured by MPR, is reported, along with factors associated with being adherent, defined as MPR ≥ 90%, to a particular ART regimen.

Methods

Study Design and Patient Selection

This retrospective database analysis obtained medical and pharmacy claims from a Mid-Atlantic MCO serving more than 1.2 million commercially insured members with medical and pharmacy benefits residing in Maryland, Virginia, and the District of Columbia. Members were eligible for inclusion if they had at least 1 *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for HIV-related manifestations or conditions (042.xx) or asymptomatic HIV infection (V08) from January 1, 2010, through December 31, 2010, in outpatient, inpatient, or emergency department claims. Members younger than 18 years on January 1, 2010, and those without continuous enrollment in both pharmacy and medical benefits from January 1, 2010, to December 31, 2011, were excluded.

Each patient was assigned an index date that was deemed the date of the last office visit from January 1, 2010, through August 31, 2010. The index date plus 120 days was used to define each patient's antiretroviral regimen in order to include 90-day refills for antiretroviral medications. The index date visit was cut off on September 1, 2010, to ensure that all patients would have at least 1 year of follow-up to evaluate adherence after the antiretroviral regimen was defined. For example, if a patient had 3 office visits during 2010—first on February 3, 2010, second on June 19, 2010, and third on November 21, 2010—the patient's regimen was assessed during the 120-day window from June 19, 2010, through October 18, 2010. Adherence to antiretroviral regimens were evaluated from October 19, 2010, to October 18, 2011.

In patients with at least 1 antiretroviral claim during the 120-day window and 1 antiretroviral claim within 12 months after the 120-day window, an index regimen during the 120-day window was defined to include the total number of antiretroviral products (i.e., marketed formulations), the use of combination products (i.e., products containing 2 or more single antiretroviral agents), and the use of single-tablet regimens (STR; i.e., once-a-day regimen). Each patient's antiretroviral regimen was also classified based upon the U.S. Department of Health and Human Services (HHS) 2011 Antiretroviral Guidelines.[1] HHS "preferred," "alternative," and "acceptable" regimens for treatment naïve patients were classified as "Recommended"; HHS regimens "not recommended" for initial therapy were classified as "Not Recommended"; all other regimens were classified as "Other." For patients receiving antiretroviral regimens classified as "Recommended," medication adherence was analyzed for 1 year after the end of the 120-day window in which the antiretroviral regimen was defined.

The University of Maryland Institutional Review Board approved the research protocol.

Primary Outcome

The primary outcome was to evaluate adherence to antiretroviral regimens as assessed by MPR in patients receiving HHS-recommended regimens. MPR was first calculated for each patient's individual antiretroviral product as the ratio of the sum of the days supply of the prescription filled by the patient divided by the number of days from the fill date of the index prescription to the last fill date plus the days supply for the final prescription fill. MPR was cut off at 1 for patients with higher than 100% adherence.

The overall antiretroviral regimen MPR for each patient was then calculated based on the weighted window of use for each individual ART product. For example, if a patient was on drug A for 6 months with an MPR = 0.8, drug B for 3 months with an MPR = 0.4, and drug C for 12 months with an MPR = 0.9, the mean MPR was calculated to be $[(0.8 \times 6 = 4.8) + (0.4 \times 3 = 1.2) + (0.9 \times 12 = 10.8)] = 16.8/21 = 0.8$. MPR for the ART regimen was then assessed as a categorical variable using the threshold adherence of ≥ 90%. Adherence was defined as MPR ≥ 90% while MPR < 90% signified poor adherence.

In the pharmacy claims database, there were both positive and negative (reversed) claims. Pharmacists generate a positive claim when prescription information is submitted to the MCO for adjudication, and a negative claim occurs when the claim is reversed. Reasons for negative claims include an error in the submission of the electronic claim and if the member does not pick up the prescription. All positive and negative matched claim duplicates were deleted to ensure that only prescriptions received by members were included in the data used in this study. For patients with changes to their index antiretroviral regimens, MPR was assessed only during the period of the index regimen.

Secondary Outcome

The secondary outcome was to explore factors associated with adherence to ART (i.e., MPR ≥ 90%) in patients receiving HHS-recommended regimens. These factors included age, sex, type of health insurance coverage, number of outpatient visits, number of hospitalizations, and the use of STRs. The frequency of resource utilization (i.e., number of outpatient visits and hospitalizations) and cost of care (including inpatient, outpatient, and pharmacy costs) were obtained during the 12 months after the 120-day window and compared.

Statistical Analysis

Descriptive statistics were reported for sociodemographic and clinical characteristics of the cohort. Patient characteristics were measured at the index date and included age, sex, and type of health plan. For the primary outcome, mean MPR as well as percentage of patients with MPR ≥ 90% were reported.

For the secondary outcome, univariate analyses examined the association between each factor (sex; age; type of health plan; use of STR; number of outpatient visits; number of hospitalizations; and the cost of inpatient, outpatient, and pharmacy care) and adherence (MPR ≥ 90%). Significant factors from univariate analyses were included in a binomial logistic regression model to determine predictors of achieving MPR ≥ 90%. Statistical significance was defined as $P \leq 0.05$.

Results

A total of 4,547 adult members were considered to have HIV (Figure 1). The mean age was 43.3 ± 10.2 years, and less than 1% of patients were over 65 years. The majority were male (73.6%), and 55.2% were enrolled in a health management organization (HMO) plan. Over one fifth of the cohort (22.4%; 1,019/4,547) had no antiretroviral claim during the 120-day window of ART establishment.

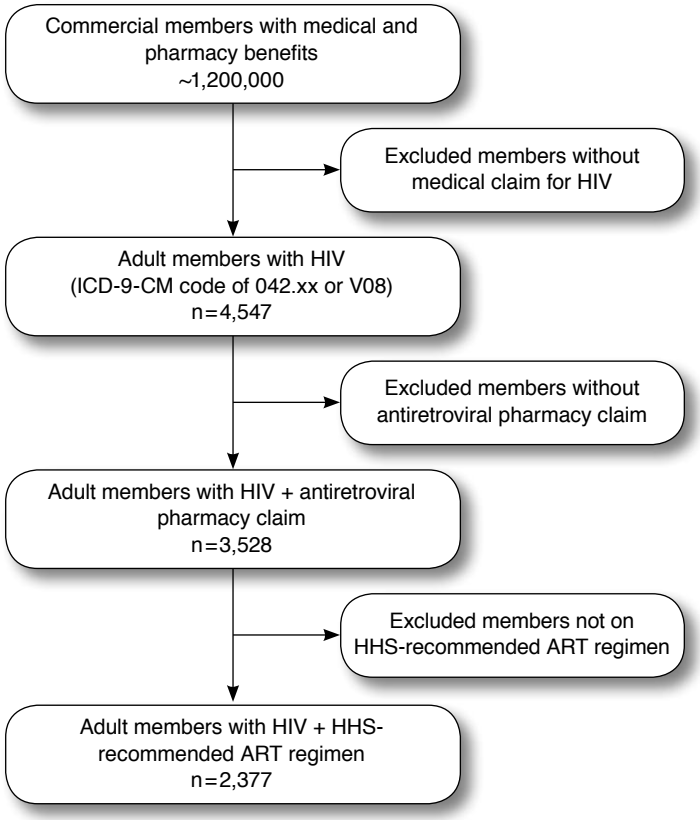
For the 3,528 patients who received ART, the mean (standard deviation [SD]) number of unique drug products was 2.2 ± 1.1 antiretroviral drugs per member with a range of 1 to 6 products. A total of 3,085 (87.4%) patients used combination products, defined as 2 or more drugs within 1 dosage form. Among those using combination products, 39.2% (1,208/3,085) were on STRs. Patients may have been receiving another ART product in addition to the STR.

About two thirds (67.4%; 2,377/3,528) of patients were on HHS "Recommended" regimens, about one third (31.4%; 1,107/3,528) were on "Other" regimens, and 1.2% (44/3,528) of patients received regimens "Not Recommended" by HHS. The use of combination products and the mean number of unique antiretroviral products differed depending on whether the ART regimen was "Recommended," "Not Recommended," or "Other" according to HHS 2011 Guidelines (Table 1). Almost half (47.8%; 1,136/2,377) of patients under HHS "Recommended" therapy were receiving STR.

For ART regimens classified as "Recommended" by HHS, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (56.6%) were most common, followed by boosted-protease inhibitor (PI) regimens (34.2%). There was little use of chemokin C-C motif receptor 5 (CCR5) inhibitors (0.3%), integrase inhibitors (6.4%), or unboosted-PI regimens (2.4%).

Of the 2,377 patients on HHS "Recommended" regimens, the mean age was 42.8 years with very few patients older than 65 years (0.7%; Table 2). The majority of patients were male (73.8%) and over half were enrolled in an HMO plan (57.7%). The mean number of outpatient visits was 3.1 visits per patient per year (PPPY), and the mean number of hospitalizations was 0.5 PPPY. The mean total health care costs (inpatient + outpatient + pharmacy) were $18,382 PPPY, of which pharmacy costs comprised 86%. Pharmacy costs for ART and non-ART prescriptions were $13,906 PPPY and $1,950 PPPY, respectively, totaling $15,856 PPPY.

FIGURE 1 Selection of Members for Study Cohort



ART=Antiretroviral therapy; HHS=U.S. Department of Health and Human Services; HIV=human immunodeficiency virus; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification.

Primary and Secondary Outcomes

For patients on HHS "Recommended" antiretroviral regimens, mean MPR was 91.5% ± 14.0 with 73.1% of patients deemed adherent (MPR ≥ 90%).

In univariate analyses, sex ($P = 0.009$), number of outpatient visits ($P = 0.015$), cost of inpatient care ($P = 0.030$), and use of STR ($P = 0.002$) were significantly associated with MPR ≥ 90% (Table 3). There was a higher percentage of men in the adherent group. This group also had higher STR use and fewer outpatient visits. The mean annual inpatient costs were $2,700 in patients who were nonadherent (MPR < 90%), which was more than double the costs for those adherent ($1,343). The type of health plan, age, number of hospitalizations, and the cost of outpatient care did not correlate significantly with MPR ≥ 90%.

TABLE 1 Characteristics of Antiretroviral Regimens Categorized by HHS 2011 Guidelines (N = 3,528)

Variable	Overall N = 3,528		HHS Recommended n = 2,377		HHS Not Recommended n = 44		Other n = 1,107	
Number of unique antiretroviral products per patient, mean [SD]	2.2	[± 1.1]	1.8	[± 0.9]	1.3	[± 0.6]	2.9	[± 1.1]
Number of patients receiving combination products, n (%)	3,085	(87.4)	2,297	(96.6)	27	(61.4)	761	(68.7)
Number of patients receiving STR, n (%)	1,208	(34.2)	1,136	(47.8)	0	(0)	72[a]	(6.5)

[a]*Patients in the "Other" category had at least 1 other antiretroviral product in addition to the STR product.*

HHS = U.S. Department of Health and Human Services; SD = standard deviation; STR = single-tablet regimen.

TABLE 2 Demographics and Clinical Characteristics of Patients on HHS-Recommended Regimens (N = 2,377)

Variable	N = 2,377	
Male, n (%)	1,754	(73.8)
Age		
Years, mean [SD]	42.8	[± 9.8]
Range (min-max), years	18-77	
18-25 years, n (%)	106	(4.5)
26-35 years, n (%)	459	(19.3)
36-45 years, n (%)	837	(35.2)
46-55 years, n (%)	752	(31.6)
56-65 years, n (%)	207	(8.7)
> 65 years, n (%)	16	(0.7)
Health plan, n (%)		
HMO	1,371	(57.7)
POS	93	(3.9)
PPO	895	(37.7)
Traditional indemnity/other	18	(0.8)
STR, n (%)	1,136	(47.8)
Office/outpatient visits		
n, mean [SD]	3.1	[± 3.0]
Hospitalizations		
n, mean [SD]	0.5	[± 3.7]
Cost, inpatient care		
$, mean [SD]	1,708	[± 12,713]
Cost, outpatient care		
$, mean [SD]	818	[± 2,333]
Cost, pharmacy		
$, mean [SD]	15,856	[± 10,134]

HHS = U.S. Department of Health and Human Services; HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization; SD = standard deviation; STR = single-tablet regimen.

In multivariate logistic regression analysis with sex, number of outpatient visits, cost of inpatient care, and use of STR as independent variables, only sex and use of STR maintained statistical significance. Male sex was positively associated with achieving MPR ≥ 90%, $P = 0.027$ (odds ratio [OR] 1.26, 95% confidence interval [CI] 1.03-1.54). Use of STR was also positively associated with achieving MPR ≥ 90%, $P \leq 0.009$ (OR 1.28, 95% CI 1.07-1.54). The number of outpatient visits and cost of inpatient care were not significantly associated with MPR ≥ 90%.

Discussion

This study adds to the current understanding of real-world prescribing of antiretroviral regimens and patient adherence to ART in the U.S. Mid-Atlantic states in recent years. About two thirds of patients who received ART were on an HHS-recommended regimen. Despite differences in study populations, a similar result was found in a study evaluating ART prescribing patterns from the Veterans Affairs Immunologic Case Registry Database. In treatment-naïve veterans, the authors reported that prescribing HHS "preferred" or "alternative" regimens in 2004 was 59.7%.[12] Our study was more recent, patients were commercially insured, HHS "acceptable" as well as "preferred" and "alternative" regimens were considered, and treatment-experienced patients were also included.

For patients on an HHS-recommended ART regimen, 73.1% were at least 90% adherent to therapy. Incomplete adherence may result in drug resistance, virologic failure, morbidity, and decreased survival.[11,13] Previous research on adherence to ART differs significantly in study methodology, reported rates of ART adherence, as well as the methods used to measure adherence. In a worldwide meta-analysis of 84 observational studies, only 62% of adults with HIV achieved adherence of at least 90% to ART.[14] A pooled analysis of 17 North American studies found that 55% of patients achieved "adequate levels of adherence," which was defined as greater than 80%, 90%, or 95% depending on the study.[15]

While recent studies suggest that a lower adherence threshold than 90% may be possible with the availability of more potent NNRTI or boosted PI regimens,[16-18] there are no definitive data. While the minimum adherence threshold needed is still being discussed, methods to improve patient adherence to ART to achieve a specific threshold have been well researched. Comprehensive, multidisciplinary approaches are required to address varied health care settings and patient populations.[19-20] Decreasing pill burden by simplifying the ART regimen is one method used to promote ART adherence.[1,21] STRs that reduce pill burden to as little as 1 pill taken once daily have been associated with improved adherence, reduced hospitalizations, and improved viral suppression.[22-26] In our study, patients who received STRs were about 1.3 times more likely to be adherent (i.e., MPR ≥ 90%) than patients receiving more than 1

antiretroviral product. Several studies showing an association with STR use and improved adherence involved the STR efavirenz/emtricitabline/tenofovir disoproxil fumarate (Atripla),[23-26] which is a recommended regimen for treatment-naïve patients per the HHS 2011 Guidelines.[1] One study concluded that patients on this fixed-dose STR reported a lower percentage of hospitalizations and emergency room visits.[24]

Over 30% of all HIV-infected patients on antiretroviral therapy in the United States already use the STR efavirenz/emtricitabine/tenofovir disoproxil fumarate, and pharmaceutical sales experts predict that it will have the highest antiretroviral sales by 2013.[27] Since the end of the time frame in which we evaluated ART regimens (i.e., 2010), 2 additional STRs have been approved by the U.S. Food and Drug Administration: emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera) in 2011 and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild) in 2012.[28,29] These regimens may differ from efavirenz/emtricitabline/tenofovir disoproxil fumarate in efficacy, adverse event profile, food restriction requirements, and tablet size, which may also affect adherence.[30]

TABLE 3 Univariate Analyses for MPR ≥ 90%

Variable	MPR < 90% n = 640		MPR ≥ 90% n = 1,737		*P* Value
Male, n (%)	447	(69.8)	1,307	(75.2)	0.009
Age					
Years, mean [SD]	42.2	[± 9.3]	43.0	[± 10.0]	0.110
Health plan, n (%)					
HMO	388	(60.6)	983	(56.6)	0.405
POS	22	(3.4)	71	(4.1)	
PPO	227	(35.5)	668	(38.5)	
Traditional indemnity/other	3	(0.5)	15	(0.9)	
STR	273	(42.7)	863	(49.7)	0.002
Office/outpatient visits					
n, mean [SD]	3.4	[± 2.9]	3.0	[± 3.1]	0.015
Hospitalizations					
n, mean [SD]	0.7	[± 4.2]	0.5	[± 3.5]	0.197
Cost, inpatient care					
$, mean [SD]	2,700	[± 18,026]	1,343	[± 10,055]	0.030
Cost, outpatient care					
$, mean [SD]	915	[± 2,476]	783	[± 2,278]	0.240
Cost, pharmacy					
$, mean [SD]	15,253	[± 7,535]	16,079	[± 10,930]	0.076

HMO = health maintenance organization; MPR = medication possession ratio; POS = point of service; PPO = preferred provider organization; SD = standard deviation; STR = single-tablet regimen.

Limitations

This retrospective claims analysis has several limitations. Since the study population included only commercially insured patients residing in the Mid-Atlantic region, results may not be representative of Medicare patients or those residing in other regions of the United States. Like other adherence studies that rely on medical and pharmacy claims and lack clinical data, this study was not able to correlate adherence directly with clinical outcomes such as viral load, progression to AIDS, or death. However, previous studies have already established the correlation between clinical outcomes and adherence, as measured by MCO prescription claims data.[10] Without clinical data, this study could not assess the exact reasons for nonadherence, switching, or discontinuation of ART.

This study did not distinguish between treatment-naïve and treatment-experienced patients but used HHS-recommended regimens for treatment-naïve patients to evaluate medication adherence. By choosing to analyze adherence only in HHS-recommended or acceptable regimens, we may have selected a more treatment-naïve population as confirmed by the lower hospitalization rates and higher adherence rates in comparison with previous studies. One large U.S. MCO study found that treatment-experienced patients are at higher risk of nonadherence to ART than treatment-naïve patients.[24]

Adherence was evaluated only for the index antiretroviral regimen and did not consider the impact of changing the antiretroviral regimen. Adherence may also be overstated for patients who switched to another ART regimen before finishing their current regimens. MPR was also only calculated for the duration of time when members had existing pharmacy claims, so we did not capture whether patients discontinued therapy completely. Proportion of days covered (PDC) is another method of calculating adherence that has been endorsed by the Pharmacy Quality Alliance and used by the Centers of Medicare and Medicaid Services (CMS) to report ART adherence starting January 2012.[31] PDC accounts for nonpersistence and is a more conservative measurement of adherence than MPR, especially when frequent switching or concomitant therapy with multiple drugs within a class is considered, such as ART. At the time of this study, PDC was not yet used by CMS to report ART adherence. Furthermore, many previous studies have used MPR as a valid measure for adherence to ART and have linked MPR with clinical outcomes such as CD4 counts, increased viral load, and decreased mortality.[6,10,11] Future studies using PDC to study adherence may be insightful, especially since CMS is using adherence to ART as a benchmark for MCO performance.

Since the ART regimen was established only within the 120-day period, patients who had medication on hand from stockpiling or patients who received drug samples may have been unintentionally excluded if they had no antiretroviral fill. This could account for why many patients had no claim for antiretroviral medications.

Research has shown that there is a decrease in treatment adherence over time.[3] Like most other adherence studies, this study assumed that adherence was stable and only evaluated adherence for 1 year. An interesting topic for future research

would be to evaluate whether adherence to ART is affected by number of years since HIV diagnosis.

Conclusions

Adherence continues to be a challenge in patients with HIV. More than a quarter of commercially insured patients who were on an HHS-recommended ART regimen failed to achieve an accepted adherence MPR threshold of ≥90%. The use of STRs was associated with achieving MPR≥90%, which supports the strategy of reducing pill burden to promote ART adherence.

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Concept and design were contributed by Cooke, Lee, and Xing. Lee was responsible for data collection, and data interpretation was performed by Cooke, Lee, and Xing. The manuscript was written by Xing, Cooke, and Lee and revised by Cooke, Xing, and Lee.

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