WEPED1418

Adherence to Antiretrovirals in Medicaid-insured Patients Living With HIV: Predictors and Economic Consequences

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BACKGROUND

- The Centers for Disease Control and Prevention estimated that over 1.2 million people were living with human immunodeficiency virus (HIV) infection in the United States (US) in 2016[1]
- With the success of highly active antiretroviral (ARV) therapy in decreasing mortality and morbidity, HIV has transitioned from being terminal to being a manageable condition for patients who consistently take their medications
- Optimal adherence to ARV therapy is critical to achieving durable virologic suppression and preventing the development of drug resistance[2,3]
- In patients living with HIV (PLWH), adherence to therapy of ≥95% has been the necessary threshold to allow for optimal ARV efficacy[4-6]
- Some studies suggest that adherence to ARV therapy varies in different patient populations and that it is particularly challenging among low-income populations[7-9]
  - We previously presented findings that demonstrated that, among a group of Medicaid beneficiaries, 70% had a proportion of days covered (PDC) <95%[9]

OBJECTIVES

- To assess the risk factors of poor adherence in a population of Medicaid beneficiaries living with HIV who initiated commonly used ARV agents
- To compare healthcare resource utilization (HRU) and associated costs between patients with suboptimal versus optimal adherence

METHODS

Data Sources

- Administrative claims from Medicaid databases from 6 states (Iowa [2012:Q2 – 2015:Q1], Kansas [2012:Q2 – 2015:Q1], New Jersey [2012:Q2 – 2014:Q1], Missouri [2012:Q2 – 2015:Q1], Mississippi [2012:Q2 – 2015:Q1], and Wisconsin [2012:Q2 – 2013:Q4]) were used for patient selection
- Medicaid databases contain information on patient eligibility (e.g., age, gender, enrollment start/end dates, and date/year of death, if applicable), medical claims (e.g., type of service, dates of service, International Classification of Diseases, 9th revision [ICD-9] diagnoses, and Current Procedural Terminology [CPT] procedure codes), and prescription drug claims (e.g., days supplied, date of dispensing, units, and National Drug Codes [NDCs])
- All data collected were de-identified in compliance with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA)[10]

Study Design and Patient Selection

- A retrospective longitudinal study was conducted
- The index date was defined as the date of the first claim for one of the following ARV agents starting from 11/2012: darunavir, atazanavir, raltegravir, elvitegravir, and efavirenz
  - These agents were selected as they were the most commonly used agents at the beginning of the study period
- The baseline period was defined as the 6 months preceding the index date
- The observation period lasted ≥6 months and spanned from the index date to either the end of eligibility (e.g., disenrollment, loss of follow-up, death) or end of data availability, whichever occurred first

Inclusion Criteria

- ≥1 claim in 11/2012 or later for one of the commonly used ARV agents at the beginning of the study period (i.e., darunavir 800 mg, atazanavir 300 mg, raltegravir 400 mg twice daily [bid], elvitegravir 150 mg, and efavirenz 600 mg) as part of a standard regimen
  - Darunavir 800 mg and atazanavir 300 mg had to be administered in combination with ≥1 boosting agent and ≥2 different nucleoside reverse transcriptase inhibitors (NRTIs) within 14 days
  - Raltegravir 400 mg bid and efavirenz 600 mg had to be administered in combination with ≥2 different NRTIs within 14 days
  - Elvitegravir 150 mg had to be administered in combination with cobicistat / emtricitabine / tenofovir disoproxil fumarate
- ≥6 months of continuous enrollment during the pre-index and post-index periods
- No use of other dosages of the index ARV agent during the 6-month baseline period
- ≥18 years of age as of the index date
- ≥1 diagnosis for HIV-1 (ICD-9 codes: 042 and V08) at any time prior to the index date
- No diagnosis for HIV-2 during the baseline period

Study Measures

- Standard demographic and clinical characteristics were assessed during the 6-month baseline (pre-index) period and are listed in **Table 1**
- Monthly HRU and healthcare costs were evaluated during the 6-month baseline period and during the observation period in total and for different types of visits (outpatient, emergency room, inpatient, long-term care, home care, and other visits)
  - All costs were expressed in constant to 2015 $US using the medical care Consumer Price Index[11]
- Adherence to any ARV, including ARVs beyond the 5 selected (excluding boosting agents), was assessed during the observation period using the PDC at 6 months
  - PDC was defined as the sum of nonoverlapping days of supply of any ARV agent during a fixed period of time divided by the length of the period
- Patients were classified into 3 groups[12,13]:
  - Patients with poor adherence to ARVs (PDC <80%)
  - Patients with suboptimal adherence to ARVs (80%≤ PDC <95%)
  - Patients with optimal adherence to ARVs (PDC ≥95%)

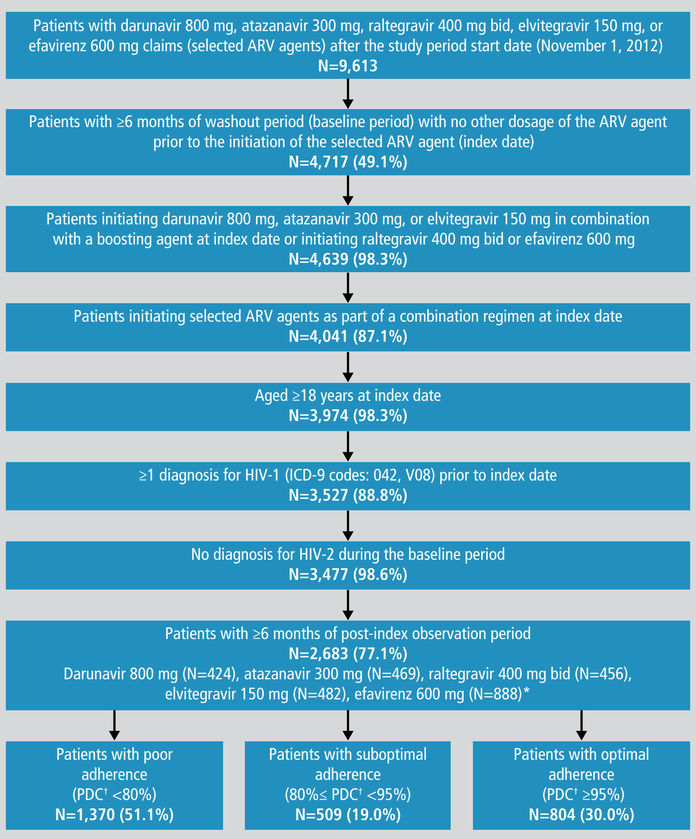
Statistical Analysis

- Descriptive statistics were generated to summarize the baseline characteristics
  - Frequency counts and percentages were used to summarize categorical variables while means, standard deviations (SDs), and medians were used for continuous variables
- Risk factors of poor adherence (PDC <80%) were assessed using odds ratios (ORs) from a multivariable logistic regression model
  - The potential risk factors of poor adherence that were considered included: age, gender, race, region characteristics, year of index date, type of insurance (capitated or dual Medicaid/Medicare coverage), baseline Quan-Charlson comorbidity index (Quan-CCI)[14] score, baseline ARV medication use (other than boosting agents), most prevalent comorbidities (based on the Elixhauser comorbidity algorithm[14] and the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* [DSM-V][15]), and baseline HIV symptoms
- Monthly HRU and healthcare costs were assessed and compared between patients with optimal (PDC ≥95%) and suboptimal (80%≤ PDC <95%) adherence. Patients with PDC <80% were excluded assuming they would have different HRU patterns and baseline characteristics than patients with suboptimal adherence
  - Inverse probability of treatment weighting (IPTW) was used to control for differences in baseline characteristics between the 2 cohorts
  - To ensure balance after weighting, baseline characteristics were compared between the 2 groups using standardized differences. Characteristics with standardized differences <10% were considered to be balanced[16]
  - HRU incidence rate ratios (IRRs) of patients with suboptimal adherence versus patients with optimal adherence were estimated using Poisson models
  - Mean monthly cost differences (MMCDs) between the 2 weighted groups were estimated using ordinary least squares models
  - Given the non-normal distribution of the HRU and healthcare costs, the comparison tests were conducted for the IRRs and MMCDs using 95% confidence intervals (CIs) and *P* values that were both estimated using a nonparametric bootstrap resampling method with 499 replications[17]

RESULTS

Demographic and Clinical Characteristics at Baseline

- A total of 2,683 PLWH met all selection criteria (darunavir 800 mg [N=424], atazanavir 300 mg [N=469], raltegravir 400 mg bid [N=456], elvitegravir 150 mg [N=482], efavirenz 600 mg [N=888]); these drug subgroups were not mutually exclusive (**Figure 1**)
- Among the study population, 1,370 (51.1%) patients had poor adherence (PDC <80%), 509 (19.0%) had suboptimal adherence (80%≤ PDC <95%), and 804 (30.0%) had optimal adherence (PDC ≥95%) at 6 months post-index (**Figure 1**)



*The different drug subgroups were not mutually exclusive.
†PDC was evaluated at 6 months post-index.

Figure 1. Identification of the study population.

- The mean age was 45.0 years (SD=10.7, median=46.6, range=18.1-83.8), 60.5% were male, 55.2% were black, 64.9% were living in an urban area, 62.9% had baseline HIV symptoms, and 74.2% were not treated with any ARV drug during the 6-month baseline period (**Table 1**)
- The mean Quan-CCI, excluding HIV symptoms, was 0.6 (SD=1.2; **Table 1**)
- The most prevalent comorbidities during the baseline period were any mental comorbidity except substance-related and addictive disorders (29.7%, based on the DSM-V), hypertension (21.3%, based on the Elixhauser comorbidity algorithm), substance-related and addictive disorders (17.8%, DSM-V), psychoses (15.9%, Elixhauser), chronic pulmonary disease (15.2%, Elixhauser), and diabetes (9.2%, Elixhauser; **Table 1**)
- The mean total monthly medical cost during the baseline period was $719, mainly driven by inpatient costs ($373; **Table 1**)

Table 1. Baseline Demographic and Clinical Characteristics Evaluated During the 6-month Baseline Period

	ARV patients (N=2,683)
Demographic characteristics	
Age, years, mean ± SD [median]	45.0 ± 10.7 [46.6]
Age categories, years, n (%)	
18-24	131 (4.9)
25-34	398 (14.8)
35-44	673 (25.1)
45-54	1,016 (37.9)
≥55	465 (17.3)
Male, n (%)	1,624 (60.5)
Race, n (%)	
White	794 (29.6)
Black	1,481 (55.2)
Hispanic	17 (0.6)
Other	218 (8.1)
Unknown	173 (6.4)
Region characteristics, n (%)	
Urban	1,742 (64.9)
Suburban	587 (21.9)
Rural	354 (13.2)
Insurance eligibility, n (%)	
Capitated or dual Medicaid/Medicare coverage	1,615 (60.2)
Capitated	1,306 (48.7)
Dual Medicaid/Medicare coverage	461 (17.2)
Year of index date, n (%)	
2012	197 (7.3)
2013	1,941 (72.3)
2014	545 (20.3)
Baseline clinical characteristics	
No baseline ARV medication use, n (%)	1,991 (74.2)
Baseline HIV symptoms	1,687 (62.9)
Quan-CCI (excluding HIV symptoms*), mean ± SD [median]	0.6 ± 1.2 [0.0]
Comorbidities	
Any mental comorbidity except substance-related and addictive disorders[15]	797 (29.7)
Hypertension[18]	571 (21.3)
Substance-related and addictive disorders[15]	478 (17.8)
Psychoses[18]	426 (15.9)
Chronic pulmonary disease[18]	408 (15.2)
Diabetes[18]	246 (9.2)
Baseline healthcare costs	
Monthly all-cause medical costs, $US 2015, mean ± SD [median]	719 ± 2,123 [49]
Outpatient costs	128 ± 320 [16]
Emergency room costs	13 ± 48 [0]
Inpatient costs	373 ± 1,830 [0]
Long-term care admission costs	24 ± 414 [0]
Home care costs	73 ± 415 [0]
Other costs	107 ± 460 [0]

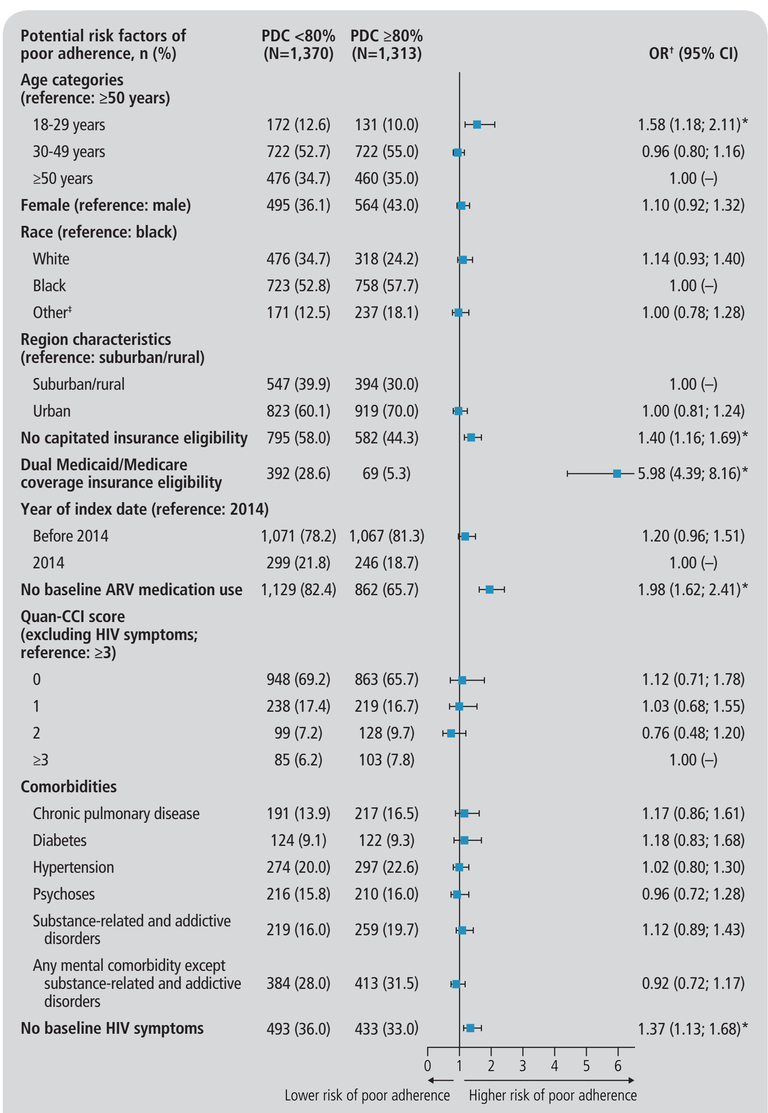
*The presence of HIV symptoms was identified using the ICD-9 code: 042.

Risk Factors of Poor Adherence

- Multivariable analysis showed that the following factors were associated with significantly higher risk of poor adherence (**Figure 2**):
  - 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 ARV treatment (OR=1.98; *P* <0.001) and no HIV symptoms (OR=1.37; *P*=0.002) during the baseline period

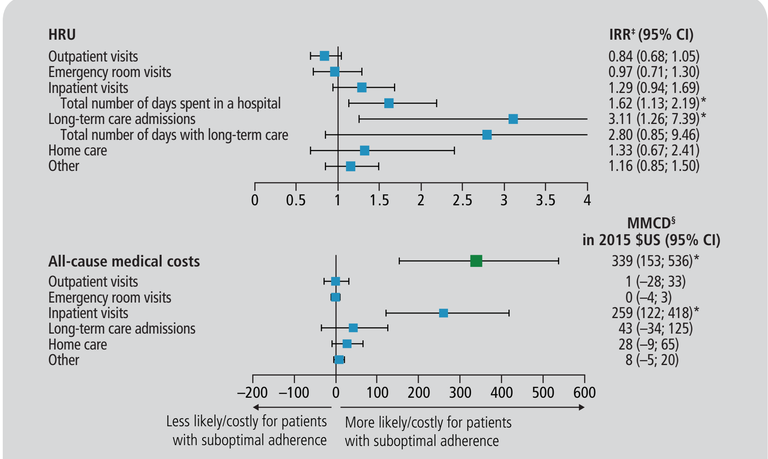
Comparison of HRU and Healthcare Costs Between Patients With Suboptimal (80%≤ PDC <95%) Versus Optimal (PDC ≥95%) Adherence

- After IPTW (optimal adherence group N=661; suboptimal adherence group N=652), most characteristics considered were well balanced (data not shown)
- Compared to PLWH with optimal adherence, those with suboptimal adherence had:
  - Significantly higher total number of days spent at the hospital (IRR=1.62; 95% CI=[1.13; 2.19]; *P* <0.05) and more long-term care admissions (IRR=3.11; 95% CI=[1.26; 7.39]; *P* <0.05; **Figure 3**)
  - Significantly higher mean monthly medical costs (MMCD=$339; 95% CI=[$153; $536]; *P* <0.05). This difference was mainly driven by inpatient visit costs (MMCD=$259; 95% CI=[$122; $418]; *P* <0.05; **Figure 3**)



*P <0.05.
†Obtained from a logistic regression model.
‡Includes Hispanic, other, and unknown races.

Figure 2. Risk factors of poor adherence (PDC <80%).



IPT=inverse probability of treatment.
*P <0.05.
†PDC was evaluated at 6 months post-index.
‡Obtained from Poisson regression models with bootstrap procedure.
§Obtained from ordinary least squares regression models with bootstrap procedure.

Figure 3. Comparison of monthly HRU and associated costs during the observation period between IPT-weighted patients with suboptimal (80%≤ PDC† <95%) versus optimal (PDC† ≥95%) adherence.

LIMITATIONS

- Claims databases may contain inaccuracies or omissions in diagnoses and other variables, although this is not expected to be differential between cohorts
- The Medicaid data used in the study came from 6 states and may not be generalizable to the overall Medicaid population, other states, or non-Medicaid patients
- Claims for ARVs were assumed to indicate their use. However, patients might not have adhered to their treatment regimen as prescribed. Thus, the adherence assessed in this study may be different from self-reported adherence and from the actual adherence
- Social factors that could affect adherence to medication, such as stigma and family support, are not available in claims data and cannot be evaluated in this study
- The population selection requirement of "commonly prescribed ARV agents" was based on a list of those most commonly prescribed at the time this study began (2012). However, this list could change over time and may not reflect current practice
- As boosting agents taken alone do not contribute to an effective ARV regimen, PDC calculation excluded boosting agents so as not to artificially inflate ARV adherence estimates, despite the fact that boosting agents were part of the ARV regimens used to identify the study population
  - Nevertheless, regimens that require boosting agents to be given separately may complicate patients' ability to fully adhere to their regimens. Therefore, there was still a risk of overestimating adherence, assuming some patients took regimens without the accompanied boosting agents
- While our study documents an increase in HRU and costs associated with suboptimal adherence, which were mainly accounted for by increased inpatient visits with longer stays, it is not able to distinctly describe the driver of these added inpatient visits

CONCLUSIONS

- **Nonoptimal adherence (PDC <95%) to ARV therapy was observed in a large proportion of Medicaid PLWH in this study, and it was associated with increased HRU and costs**
- **Younger age, noncapitated insurance coverage, dual Medicaid/Medicare coverage, no prior use of ARVs, and absence of HIV symptoms were found to be significantly associated with poor adherence**
- **Given that one of the most common causes of virologic failure and development of ARV drug resistance is nonadherence, clinicians should consider patient risk factors for nonadherence when selecting ARV regimens**
- **While further research is needed to directly associate nonadherence to incremental costs associated with virologic failure and resistance, clinicians may consider fixed-dose combinations, which may improve adherence, and ARVs with a high genetic barrier, which may help prevent the development of virologic failure with HIV drug resistance**

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ACKNOWLEDGMENTS

All authors participated in the design of the study, interpretation of the results, and preparation of the poster. MHL, HR, BE, and PL conducted the statistical analyses. This study was supported by Janssen Scientific Affairs, LLC. Editorial assistance was provided by Shannon O'Sullivan, ELS, of MedErgy, and was funded by Janssen Scientific Affairs, LLC.

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Presented at the 9th International AIDS Society (IAS) Conference; July 23-26, 2017; Paris, France.