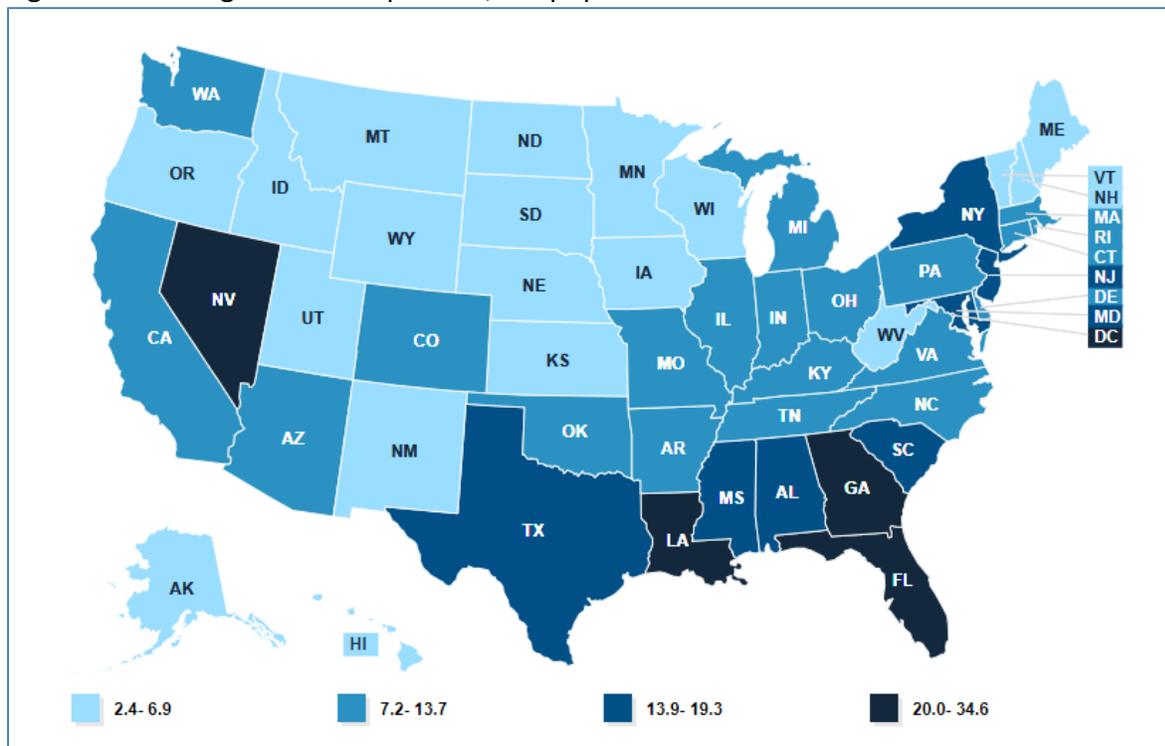


ANTIRETROVIRAL ADHERENCE IN THE TREATMENT OF HIV

BACKGROUND

In 2018, an estimated 37.9 million individuals worldwide were living with human immunodeficiency virus (HIV).¹ Over 1.1 million individuals in the United States (US) currently live with the disease, with an estimated 38,000 new infections annually.² In 2018, HIV/AIDS and related infections were responsible for over 770,000 deaths worldwide with over 17,000 deaths in the United States alone.³ Populations at greatest risk of contracting HIV include men who have sex with men, injection drug users, African Americans, and Hispanics.⁴ Within the US, new HIV diagnoses are not distributed evenly across the country. Southern states experience the greatest disease burden and account for 52% of new US HIV/AIDS diagnoses.^{2,5} The Centers for Disease Control and Prevention stated in 2019 that there was an “HIV epidemic” affecting Southern states, including Mississippi.⁵ According to the 2018 HIV Surveillance Report, there are over 9,000 people living with HIV in Mississippi.⁶ In 2018, Mississippi was tied with Maryland as having the 6th highest incidence of HIV infection in the US with a diagnosis rate of approximately 19.3 per 100,000 population.⁷ (Figure 1) The US average diagnosis rate was 13.6 per 100,000 population. More specifically, Jackson, Mississippi had the 7th highest diagnosis rate of HIV infections (23.6) for all metropolitan statistical areas measured in the US.⁶

Figure 1: HIV Diagnosis Rates per 100,000 population for the US in 2018.⁷



To prevent disease progression, the National Institutes of Health (NIH) recommends immediate initiation of antiretroviral therapy (ART) in all patients diagnosed with HIV.⁸ ART works to suppress viral replication, prevent disease progression and complications, and to prevent disease transmission.⁸ In treatment-naïve patients, initial treatment generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) paired with one of the following: a non-nucleoside reverse transcriptase inhibitor (NNRTI); integrase strand transfer inhibitor (INSTI); or a protease inhibitor (PI) combination with a pharmacokinetic enhancing agent.⁸

Adherence to ART has been found to be critical to achieving viral load suppression. For appropriate suppression of HIV and prevention of progression to AIDS, a 90% adherence rate is recommended.

- The World Health Organization (WHO) recommends a goal of 90% adherence to ART therapy.⁹ Studies have shown additional benefits when individuals taking ART attain adherence rates of 95% or greater.¹⁰⁻¹²
- The NIH guidelines do not recommend a specific threshold for adherence, but state that patients should maintain high adherence to achieve suppressed HIV replication, which is defined as plasma HIV-RNA less than 20-50 copies/mL blood.⁴
- WHO and NIH both emphasize the importance of adherence in attaining viral suppression and optimal outcomes and caution against nonadherence within this population.^{8,9}

Lack of appropriate adherence to ART therapy may result in treatment failure, increased HIV transmission rates, and the emergence of viral drug resistance.⁸ Despite severe consequences associated with nonadherence, the proportion of patients achieving WHO-defined 90% adherence threshold has been reported to be roughly half of all adults on ART.⁹

Factors associated with poor ART adherence include the following:

- psychiatric disorders,
- cognitive impairment,
- substance use disorder,
- unstable housing environment,
- concerns with adverse effects,
- low socioeconomic status,
- poor adherence to clinic visits.^{8,13}

Not only is nonadherence a threat to population health, but it places an additional burden on payers with an estimated cost of non-adherence exceeding \$30,000 per patient annually.¹⁴

The purpose of this report is to examine adherence to ART among Mississippi Medicaid beneficiaries. Understanding the scope of nonadherence within the Medicaid beneficiaries receiving ART for HIV/AIDS assists the Division of Medicaid (DOM) to develop interventions for improving ART adherence.

METHODS

A retrospective analysis of Medicaid point of sale (POS) pharmacy claims data from fee-for-service (FFS) and the three coordinated care organizations (CCOs) was conducted for the measurement period, calendar year 2019 (January 1, 2019 – December 31, 2019). Pharmacy Quality Alliance’s (PQA) Proportion of Days Covered: Antiretroviral Medications Measure (PDC-ARV-2019) was utilized to assess adherence to antiretroviral therapy.

- PDC-ARV-2019 measures the percentage of individuals 18 years and older who meet the proportion of days covered (PDC) of 90% for ≥ 3 antiretroviral medications during the measurement year.
- The eligible population included all individuals 18 years and older on the first day of the measurement period with continuous enrollment who filled a prescription for ≥ 3 distinct antiretrovirals (as a single agent or as a combination) on 2 different dates of service during the measurement year. From this population, PDC was calculated.
- The earliest date of service with an overlap of ≥ 3 distinct antiretrovirals during the measurement period was designated as the index prescription start date (IPSD).

Figure 2 displays antiretroviral medications included in the measure.

Figure 2: PQA PDC-ARV-2019 Medication List

PDC-ARV-A: Antiretroviral Medications ^{a,b}		
Single Agents		
<ul style="list-style-type: none"> • abacavir • atazanavir • darunavir • delavirdine • didanosine • dolutegravir • doravirine • efavirenz • emtricitabine 	<ul style="list-style-type: none"> • enfuvirtide • etravirine • fosamprenavir • indinavir • lamivudine • maraviroc • nelfinavir • nevirapine 	<ul style="list-style-type: none"> • raltegravir • rilpivirine • ritonavir • saquinavir • stavudine • tenofovir • tipranavir • zidovudine
Combination Agents:		
<ul style="list-style-type: none"> • abacavir & dolutegravir & lamivudine • abacavir & lamivudine • abacavir & lamivudine & zidovudine • atazanavir & cobicistat • bictegravir & emtricitabine & tenofovir • darunavir & cobicistat 	<ul style="list-style-type: none"> • darunavir & cobicistat & emtricitabine & tenofovir • dolutegravir & rilpivirine • doravirine & lamivudine & tenofovir • efavirenz & emtricitabine & tenofovir • elvitegravir & cobicistat & emtricitabine & tenofovir 	<ul style="list-style-type: none"> • emtricitabine & rilpivirine & tenofovir • emtricitabine & tenofovir • lamivudine & tenofovir • lamivudine & zidovudine • lopinavir & ritonavir

^a Active ingredients are limited to oral and subcutaneous formulations only.
^b Excludes zidovudine IV and products indicated for chronic hepatitis B (e.g., lamivudine 100mg [Epir HBV 100mg]).

RESULTS

Table 1 describes the demographic characteristics of Medicaid beneficiaries included in the analysis and Tables 2, 2a, and 2b address ART adherence.

- 78.7% of beneficiaries were between ages 36 and 65 years.
- African Americans accounted for 75.8% of beneficiaries taking antiretroviral therapy.
 - *African Americans comprise a disproportionate amount of individuals diagnosed with HIV in the US. According to the CDC, in 2018 African Americans composed approximately 13% of the US population but account for 42% of new HIV diagnoses in the US and dependent areas.*

TABLE 1. Demographic Characteristics of Mississippi Medicaid Beneficiaries on Antiretroviral Therapy (Jan 2019 - Dec 2019)					
Characteristic	FFS n = 209	UHC n = 296	Mag n = 444	Mol n = 53	Total n = 1002
Age					
18 to 35	54 (25.8%)	62 (21.0%)	77 (17.3%)	19 (35.9%)	212 (21.2%)
36 to 65	154 (73.7%)	234 (79.1%)	367 (82.7%)	34 (64.2%)	789 (78.7%)
66+	1 (0.5%)	0	0	0	1 (0.1%)
Sex					
Female	100 (47.9%)	143 (48.3%)	260 (58.6%)	26 (49.1%)	529 (52.8%)
Male	109 (52.2%)	153 (51.7%)	184 (41.4%)	27 (50.9%)	473 (47.2%)
Race					
African American	154 (73.7%)	224 (75.7%)	343 (77.3%)	38 (71.7%)	759 (75.8%)
Caucasian	35 (16.8%)	22 (7.4%)	40 (9.0%)	5 (9.4%)	102 (10.2%)
Other	20 (9.6%)	50 (16.9%)	61 (13.7%)	10 (18.9%)	141 (14.1%)
Note: FFS = Fee-for-service, UHC = UnitedHealthcare, Mag = Magnolia, Mol = Molina					

TABLE 2. Medication Adherence by Days Supply for Antiretroviral Therapy Among Mississippi Medicaid Beneficiaries (Jan 2019 - Dec 2019)

Proportion of Days Covered (PDC)	Days supply*							
	FFS		UHC		Mag		Mol	
	Less than 90-days n=185	90-days n=24	Less than 90-days n=261	90-days n=35	Less than 90-days n=386	90-days n=58	Less than 90-days n=51	90-days n=2
50 and lower	43 (23.2%)	0	56 (21.5%)	3 (8.6%)	57 (14.8%)	3 (5.2%)	9 (17.7%)	1 (50.0%)
50 to 79	56 (30.3%)	3 (12.5%)	72 (27.6%)	9 (25.7%)	78 (20.2%)	13 (22.4%)	20 (39.2%)	1 (50.0%)
80 to 89	23 (12.4%)	6 (25.0%)	37 (14.2%)	6 (17.1%)	60 (15.5%)	15 (25.9%)	9 (17.7%)	0
90 to 94	18 (9.7%)	2 (8.3%)	22 (8.4%)	6 (17.1%)	47 (12.2%)	4 (6.9%)	6 (11.8%)	0
95+	45 (24.3%)	13 (54.2%)	74 (28.4%)	11 (31.4%)	144 (37.3%)	23 (39.7%)	7 (13.7%)	0

Note: FFS = Fee-for-service, UHC = UnitedHealthcare, Mag = Magnolia, Mol = Molina

Medication adherence was calculated according to Pharmacy Quality Alliance's measure specification for Proportion of days covered: Antiretroviral medications (2019 update).

* Beneficiaries who filled at least one prescription for a 90-day supply during the measurement period were classified into the 90-day group.

Program	Overall PDC	PDC by Days Supply	
		< 90 days	90 days
FFS	37.3%	< 90 days	34.1%
		90 days	62.5%
UHC	38.2%	< 90 days	36.8%
		90 days	48.6%
MAG	49.1%	< 90 days	49.5%
		90 days	46.6%
MOL	24.5%	< 90 days	25.5%
		90 days	0.0%

Program	Overall PDC	PDC by Days Supply	
		< 90 days	90 days
FFS	27.8%	< 90 days	24.3%
		90 days	54.2%
UHC	28.7%	< 90 days	28.4%
		90 days	31.4%
MAG	37.6%	< 90 days	37.3%
		90 days	39.7%
MOL	13.2%	< 90 days	13.7%
		90 days	0.0%

- Across all pharmacy programs, 42.1% (422/1002) of beneficiaries had a PDC > 90%.
- Magnolia had the highest proportion of beneficiaries with 49.1% having a PDC > 90%.
- Beneficiaries receiving antiretrovirals for 90 days supply did not appear to negatively impact PDC overall.
 - *The number of beneficiaries receiving 90 days supply was limited and the study period limited the number of subsequent claims observed. Antiretrovirals were added to DOM's 90 day list effective April 1, 2019.*

CONCLUSIONS

Adherence to antiretroviral therapy is crucial in attaining viral suppression and optimal outcomes in individuals treated for HIV. A 90% adherence is the minimum threshold established for achieving viral suppression, with many experts emphasizing the benefits of attaining 95% adherence or better. Among Medicaid beneficiaries, only 42.1% of beneficiaries achieved PDC \geq 90%. Opportunities exist to improve adherence to antiretroviral therapy.

RECOMMENDATIONS -

1. DOM to collaborate with MSDH, UMMC Infectious Disease Department, and state medical/pharmacy/nursing associations on ART adherence issues.
2. DOM to conduct targeted outreach to providers:
 - a. Commend providers having patients with PDCs \geq 90 and seek guidance on best practices;
 - b. Educate providers with patients having PDCs $<$ 90.

References:

1. Global HIV & AIDS statistics — 2019 fact sheet. <https://www.unaids.org/en/resources/fact-sheet>. Accessed February 21, 2020.
2. January 16 P last updated: U.S. Statistics. HIV.gov. <https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics>. Published January 16, 2020. Accessed February 5, 2020.
3. WHO | Number of deaths due to HIV/AIDS. WHO. http://www.who.int/gho/hiv/epidemic_status/deaths_text/en/. Accessed February 5, 2020.
4. Anderson PL, Yager J, Fletcher CV. Human Immunodeficiency Virus Infection. In: DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V, eds. *Pharmacotherapy: A Pathophysiologic Approach, 11e*. New York, NY: McGraw-Hill Education; 2020. accesspharmacy.mhmedical.com/content.aspx?aid=1164179826. Accessed February 5, 2020.
5. *HIV In the Southern United States*. CDC; 2019. <https://www.cdc.gov/hiv/pdf/policies/cdc-hiv-in-the-south-issue-brief.pdf>.
6. HIV Surveillance Report 2018 (Preliminary). 30:129.
7. HIV Diagnoses, Adults and Adolescents. *The Henry J Kaiser Family Foundation*. February 2020. <https://www.kff.org/hiv/aids/state-indicator/hiv-diagnoses-adults-and-adolescents/>. Accessed February 26, 2020.
8. HIV/AIDS Treatment Guidelines. AIDSinfo. <http://aidsinfo.nih.gov/guidelines>. Accessed February 5, 2020.
9. Iacob SA, Iacob DG, Jugulete G. Improving the Adherence to Antiretroviral Therapy, a Difficult but Essential Task for a Successful HIV Treatment—Clinical Points of View and Practical Considerations. *Front Pharmacol*. 2017;8. doi:10.3389/fphar.2017.00831
10. Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection | Annals of Internal Medicine | American College of Physicians. <https://annals-org.umiss.idm.oclc.org/aim/article-abstract/713596/adherence-protease-inhibitor-therapy-outcomes-patients-hiv-infection>. Accessed February 28, 2020.
11. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. <https://insights-ovid-com.umiss.idm.oclc.org/pubmed?pmid=10770537>. Accessed February 28, 2020.
12. Adherence-resistance relationships to combination HIV antiretroviral therapy. - PubMed - NCBI. <https://www.ncbi.nlm.nih.gov.umiss.idm.oclc.org/pubmed/?term=adherence-resistance+relationships+to+combination+HIV>. Accessed February 28, 2020.
13. Kim J, Lee E, Park B-J, Bang JH, Lee JY. Adherence to antiretroviral therapy and factors affecting low medication adherence among incident HIV-infected individuals during 2009–2016: A nationwide study. *Sci Rep*. 2018;8. doi:10.1038/s41598-018-21081-x
14. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*. 2018;8(1). doi:10.1136/bmjopen-2017-016982