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Correlates of Combination Antiretroviral Adherence Among Recently Diagnosed Older HIV-Infected Adults Between 50 and 64 years

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Abstract Optimal adherence to combination antiretroviral therapy is essential to the health of older people living with HIV (PLWH), however, the literature on adherence and aging is limited. Using Medicaid data from 29 states (N = 5177), we explored correlates of optimal adherence among older PLWH. The prevalence of optimal adherence was low (32 %) in this study. Males were more adherent than females (APR = 1.11, 95 % CI 1.02–1.21, P = 0.0127); persons with three or more co-morbidities (APR = 0.67, 95 % CI 0.60–0.74, P < 0.001), two co-morbidities (APR = 0.86, 95 % CI 0.75–0.98, P = 0.0319) and one co-morbidity (APR = 0.82, 95 % CI 0.73–0.92, P = 0.0008) were less adherent than those without any co-morbidity; and residents of rural areas (APR = 0.90, 95 % CI 0.63–0.98, P = 0.0385) and small metropolitan areas (APR = 0.82, 95 % CI 0.72–0.94, P = 0.0032) were less adherent than residents of large metropolitan areas. There were no racial differences in optimal adherence. Targeted interventions that provide adherence support, case management, and peer navigation services may be of benefit in achieving optimal adherence in this population.

Resumen Alcanzar una óptima adherencia a la terapia antiretroviral es esencial para mantener la salud de adultos mayores viviendo con VIH (PVVIH). Sin embargo, hay una escasez de estudios enfocados en adherencia en adultos mayores. Usando datos de Medicaid provenientes de 29 estados, exploramos factores que afectan la adherencia en PVVIH que son adultos mayores. La prevalencia de adherencia óptima fue baja (32 %) entre los 5177 participantes. Los hombres fueron más adherentes que las mujeres [razón de prevalencia ajustada (RPA) = 1.11, 95 % intervalo de confianza (IC) = 1.02–1.21, P = 0.0127]; mientras que personas con tres o más comorbilidades (RPA = 0.67, 95 % IC 0.60–0.74, P < 0.001), dos comorbilidades (RPA = 0.86, 95 % IC 0.75–0.98, P = 0.0319), y una comorbilidad (RPA = 0.82, 95 % IC 0.73–0.92, P = 0.0008) fueron menos adherentes que aquellos sin comorbilidades. Residentes de áreas rurales (RPA = 0.90, 95 % IC 0.63–0.98, P = 0.0385) y áreas metropolitanas pequeñas (RPA = 0.82, 95 % IC 0.72–0.94, P = 0.0032) fueron menos adherentes que los residentes de grandes áreas metropolitanas. No hubo diferencias raciales en adherencia óptima. Intervenciones enfocadas a proveer apoyo de adherencia, coordinación de servicios y navegación por pares son críticas para alcanzar una adherencia óptima en esta población.

Keywords HIV/AIDS · Antiretroviral adherence · People living with HIV · Older adults · Aging

Palabras Clave VIH/SIDA · Adherencia antiretroviral · Personas viviendo con VIH · Adulto mayor · Envejecimiento

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Introduction

There is a major shift in the age demographic of people living with HIV/AIDS (PLWH) in the US [1]. Older adults (≥50 years) currently account for approximately half of all PLWH in the US [1]. Among all persons diagnosed with HIV in 2014, 17 % were older adults [2]. Based on current trends, it is estimated that by 2020, more than half of all PLWH in the US will be age 50 years and older [1]. The aging population of PLWH can be attributed to both new HIV infections among older people and the improved life expectancy of HIV-infected persons. Racial and sex disparities exist among older PLWH with African Americans and males bearing a disproportionate burden [3]. Older African Americans and Hispanics are 13 times and 5 times more likely to be diagnosed with HIV, respectively, than older Whites. Older males account for approximately 72 % of all infections among older PLWH [3]. The rise in the population of older PLWH in the US has spurred an emerging literature on aging and HIV with most research focusing on the immunological and clinical response to antiretroviral therapy (ART) and combination ART (cART) [4–6], ART receipt and initiation [7, 8], HIV risk behavior [9, 10], HIV stigma and ageism [11, 12], and the health of older PLWH [13–15].

The literature on adherence to cART among older PLWH is limited [16]. Optimal adherence to cART has individual health and public health benefits and is the foundation of successful HIV treatment and prevention [17–19]. Optimal cART adherence plays a critical role in the health of older PLWH as older persons are more likely to be diagnosed with HIV late in the course of their disease and progress more rapidly to AIDS when compared to younger PLWH [3]. Optimal adherence to cART suppresses viral load, improves CD4 counts and delays progression to AIDS [17–19]. The public health benefits of optimal adherence center on the reduced risk of HIV transmission and the prevention of new HIV infections following viral suppression [18, 19]. The majority of studies on HIV medication adherence have included samples composed predominantly of participants less than 50 years [20–26]. However, the factors associated with adherence among younger PLWH may be different from that of older PLWH. Findings of the few studies that have examined adherence among older PLWH have shown that suboptimal adherence to HIV medications is associated with neuro-cognitive impairment, substance and alcohol use, complex drug regimens and a greater pill burden that comes with older age [27–31]. Co-morbidities (medical, surgical, and mental health) are more common among older PLWH than younger PLWH and may affect cART adherence [32].

As the number of older PLWH continues to increase, it is critical that the factors associated with cART adherence in this population are explored. An improved understanding of the correlates of adherence among older PLWH has implications for identifying subgroups of older PLWH that may be in need of adherence support and informing targeted interventions that facilitate optimal cART adherence and health outcomes. The purpose of this study was to determine the prevalence of optimal adherence among older PLWH and assess the association between optimal adherence to cART among older PLWH and race, sex, co-morbidity, residential status, and age.

Methods

A retrospective cohort design was used to assess the correlates of cART adherence among older PLWH who received a diagnosis of symptomatic HIV or AIDS (*International Classification of Diseases, Ninth Revision, Clinical Modification code 042*). The data for this analysis were obtained from Medicaid claims from 29 states in the US (Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Louisiana, Maryland, Massachusetts, Michigan, Mississippi, Missouri, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, Washington, and Washington, D.C.) between January 1, 2008 and November 30, 2009. These states were selected based on data availability. Institutional review board approval was obtained from the Morehouse School of Medicine, Atlanta, Georgia.

Patient Selection

In order to be eligible for the study, participants had to (1) be between 50 and 64 years, (2) be enrolled in Medicaid between January 1, 2008 and November 30, 2009, (3) have received a diagnosis of symptomatic HIV or AIDS (*International Classification of Diseases, Ninth Revision, Clinical Modification code 042*) between January 1, 2008 and November 30, 2008, and (4) have received cART. We limited study inclusion criteria to Medicaid enrollees between 50 and 64 years in order to ensure that we had access to all participants' cART medications. Participants older than 64 years are eligible for Medicare and could have been accessing their medications through Medicare claims, which we did not have access to, hence the inclusion of study participants older than 64 years could have affected our evaluation of cART and cART adherence. We assessed cART adherence for 11 months between January 1, 2009 and November 30, 2009. The guidelines for cART

use during the study period included (1) one non-nucleoside reverse transcriptase inhibitor and two nucleoside reverse transcriptase inhibitors or (2) one ritonavir-boosted HIV protease inhibitor and two nucleoside reverse transcriptase inhibitors [33]. Five types of Food and Drug Administration approved ART drugs were recommended and available in Medicaid during the observation period, namely, (1) nucleoside reverse transcriptase inhibitors—zidovudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine, and tenofovir, (2) non-nucleoside reverse transcriptase inhibitors—efavirenz, nevirapine, delavirdine, and etravirine, (3) protease inhibitors—atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir, lopinavir, (4) entry inhibitors—enfuvirtide and maraviroc, and (5) integrase inhibitor-raltegravir.

Variables

Data on study participants' race, sex, residential status, co-morbidity, age, state of Medicaid enrollment and cART adherence were obtained. The study's independent variables were race (African American, White, Hispanic, and other), sex (male and female), co-morbidity (no co-morbidity [0], 1 co-morbidity, 2 co-morbidities, and 3 or more co-morbidities) residential status (large metropolitan area, small metropolitan area, and rural area) and age (50–54, 55–59, and 60–64). State of Medicaid enrollment was included as a covariate because of the different state Medicaid eligibility criteria. Participants who were identified as Asian, American Indian, Alaska Native, Pacific Islander, multiple races or unknown were categorized as other race because of their small sample size. The reference groups for the these variables were white (race), female (sex), large metropolitan area (residential status), and 50-54 (age), while the reference groups for the covariate was Georgia (state).

The Elixhauser Co-morbidity Index (ECI) [34] was used to measure non-HIV-related co-morbidity using an algorithm developed by Quan et al. [35]. Co-morbidity was categorized into three groups depending on the number of co-morbidities (0, 1, 2, $\geq$3). The ECI is a method of categorizing 30 co-morbidities based on whether a comorbidity is present or not and is used with administrative data like Medicaid [34, 35]. The ECI accounts for medical, surgical, behavioral and mental health co-morbidities [34, 35]. The reference group for this variable was no co-morbidity (0).

The outcome variable was cART adherence (optimal and suboptimal). cART adherence was measured using the proportion of prescribed days covered (PPDC). The PPDC is a commonly used method of assessing medication adherence, particularly when all medications are billed to one payer, Medicaid in this case [36]. The PPDC measures the number of days ART is available to the patient, divided by the number of days in the study period, and multiplied by 100 [36]. We averaged the PPDC from all cART to yield a summary adherence measure. The use of average PPDC for combination medications has been used in previous studies [37]. This study used a cut-off point of 95 % and above to determine optimal adherence because adherence of at least 95 % is sufficient to consistently suppress HIV [38]. A PPDC value less than 95 % was considered suboptimal adherence.

Analysis

Descriptive statistics were conducted to characterize the sample overall and by adherence (optimal and suboptimal). Unadjusted prevalence ratios (UPRs) and 95 % confidence intervals (CI) were calculated to evaluate the bivariate association between adherence and race, sex, co-morbidity, age, and residential status. A multivariable poisson regression model with robust error variance was used to estimate adjusted prevalence ratios (APRs) and 95 % CIs of the association between adherence and race, sex, co-morbidity and residential status after adjusting for study confounders (age and state). A two-tailed level of statistical significance was set at 0.05 and all analyses were conducted using SAS version 9.3.

Results

Table 1 describes the study sample overall and by adherence. A total of 5177 participants met the study's inclusion criteria. Of these, 32 % had optimal cART adherence rates ($\geq$95 %) while 68 % had suboptimal adherence rates (<95 %). The sample was predominantly African American (57.4 %), male (62 %), between 50 and 54 years (52.7 %), and resided in a large metropolitan area (82.2 %). Approximately 49.5 % of the study's participants had at least one co-morbid condition. The UPRs and 95 % CIs are shown in Table 2. Male participants (UPR = 1.15, 95 % CI 1.06–1.26, $P = 0.0008$) were significantly more likely than female participants to demonstrate optimal cART adherence. Participants with three or more co-morbidities (UPR = 0.65, 95 % CI 0.58–0.72, $P < 0.0001$), two co-morbidities (UPR = 0.83, 95 % CI 0.72–0.96, $P = 0.0105$), and one co-morbidity (UPR = 0.80, 95 % CI 0.71–0.89, $P < 0.001$) were significantly less likely than those without any co-morbidity to demonstrate optimal cART adherence. Participants who resided in a rural area (UPR = 0.76, 95 % CI 0.61–0.96, $P = 0.0190$) and participants who resided in a small metropolitan area (UPR = 0.79, 95 % CI 0.70–0.90, $P = 0.0005$) were significantly less likely than those residing in a large

Table 1 Characteristics of older people living with HIV enrolled in Medicaid (n = 5177) by adherence: Medicaid claims data, 29 U.S States, 2008–2009

Variable	Adherence		Total
	Optimal (≥95 %) n (%) 1670 (32)	Sub-optimal (<95 %) n (%) 3507 (68)	n (%) 5177
Race			
African American	890 (30)	2080 (70)	2970 (57.4)
White	290 (33)	585 (67)	875 (16.9)
Hispanic	107 (39)	169 (61)	276 (5.3)
Other	383 (36)	673 (64)	1056 (20.4)
Sex			
Male	1091 (34)	2119 (66)	3210 (62)
Female	579 (29)	1388 (71)	1967 (38)
Age			
50–54	855 (31)	1873 (69)	2728 (52.7)
55–60	554 (33)	1107 (67)	1661 (32.1)
60–64	261 (33)	527 (67)	788 (15.2)
Residential status			
Large metropolitan area	1426 (34)	2826 (66)	4252 (82.2)
Small metropolitan area	185 (27)	510 (73)	695 (13.4)
Rural area	59 (26)	171 (74)	230 (4.4)
Number of co-morbidities			
0	973 (37)	1641 (63)	2614 (50.4)
1	250 (29)	594 (71)	844 (16.4)
2	153 (31)	341 (69)	494 (9.5)
≥3	294 (24)	931 (76)	1225 (23.7)

metropolitan area to demonstrate optimal cART adherence. There were no significant differences in cART adherence by race and age in the bivariate analyses.

The results of the multivariable model with the APRs and 95 % CI are shown in Table 3. Similar to the bivariate models, sex, co-morbidity and residential status remained significantly associated with cART adherence. Male participants (APR = 1.11, 95 % CI 1.02–1.21, $P = 0.0127$) were significantly more likely to demonstrate optimal cART adherence than female participants; study participants with three or more co-morbidities (APR = 0.67, 95 % CI 0.60–0.74, $P < 0.0001$), two co-morbidities (APR = 0.86, 95 % CI 0.75–0.98, $P = 0.0319$), and one co-morbidity (APR = 0.82, 95 % CI 0.73–0.92, $P = 0.0008$) were significantly less likely than those without any co-morbidity to demonstrate optimal cART adherence; and participants who resided in a rural area (APR = 0.79, 95 % CI 0.63–0.98, $P = 0.0385$) and those who resided in a small metropolitan area (APR = 0.82, 95 % CI 0.72–0.94, $P = 0.0032$) were significantly less likely than particpants residing in a large metropolitan area to demonstrate optimal cART adherence. There were no racial or age differences in cART adherence in the multivariable model.

Discussion

This study examined the prevalence of optimal cART adherence and its correlates among a cohort of recently-diagnosed older PLWH between 50 and 64 years of age enrolled in Medicaid. The study findings showed that approximately one-third of older PLWH demonstrated optimal adherence. Though the prevalence of optimal adherence in this study is low compared to other studies of older PLWH [27–31], the cART adherence measure, study sample, and the length of the observation period in this study differed significantly from these other studies. However, the prevalence of optimal adherence among this sample of Medicaid-enrolled older PLWH is similar to the prevalence of optimal adherence (17–33 %) reported by other studies on age-diverse Medicaid samples [21, 39–41]. The low level of optimal adherence among older PLWH in this study underscores the need for adherence counseling and support programs targeted towards older PLWH enrolled in Medicaid.

Optimal adherence to cART differed by sex, residential status and co-morbidity. Males were more likely than females to be optimally adherent to cART. HIV stigma,

Table 2 Bivariate (Unadjusted) model showing associations between variables and adherence among older people living with HIV: Medicaid claims data, 29 U.S States, 2008–2009

Variable	UPR	95 % CI	*P* value
Race			
African American	0.90	0.81–1.01	0.0700
Hispanic	1.17	0.98–1.39	0.0802
Other	1.09	0.97–1.24	0.1525
White (ref)	1.00	N/A	N/A
Sex			
Male	1.15	1.06–1.26	0.0008
Female (ref)	1.00	N/A	N/A
Age			
50–54	0.95	0.84–1.06	0.3409
55–60	1.01	0.89–1.14	0.9090
60–64 (ref)	1.00	N/A	N/A
Number of co-morbidities			
≥3	0.65	0.58–0.72	<0.0001
2	0.83	0.72–0.96	0.0105
1	0.80	0.71–0.89	0.0001
0 (ref)	1.00	N/A	N/A
Residential status			
Rural area	0.76	0.61–0.96	0.0190
Small metropolitan area	0.79	0.70–0.90	0.0005
Large metropolitan area (ref)	1.00	N/A	N/A

UPR unadjusted prevalence ratio, *CI* confidence interval, significant at $P < 0.05$

Table 3 Multivariable (Adjusted) model showing associations between variables and adherence among older people living with HIV: Medicaid claims data, 29 U.S States, 2008–2009

Variable	APR*	95 % CI	*P* value
Race			
African American	0.90	0.80–1.00	0.0503
Hispanic	1.14	0.96–1.36	0.1275
Other	1.02	0.90–1.16	0.7156
White (ref)	1.00	N/A	N/A
Sex			
Male	1.11	1.02–1.21	0.0127
Female (ref)	1.00	N/A	N/A
Age			
50–54	0.95	0.85–1.07	0.4166
55–60	1.02	0.91–1.15	0.7466
60–64 (ref)	1.00	N/A	N/A
Number of co-morbidities			
≥3	0.67	0.60–0.74	<0.0001
2	0.86	0.75–0.98	0.0319
1	0.82	0.73–0.92	0.0008
0 (ref)	1.00	N/A	N/A
Residential status			
Rural area	0.79	0.63–0.98	0.0385
Small metropolitan area	0.82	0.72–0.94	0.0032
Large metropolitan area (ref)	1.00	N/A	N/A

APR adjusted prevalence ratio, *CI* confidence interval, significant at $P < 0.05$

* Adjusted for state of Medicaid enrollment

depression, lack of support from interpersonal relationships, poverty, increased level of emotional distress and medication side-effects are some factors that have been associated with sex differences in optimal adherence [42]. These findings suggest that healthcare providers should be sensitive to sex differences in cART adherence. They also point to the utility and importance of frequently screening older HIV-infected females for factors that place them at risk for suboptimal adherence and offering patient-centered strategies to mitigate this during patient encounters. Adherence support programs targeting older HIV-infected females that promote self-efficacy, offer personal and peer support, and provide adaptive coping strategies may be beneficial.

In comparison to residents of large metropolitan areas, residents of rural and small metropolitan areas were less likely to be optimally adherent to cART. The differential access to and availability of HIV healthcare between urban and rural areas can present challenges to regular medical care and follow-up appointments in rural areas [43]. Furthermore, healthcare services in rural and small metropolitan areas are less likely than large metropolitan areas to have the infrastructure to support the delivery of HIV support and comprehensive services like adherence support, case management, and patient transportation services. Other factors like poverty, health literacy, anonymity and confidentiality, and HIV stigma, which are more prevalent in rural communities [43] can lead to suboptimal adherence to cART among residents of these communities.

Older PLWH with one or more co-morbidities were less likely to be optimally adherent than those without a co-morbidity. Co-morbidities are especially prevalent among older PLWH. Polypharmacy (concomitant use of multiple medications for health conditions) increases the likelihood of drug–drug interactions and may lead to suboptimal medication adherence among older PLWH with co-morbidities [44, 45]. Co-morbidities can also exacerbate drug toxicity and contribute to suboptimal adherence in this population. Psychiatric and neuro-cognitive conditions may also affect adherence to cART by affecting older PLWH's willingness and the desire and the cognitive skills required to access, adhere and understand the benefits of cART [27, 29]. The complexities of cART medication regimen and other medication regimens that accompany co-morbidities can also increase pill burden and present

challenges to cART adherence [46]. Personal beliefs about the severity of co-morbidities and HIV can also affect cART adherence in respondents with co-morbidities [47]. Older PLWH may perceive other co-morbidities like diabetes or hypertension as more severe than HIV because, unlike HIV, they may become symptomatic more quickly if medication adherence is suboptimal [47].

There were no racial differences in optimal cART adherence rates in this study. Though some studies on age-diverse samples of PLWH have reported racial differences in adherence [39, 40] while others have not [26], to our knowledge, no study has examined racial differences in older PLWH. Further investigation into this association among older PLWH is merited, especially given the disproportionate burden of disease among racial and ethnic minorities.

Given the importance of optimal treatment for both HIV treatment and prevention, it is critical that all practice and policy-based strategies and solutions are maximized. Routinely evaluating cART adherence during clinic visits, screening for and addressing identified risk-factors among older PLWH, simplifying and explaining medication regimens where possible, and emphasizing the utility and effectiveness of optimal cART adherence to overall health and quality of life are clinical interventions that can help address suboptimal adherence in this population. Proactive discussions about the potential side-effects of cART medications and helping patients to incorporate HIV medications into their routines, especially for those on medications for co-morbid conditions is also important. It is important for providers to address self-efficacy to cART adherence, beliefs and concerns about HIV and cART use and build trust with older PLWH during clinical encounters.

Pharmacy/pharmacist-based interventions are other effective avenues to improve cART adherence among PLWH [48, 49]. Pharmacist-based interventions that include visits with a clinical pharmacist and a focus on the management of cART side-effects, adherence education, minimizing pill burden, and refill reminders have been shown to result in a significant increase in cART adherence [49, 50]. Given the social and economic barriers faced by Medicaid enrollees, cART adherence support programs are vital to achieving improved adherence and patient outcomes [51]. These include case management services, peer navigation support services, and medical transport services, which are especially important for rural residents. Coordinated care between all healthcare providers and pharmacists is vital to mitigating medication complexity and polypharmacy, and facilitating optimal cART adherence among older PLWH. The Ryan White Program (RWP) also has some utility in addressing many of the barriers to optimal cART adherence that low-income older PLWH face [52]. The evidence regarding the positive impact of adherence support programs funded by the RWP underscores the critical role it plays in cART adherence and lends evidence to the continued support and funding of the RWP [52].

This study is not without limitations. Given our reliance exclusively on Medicaid data, we underrepresented older PLWH who were uninsured, underinsured or had other forms of health insurance. Several important and relevant factors that can confound adherence such as income, educational level, employment status, pill burden, dosing frequency, and level of engagement in care were not adjusted for because Medicaid data does not include information on these factors. Persons receiving Medicaid during the study period needed to meet certain income and categorical eligibility criteria, therefore our study findings are neither representative of nor generalizable to all older PLWH. Pharmacy claims were used to evaluate medication adherence. Though pharmacy claims and PPDC are a widely used measure of adherence [36], they assess drug refill adherence and are not the most optimal measure of medication adherence. The use of pharmacy claims to evaluate cART is further limited by its inability to determine whether patients actually took the medication. This sample was comprised of recently diagnosed PLWH, hence the findings may not be applicable to older adults who have been living with HIV for a longer period of time. Finally, we used a benchmark of 95 % adherence to define optimal adherence, however studies have shown that newer cART combinations are robust enough to lead to virologic suppression at <95 % adherence [53].

Optimal adherence to cART is essential to optimizing health outcomes and preventing HIV transmission among older PLWH. The study findings demonstrated a low prevalence of optimal cART adherence as well as differences by sex, residential status, and co-morbidities among older Medicaid-enrolled PLWH. Multiple levels of interventions are needed to address this at both practice and policy levels. Providing adherence support, case management and patient navigation support programs and ensuring that healthcare providers educate older PLWH on the importance of optimal cART adherence are essential to achieving optimal adherence. Regularly screening for risk factors for suboptimal adherence and working with other members of the healthcare staff (pharmacists and other specialists) to mitigate pill burden among older PLWH are other strategies that should be employed to achieve this. Finally, at the policy level, it is also essential that funding for the RWP continues and that the RWP is leveraged to ensure barriers to cART adherence both within and outside the healthcare system are mitigated.

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