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Examination of Polypharmacy Trajectories Among HIV-Positive and HIV-Negative Men in an Ongoing Longitudinal Cohort from 2004 to 2016

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Abstract

Polypharmacy is the concurrent use of five or more medications. We used group-based trajectory analysis to identify groups of non-HIV medication polypharmacy and investigate associated risk factors among HIV-positive and HIV-negative men in the Multicenter AIDS Cohort Study (MACS) from 2004 to 2016. Each participant was assigned to mutually exclusive groups based on their observed patterns of polypharmacy over time. Risk factors associated with membership with resulting groups were investigated using a multinomial generalized logit model with repeated measures. There were 3160 participants (54.3% HIV positive) included in the study. The overall prevalence of polypharmacy was 33.1% and was higher in HIV-positive than HIV-negative participants (36.2% vs. 30.0%; $p < 0.001$). Four distinct groups of polypharmacy emerged over time among all participants and among HIV-positive participants only: (1) nonpolypharmacy, (2) slow increasing polypharmacy, (3) rapid increasing polypharmacy, and (4) sustained polypharmacy. Being HIV positive, being 50 years of age or older, having medication insurance coverage, and having increased health care use were positively associated with membership in groups with sustained or increasing polypharmacy. Half of participants in each analysis had membership in one of the three high polypharmacy groups. This study revealed that access to care, through medication insurance coverage and health care use, was a key driver of polypharmacy in this cohort. Further exploration of medically appropriate and inappropriate prescribing practices in the context of polypharmacy and its impact on health outcomes in this and other populations is warranted.

Keywords: polypharmacy, HIV/AIDS, MSM, longitudinal cohort, medications

Introduction

THE ADOPTION OF highly active antiretroviral therapy (HAART) has extended the life span of individuals infected with HIV.[1] However, with increasing age, HIV-positive individuals are at greater risk for cardiovascular disease, dyslipidemia, diabetes, and other chronic age-related non-HIV medical conditions compared with HIV-negative counterparts.[2,3] While the number of pills in a typical anti-retroviral therapy (ART) regimen has decreased over time,

overall medication burden among aging HIV-positive patients increasingly comprise medications prescribed to treat chronic age-related non-HIV comorbidities.[4] Polypharmacy has been defined as the concurrent use of five or more medications.[5] There are several factors that contribute to polypharmacy among HIV-positive persons. Lower-income individuals have a greater risk of polypharmacy.[5] Medication insurance coverage has also been shown to correlate with excessive polypharmacy.[5] Harms of polypharmacy include more frequent and serious adverse drug-related events

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(including drug–drug interactions), geriatric syndromes (falls, bone fractures, and impaired cognition), organ system injury, hospitalization, decreased medication adherence, and mortality.[6] HIV-positive patients older than 50 years may have an enhanced susceptibility to harm from polypharmacy due to ongoing immune dysfunction, decreased organ system reserve, and chronically elevated systemic levels of inflammation that contribute to adverse health outcomes.[7]

To our knowledge, there are limited data regarding longitudinal patterns of polypharmacy. In the general United States population, polypharmacy prevalence has nearly doubled from 8.2% in 1999–2000 to 15% in 2011–2012.[8] Among adults 65 years of age and older, the proportion taking five or more medications tripled from 12.8% in 1988 to 39.0% in 2010.[9] Among HIV-positive cohorts, the reported prevalence of polypharmacy has ranged from 23% to 39%, with two studies noting higher polypharmacy among HIV-positive than HIV-negative individuals.[10–12] Kong et al. explored the differences in non-HIV medication polypharmacy between persons living with HIV (PLWH) and HIV-negative persons 65 years of age and older and found greater non-HIV disease and medication burden among PLWH compared with HIV-negative counterparts.[13] In previous research, we reported polypharmacy prevalence over a 12-year period among HIV-positive and HIV-negative men at 25.3% and 18.7%, respectively.[14] While these aggregated rates described the overall burden of polypharmacy over time, they did not elucidate individual-level burden. Group-based analyses can reveal different patterns of response to a particular outcome within heterogeneous populations, such that the most vulnerable individuals can be identified. Therefore, we used group-based trajectory modeling, developed by Jones et al., to identify clusters of individuals based on their patterns of polypharmacy over time.[15,16] To our knowledge, no other study has used this approach to longitudinally examine patterns of polypharmacy among HIV-positive and HIV-negative individuals. We sought to determine trajectories of polypharmacy and investigate associated risk factors among HIV-positive and HIV-negative participants in the Multicenter AIDS Cohort Study (MACS) from October 2004 to April 2016.

Methods

Study population

The MACS is an ongoing prospective cohort study that examines the natural history of HIV/AIDS among men who have sex with men in four United States sites: (1) Baltimore, Maryland/Washington, DC; (2) Chicago, Illinois; (3) Los Angeles, California; and (4) Pittsburgh, Pennsylvania/Columbus, Ohio. Since its inception in 1984, a total of 7352 HIV-positive and HIV-negative men who have sex with men have enrolled into the study during four time periods: 4954 in 1984–1985; 668 in 1987–1991; 1350 in 2001–2003; and 380 in 2011–current. MACS participants attend semiannual clinic visits that involve an Audio Computer-Assisted Self-Interview and a standardized clinical examination where data and specimens are collected. The study design of the MACS has been described elsewhere.[17–19] Detailed information regarding non-HIV medication use has been collected at every visit since the beginning of the study. Questionnaires are available at www.aidscohortstudy.org. Institutional review

boards at each study site approved the MACS protocol and informed consent was obtained from all study participants. In this study, we included 3160 participants (1715 HIV positive and 1445 HIV negative) from all four sites, who were involved in the MACS at any time across 25 study visits (October 2004 to April 2016). Non-HIV medications included prescription and nonprescription drugs and excluded recreational drug use.

Outcome measures

Non-HIV medications. As part of routine data collection and processing during each semiannual visit, information regarding self-reported non-HIV medications was collected and drug codes were assigned, which were created for use within the MACS. Drug codes were generated using guidelines from the World Health Organization's Anatomical Therapeutic Chemical Index. Non-HIV medications were grouped into general drug classifications corresponding to the following classes: cholesterol, hypertensive, diabetes, hepatitis C virus, hepatitis B virus (including antiretroviral treatments), steroid, hormone, anticancer, antidepressant, tranquilizer, aspirin, antibiotic, and "unclassified" drugs. For this analysis, additional drug classifications were created for drug codes that were originally "unclassified." These new classes were antihistamines, appetite suppressants, antianginals, anticoagulants, antidiarrheals, antifungals, antiulcers, central nervous system stimulants, digestive/biliary drugs, dopamine, herbal supplements, muscle relaxants, nonsteroidal anti-inflammatory drugs, opioids, substance abuse treatments, antituberculosis treatments, and vitamins. Medications with very low prevalence were combined into an "other" medication category. Non-HIV medications included prescription and nonprescription drugs and excluded recreational drugs.[14] We did not differentiate between prescription and nonprescription drugs to count all non-HIV medications. Prescription medication polypharmacy has been fairly well researched; however, there is limited knowledge on polypharmacy that includes over-the-counter medications, dietary supplements, and as-needed medications.[5]

Polypharmacy. Polypharmacy was defined using a dichotomous indicator of five or more non-HIV medications taken since the prior visit. This definition was consistent with previous literature and has been noted to be associated with negative health outcomes.[5,6,9,10,12,14] Routinely used and as-needed medications were treated similarly to assess total pill burden at each visit. All HIV antiretroviral medication was excluded from the polypharmacy count to have comparable analyses between HIV-positive and HIV-negative participants.[12]

Co-factors

Sociodemographic characteristics. Self-reported race/ethnicity at baseline was categorized as non-Hispanic white, non-Hispanic black, and other. Geographic location was categorized by the four MACS sites: Baltimore, Maryland/Washington, DC; Pittsburgh, Pennsylvania; Chicago, Illinois; and Los Angeles, California. Enrollment was classified into early recruitment (1987–1991) and later recruitment (2001–current). Educational attainment was classified into less than a high school education, high school education, and

college degree or higher. Age at each visit was calculated from the self-reported date of birth and date at visit, and categorized as younger than 50 and older than or equal to 50 years. Race/ethnicity and enrollment were collected at the participants' study entry (index visit). Age was allowed to vary with time (i.e., participants were recategorized when they aged from younger than 50 to 50 years of age or older over the follow-up period).

Insurance type, medication insurance coverage, and health care use. Participants reported the insurance type at each visit from the following choices: (1) health mainte-nance organization, (2) employer-provided insurance, (3) self-purchased insurance, (4) Medicare, (5) Medicaid, (6) Veteran Affairs health coverage, (7) Ryan White, and (8) other. Three dichotomous variables (yes/no) were generated based on the reported choices: (1) private insurance (health maintenance organization, employer-provided, and self-purchased insurances), (2) public insurance (Medicare, Medicaid, Veterans Affairs, and Ryan White), and (3) other (reported other type of insurance). Current medication in-surance coverage was defined using self-reported responses to the question, ''Do you have health insurance that covers the cost of medications? (Yes/No).'' For each participant, the number of visits to a physician's office, emergency de-partment, or other health care clinic (health care use) was calculated at each visit.

HIV-related risk factors. HIV status (HIV positive/HIV negative) was assessed using enzyme-linked immunosorbent assay with confirmatory Western blot for all MACS partici-pants at their initial visit and at every visit for HIV-negative participants. HIV-positive participants included all those who were HIV positive at baseline and those who seroconverted during study observation. CD4+ T cell counts/mm^3 (CD4) and plasma HIV RNA levels [viral load (VL), copies/mL] were collected through blood draw among HIV-positive participants at every visit. CD4 and VL were dichotomized into <200 cells/mm^3 and 200 cells/mm^3 or more, and detectable (≥40 copies/mL) and undetectable (<40 copies/mL), respectively.

ART use. ART medication use was categorized into four categories according to the Panel on Antiretroviral Guide-lines for Adults and Adolescents: (1) HAART, (2) combi-nation therapy, (3) monotherapy, and (4) none.[20] In modeling, ART medication use was a dichotomous variable (yes/no) for participants reporting any HAART, combination therapy, or monotherapy use. ART adherence was assessed by the question, ''On average, how often did you take your medication as prescribed?'' to which participants had the following choice of responses: (1) 100% of the time, (2) 95–99% of the time, (3) 75–94% of the time, and (4) <75% of the time.[21]

Attrition. Binary variables (lost to follow-up and death) were constructed. Lost to follow-up was defined as more than 1 year of missed consecutive visits through the last visit in 2016. Death was any death that occurred during the obser-vation period.

Statistical analysis

We generated descriptive statistics using frequencies, medians, and interquartile ranges (IQRs) where appropriate. Comparisons of sample characteristics were performed using a χ^2 test (frequencies) and Wilcoxon signed-rank test (me-dians). Using a group-based semiparametric modeling strat-egy, we identified groups of individuals who followed similar patterns arising from their probability of polypharmacy (patterns of polypharmacy) from October 2004 (visit 40) to April 2016 (visit 65). Details on the SAS procedure for group-based trajectory analysis have been described else-where.[15,16] Each participant was assigned to mutually ex-clusive groups based on their patterns of polypharmacy over time using the maximum-probability assignment rule, for which participants were assigned to the group for which their probability of membership was highest.[15,16] We used the Bayesian Information Criterion (BIC), group size, statistical significance of group membership, and the mean posterior probability of membership within each group (entropy) to select the appropriate number of groups. Trajectory models were generated for 1, 2, 3, 4, 5, and 6 groups. BIC, group size, statistical significance, and entropy were recorded at each step. We selected the model with the lowest BIC, statistically significant groups ($p < 0.05$), groups that were greater than or equal to 10% in size, and entropy values >0.7.[15,16,22] After the optimal number of trajectory groups was established, we determined the appropriate shape of trajectory for each group. Trajectory shapes were adjusted using higher- or lower-order terms (linear, quadratic, or cubic), depending on the signifi-cance of those terms. Trajectory models were produced first for the entire sample and then separately for HIV-positive participants using identical model selection criteria.

Descriptive statistics were generated for the resulting groups. Using a multinomial generalized logit model with repeated measures, we modeled the risk factors associated with the likelihood of group membership compared with the group with the lowest probability of polypharmacy (referent). Our primary independent variable was HIV status. We in-cluded age, race/ethnicity, geographic location, educational attainment, enrollment period, health care use, insurance type (private, public, or other), and medication insurance coverage as co-factors. Binary indicators for loss to follow-up and death were also included to adjust for the effect of attrition. For the HIV-positive trajectory groups, we added current CD4 count (≥200 cells/mm^3 or <200 cells/mm^3), VL (de-tectable or undetectable), and ART medication use (yes or no) as time-varying co-factors. Each co-factor was modeled independently and selected for the final model if the p value was <0.10. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were reported. All analyses were performed in Statistical Analysis Software (SAS) version 9.4 (SAS In-stitute, Inc.).

Results

Descriptive statistics

There were 3160 participants (54.3% HIV positive) in-cluded in the analytic sample. The median follow-up time for all participants was 12.0 years (IQR, 5.0–12.5). The rates of loss to follow-up and death were 21.8% and 9.6%, respec-tively. Most participants identified as non-Hispanic white

	HIV negative	HIV positive	All participants
Follow-up duration, median (IQR), years	11.5 (3.0–12.5)	12.5 (8.5–12.5)	12.0 (5.0–12.5)
Age distribution, median (IQR), years	56.0 (48.0–62.0)	51.0 (44.0–57.0)	53.0 (46.0–60.0)
Race/ethnicity, n (%)[a]			
Non-Hispanic white	991 (68.6)	904 (52.7)	1895 (60.0)
Non-Hispanic black	303 (21.0)	511 (29.8)	814 (25.8)
Other	151 (10.5)	300 (17.5)	451 (14.3)
Educational attainment, n (%)[a]			
<High school	242 (16.8)	457 (26.7)	699 (22.1)
High school	697 (48.2)	883 (51.5)	1580 (50.0)
≥College degree	506 (35.0)	375 (21.9)	881 (27.9)
Geographic location, n (%)[a]			
Baltimore, MD/Washington, DC	348 (24.1)	418 (24.4)	766 (24.2)
Chicago, IL	203 (14.1)	367 (21.4)	569 (18.0)
Pittsburgh, PA	391 (27.1)	392 (22.9)	783 (24.8)
Los Angeles, CA	503 (34.8)	538 (31.4)	1041 (32.9)
Enrollment period, n (%)[a]			
Early recruitment (1987–1991)	921 (63.7)	743 (43.3)	1664 (52.7)
Late recruitment (2001–current)	524 (36.3)	972 (56.7)	1496 (47.3)
Private insurance, n (%)			
Yes	18,117 (68.3)	13,869 (51.3)	31,986 (59.7)
No	4188 (15.8)	8964 (33.1)	13,152 (24.5)
Missing	4227 (15.9)	4218 (15.6)	8445 (15.8)
Public insurance, n (%)			
Yes	5977 (22.5)	9585 (35.4)	15,562 (29.0)
No	16,324 (61.5)	13,245 (49.6)	29,569 (55.2)
Missing	4321 (16.0)	4221 (15.6)	8452 (15.8)
Other type of insurance, n (%)			
Yes	721 (2.7)	1561 (5.8)	2282 (4.3)
No	21,495 (81.0)	21,151 (78.2)	42,646 (79.6)
Missing	4316 (16.3)	4339 (16.0)	8655 (16.2)
Medication insurance coverage, n (%)			
Yes	21,161 (79.8)	22,498 (83.2)	43,659 (81.5)
No	3392 (12.8)	2598 (9.6)	5990 (11.2)
Missing	1979 (7.5)	1955 (7.2)	3934 (7.3)
Health care visits, median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–5.0)	2.0 (1.0–4.0)
ART medication type, n (%)			
None	—	4085 (15.1)	—
Monotherapy	—	144 (0.5)	—
Combination therapy	—	1125 (4.2)	—
HAART	—	21,161 (78.2)	—
Missing	—	536 (2.0)	—
Viral load, n (%)			
Detectable (≥40 copies/mL)	—	7665 (28.3)	—
Undetectable (<40 copies/mL)	—	15,607 (57.7)	—
Missing	—	3779 (14.0)	—
ART adherence, n (%)			
100%	—	9601 (35.5)	—
95–99%	—	10,861 (40.2)	—
75–94%	—	1686 (6.2)	—
<75%	—	431 (1.6)	—
Missing	—	4472 (16.5)	—
CD4$^+$ count, n (%)			
<200 cells/mm^3	—	8985 (33.2)	—
≥200 cells/mm^3	—	14,470 (53.5)	—
Missing	—	3596 (13.3)	—
No. of non-HIV medications, median (IQR)	3.0 (1.0–5.0)	4.0 (2.0–6.0)	3.0 (2.0–5.0)
Polypharmacy, n (%)			
≥5 Non-HIV medications	7963 (30.0)	9782 (36.2)	17,745 (33.1)
<5 Non-HIV medications	18,569 (70.0)	17,269 (63.8)	35,838 (66.9)

[a]Measured at baseline; the number of participants used to calculate baseline visit percentages was 3160 (HIV positive: n=1715; HIV negative: n=1445).

ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; IQR, interquartile range.

(60.0%) had obtained at least a high school education (77.9%) and were recruited in the earlier enrollment period (52.7%) (Table 1). Across follow-up, participants had a median age of 53.0 years (IQR, 46.0–60.0) and most (81.5%) reported medication insurance coverage and had a median of two health care visits (health care use) before each semiannual MACS visit (IQR, 1.0–4.0). Details on insurance type and characteristics stratified by HIV status are reported in Table 1. Among HIV-positive participants, most indicated using HAART (78.2%) and self-reported at least 95% adherence (75.7%). More than half maintained an undetectable VL (57.7%) and had a CD4 count ≥200 (53.5%) (Table 1). The overall median number of non-HIV medications used at each visit was three (IQR, 2.0–5.0), with a higher number among HIV-positive than HIV-negative participants (four vs. three; $p < 0.001$). The overall prevalence of polypharmacy across all study visits was 33.1% and was more common among HIV-positive (36.2%) compared with HIV-negative (30.0%) participants ($p < 0.001$).

Polypharmacy trajectories among all participants

Four distinct trajectory groups of polypharmacy emerged in the overall sample: (1) nonpolypharmacy, (2) slowly increasing polypharmacy, (3) rapidly increasing polypharmacy, and (4) sustained polypharmacy (Fig. 1). The best-fitting model had an observed BIC of −27,497.70, with the sizes of the groups ranging from 12.8% to 46.0%, and entropy values ranging from 0.85 to 0.90. Figure 1A illustrates the probability of polypharmacy in each group from 2004 to 2016 (visits 40–65). Participants in the nonpolypharmacy group (46.0% of participants) maintained the lowest probability of polypharmacy at <6% across the observation period. The slowly increasing polypharmacy group (25.9% of participants) began with a 16.7% probability of polypharmacy at visit 40, which steadily increased to 58.6% at visit 65. The rapidly increasing polypharmacy group (12.8% of participants) began with a 12.6% probability of polypharmacy at visit 40, which quickly increased around visit 45 to 40.0%, ending at more than 85.8%
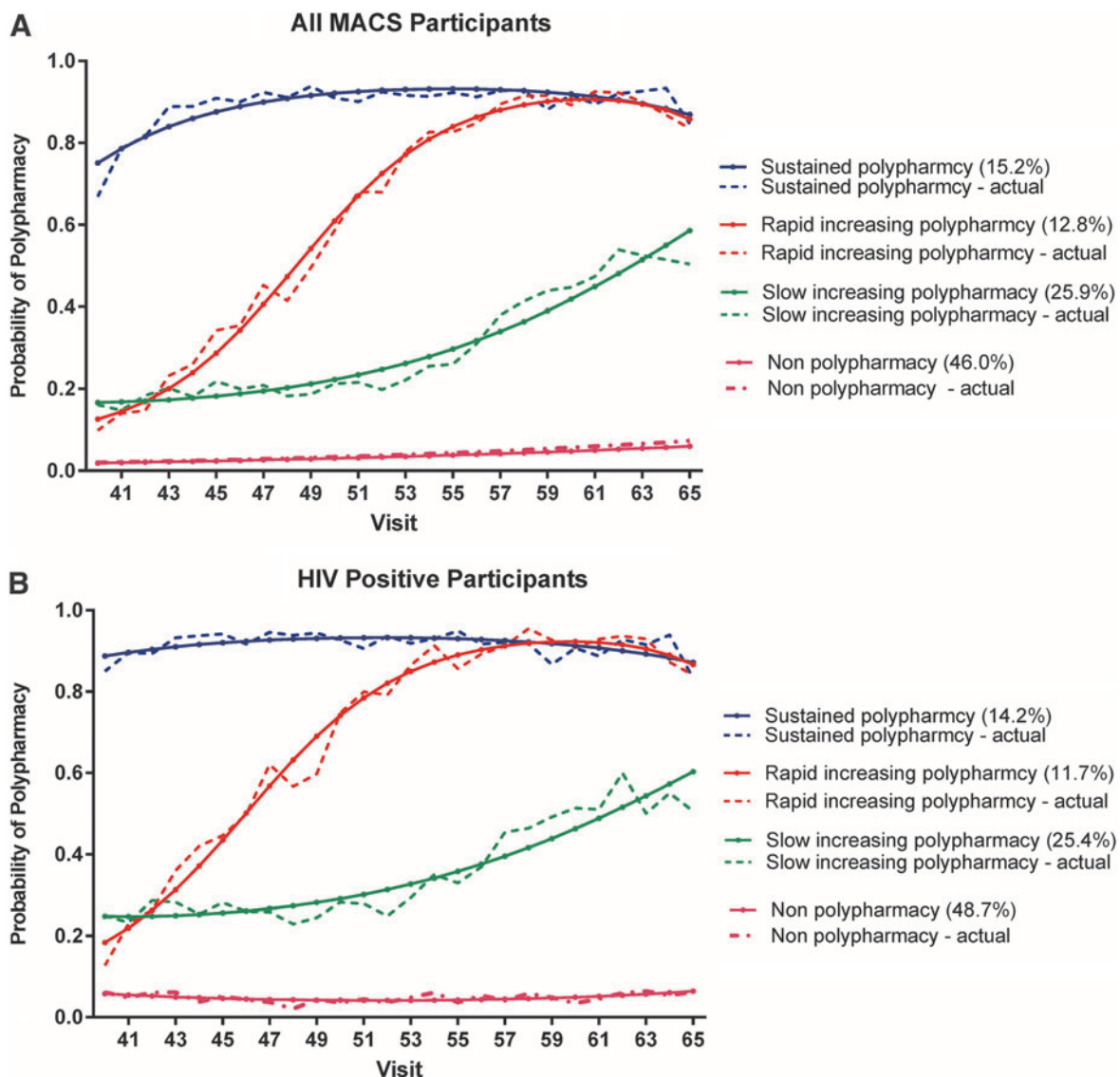

FIG. 1. Trajectories of polypharmacy among all MACS and HIV-positive MACS participants. MACS, Multicenter AIDS Cohort Study.

at visit 65. The sustained polypharmacy group (15.2% of participants) maintained the highest probability (above 75%) of polypharmacy across the observation period.

Table 2 displays the characteristics of all participants by group membership. Approximately half of the participants in the nonpolypharmacy group were HIV positive (52.7%) and non-Hispanic white (48.0%), with 60.6% recruited in the late period. Half reported private insurance (52.8%) with most

having medication insurance coverage (73.4%). They were also the youngest [median age, 50.0 years (IQR, 42.0–57.0)] among the four groups. Among participants in the slowly increasing polypharmacy group, 57.9% were HIV positive, 67.6% were non-Hispanic white, 60.2% were recruited in the earlier period, and 82.6% reported insurance coverage. The median age in this group was 53.0 years (IQR, 47.0–60.0). In the rapidly increasing polypharmacy group, 52.2% were HIV

TABLE 2. BASELINE (N=3160) AND TIME-VARYING CHARACTERISTICS (N=53,583) OF TRAJECTORY GROUPS IN THE FULL MULTICENTER AIDS COHORT STUDY (MACS) SAMPLE

	Nonpolypharmacy	Slowly increasing polypharmacy	Rapidly increasing polypharmacy	Sustained polypharmacy	p Value
Age, median (IQR), years	50.0 (42.0–57.0)	53.0 (47.0–60.0)	57.0 (50.0–63.0)	58.0 (52.0–63.0)	<0.001
Baseline HIV status, n (%)[a]					
Positive	828 (52.7)	411 (57.9)	165 (47.8)	311 (62.7)	<0.001
Negative	742 (47.3)	338 (45.1)	180 (52.2)	185 (37.3)	
Race/ethnicity, n (%)[a]					
Non-Hispanic white	753 (48.0)	506 (67.6)	263 (76.2)	373 (75.2)	<0.001
Non-Hispanic black	527 (33.6)	154 (20.6)	58 (16.8)	75 (15.1)	
Other	290 (18.5)	89 (11.9)	24 (7.0)	48 (9.7)	
Geographic location, n (%)[a]					
Baltimore, MD/ Washington, DC	330 (21.0)	175 (23.4)	89 (25.8)	172 (34.7)	<0.001
Pittsburgh, PA	274 (17.5)	136 (18.2)	60 (17.4)	100 (20.2)	
Chicago, IL	369 (23.5)	175 (23.4)	127 (36.8)	112 (22.6)	
Los Angeles, CA	597 (38.0)	263 (35.1)	69 (20.0)	112 (22.6)	
Educational attainment, n (%)[a]					
<High school	445 (28.3)	135 (18.0)	56 (16.2)	63 (12.7)	<0.001
High school	798 (50.8)	391 (52.2)	159 (46.1)	232 (46.8)	
≥College degree	327 (20.8)	223 (29.8)	130 (37.7)	201 (40.5)	
Enrollment period, n (%)[a]					
Early recruitment (1984–1991)	618 (39.4)	451 (60.2)	227 (65.8)	368 (74.2)	<0.001
Late recruitment (2001–current)	952 (60.6)	298 (39.8)	118 (34.2)	128 (25.8)	
Private insurance, n (%)					
Yes	12,090 (52.8)	8703 (60.9)	5196 (70.0)	5997 (66.7)	<0.001
No	5367 (23.5)	3483 (24.4)	1730 (23.3)	2572 (28.6)	
Missing	5429 (23.7)	2095 (14.7)	497 (6.7)	424 (4.7)	
Public insurance, n (%)					
Yes	5343 (23.4)	4219 (29.5)	2333 (31.4)	3667 (40.8)	<0.001
No	12,110 (52.9)	7965 (55.8)	4592 (61.9)	4902 (54.5)	
Missing	5433 (23.7)	2097 (14.7)	498 (6.7)	424 (4.7)	
Other type of insurance, n (%)					
Yes	792 (3.5)	607 (4.3)	360 (4.9)	523 (5.8)	<0.001
No	16,588 (72.5)	11,516 (80.6)	6547 (88.2)	7995 (88.9)	
Missing	5506 (24.1)	2158 (15.1)	516 (7.0)	475 (5.3)	
Medication insurance coverage, n (%)					
Yes	16,800 (73.4)	11,789 (82.6)	6759 (91.1)	8311 (92.4)	<0.001
No	3799 (16.6)	1298 (9.1)	492 (6.6)	401 (4.5)	
Missing	2287 (10.0)	1194 (8.5)	172 (2.3)	281 (3.1)	
Health care visits, median (IQR)	1.0 (0.0–3.0)	2.0 (1.0–4.0)	3.0 (1.0–5.0)	4.0 (2.0–8.0)	<0.001
No. of non-HIV medications, median (IQR)	2.0 (1.0–3.0)	3.0 (2.0–5.0)	5.0 (4.0–7.0)	8.0 (6.0–10.0)	<0.001
Polypharmacy, n (%)					
<5 Non-HIV medications	22,109 (96.6)	9938 (69.6)	2845 (38.3)	946 (10.5)	<0.001
≥5 Non-HIV medications	777 (3.4)	4343 (30.4)	4578 (61.7)	8047 (89.5)	

[a]Measured at baseline; number of participants used to calculate baseline visit percentages was 3160 (HIV positive: n=1715; HIV negative: n=1445).

IQR, interquartile range.

	Nonpolypharmacy	Slowly increasing polypharmacy	Rapidly increasing polypharmacy	Sustained polypharmacy	p Value
Age, median (IQR), years	48.0 (40.0–54.0)	52.0 (46.0–57.0)	55.0 (49.0–60.0)	56.0 (50.0–62.0)	<0.001
Race/ethnicity, *n* (%)[a]					
Non-Hispanic white	359 (40.6)	237 (58.8)	119 (70.0)	189 (73.5)	<0.001
Non-Hispanic black	336 (38.0)	104 (25.8)	30 (17.7)	41 (16.0)	
Other	190 (21.5)	62 (15.4)	21 (12.4)	27 (10.5)	
Educational attainment, *n* (%)[a]					
<High school	281 (33.9)	94 (22.9)	33 (20.0)	49 (15.8)	<0.001
High school	425 (51.3)	226 (55.0)	84 (50.9)	148 (47.6)	
≥College degree	122 (14.7)	91 (22.1)	48 (29.1)	114 (36.7)	
Geographic location, *n* (%)[a]					
Baltimore, MD/Washington, DC	188 (22.7)	88 (21.4)	40 (24.2)	102 (32.8)	<0.001
Pittsburgh, PA	162 (19.6)	88 (21.4)	40 (24.2)	77 (24.8)	
Chicago, IL	191 (23.1)	95 (23.1)	50 (30.3)	56 (18.0)	
Los Angeles, CA	287 (34.7)	140 (34.1)	35 (21.2)	76 (24.4)	
Enrollment period, *n* (%)[a]					
Early recruitment (1987–1991)	268 (30.3)	210 (52.1)	101 (59.4)	164 (63.8)	<0.001
Late recruitment (2001–current)	617 (69.7)	193 (47.9)	69 (40.6)	93 (36.2)	
Private insurance, *n* (%)					
Yes	4701 (43.5)	3648 (50.0)	2171 (61.9)	3349 (61.6)	<0.001
No	3648 (33.8)	2468 (33.8)	1053 (30.0)	1795 (33.0)	
Missing	2450 (22.7)	1186 (16.2)	285 (8.1)	297 (5.5)	
Public insurance, *n* (%)					
Yes	3382 (31.3)	2623 (35.9)	1213 (34.6)	2367 (43.5)	<0.001
No	4966 (46.0)	3492 (47.9)	2010 (57.3)	2777 (51.0)	
Missing	2451 (22.7)	1187 (16.3)	286 (8.2)	297 (5.5)	
Other type of insurance, *n* (%)					<0.0001
Yes	560 (5.2)	365 (5.0)	235 (6.7)	401 (7.4)	
No	7753 (71.8)	5717 (78.3)	2976 (84.8)	4705 (86.5)	
Missing	2486 (23.0)	1220 (16.7)	298 (8.5)	335 (6.2)	
Medication insurance coverage, *n* (%)[b]					
Yes	9069 (76.8)	6033 (83.2)	3324 (92.4)	4072 (92.4)	<0.001
No	1681 (14.2)	552 (7.6)	185 (5.1)	180 (4.1)	
Missing	1052 (8.9)	663 (9.2)	87 (2.4)	153 (3.5)	
Health care visits, median (IQR)	2.0 (1.0–3.0)	3.0 (1.0–5.0)	3.0 (2.0–6.0)	4.0 (2.0–8.0)	<0.001
ART medication type					
None	2488 (21.1)	963 (13.3)	340 (9.5)	294 (6.7)	<0.001
Monotherapy	67 (0.6)	36 (0.5)	11 (0.3)	30 (0.7)	
Combination therapy	353 (3.0)	384 (5.3)	172 (4.8)	216 (4.9)	
HAART	8592 (72.8)	5682 (78.9)	3049 (84.8)	3838 (87.1)	
Missing	302 (2.6)	183 (2.5)	24 (0.7)	27 (0.6)	
ART adherence, *n* (%)					
100%	3977 (33.7)	2365 (32.6)	1473 (41.0)	1786 (40.5)	<0.001
95–99%	4116 (34.9)	3120 (43.1)	1543 (42.9)	2082 (47.3)	
75–94%	815 (6.9)	520 (7.2)	168 (4.7)	183 (4.2)	
<75%	197 (1.7)	147 (2.0)	65 (1.8)	22 (0.5)	
Missing	2697 (22.9)	1096 (15.1)	347 (9.7)	332 (7.5)	
Viral load, *n* (%)					
Detectable (≥40 copies/mL)	3904 (33.1)	2009 (27.7)	914 (25.4)	838 (19.0)	<0.001
Undetectable (<40 copies/mL)	7898 (66.9)	5239 (72.3)	2682 (74.6)	3567 (81.0)	
CD4$^+$ count, *n* (%)					
<200 cells/mm^3	4188 (35.5)	2244 (31.0)	1065 (29.6)	1488 (33.8)	<0.001
≥200 cells/mm^3	6076 (51.5)	3930 (54.2)	2039 (56.7)	2425 (55.1)	
Missing	1538 (13.0)	1074 (14.8)	492 (13.7)	492 (11.2)	
No. of non-HIV medications, median (IQR)	2.0 (1.0–3.0)	4.0 (3.0–5.0)	6.0 (4.0–8.0)	8.0 (6.0–10.0)	<0.001
Polypharmacy, *n* (%)					
<5 Non-HIV medications	553 (4.7)	2664 (36.8)	2505 (69.7)	4060 (92.2)	<0.001
≥5 Non-HIV medications	11,249 (95.3)	4584 (63.3)	1091 (30.3)	345 (7.8)	

[a]Measured at baseline; number of participants used to calculate baseline visit percentages was 3160 (HIV positive: $n=1715$; HIV negative: $n=1445$).

ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; IQR, interquartile range.

negative, 76.2% were non-Hispanic white, 65.8% were recruited in the earlier period, and 91.1% reported medication insurance coverage, with a median age of 57.0 years (IQR, 50.0–63.0). Participants in the sustained polypharmacy group were the oldest [58.0 years (IQR, 52.0–63.0)], majority HIV positive (62.7%), mostly non-Hispanic white (75.2%), recruited in the earlier period (74.2%), had private insurance (66.7%), and 92.4% reported medication insurance coverage. Health care use (in median visits) was the lowest in the nonpolypharmacy group [1.0 (IQR, 0.0–3.0)] and the highest in the sustained polypharmacy group [4.0 (IQR, 2.0–8.0)].

Polypharmacy trajectories among HIV-positive participants

We identified similar trajectory groups among the HIV-positive participants, as illustrated in Fig. 1B: 48.7% in the nonpolypharmacy group, 25.4% in the slowly increasing polypharmacy group, 11.7% in the rapidly increasing polypharmacy group, and 14.2% in the sustained polypharmacy group. The best-fitting model had an observed BIC of −15,797.95, with group sizes ranging from 11.7% to 48.7%, and entropy values

ranging from 0.88 to 0.95. Table 3 displays the characteristics of the HIV-positive participants in each of the polypharmacy groups. These characteristics were similar to those found in the full sample trajectory groups. In regard to HIV-related factors, 21.1% of nonpolypharmacy group members indicated no ART use and only 68.6% were at least 95% adherent to their ART medications. They also experienced the highest rate of detectable viremia and CD4 count <200 cells/mm^{3} at 33.1% and 35.5%, respectively ($p < 0.001$) (Table 3).

Factors associated with membership in sustained, rapid, and slow increasing polypharmacy groups among all participants

After adjustment for co-factors, HIV-positive participants (vs. HIV-negative participants) were more likely to be in the sustained [aOR, 2.24 (95% CI, 1.69–2.96)], rapidly increasing [aOR, 1.19 (95% CI, 0.90–1.58)], and slowly increasing [aOR, 1.23 (95% CI, 0.98–1.54)] polypharmacy groups than in the nonpolypharmacy group (Table 4). Compared with non-Hispanic white participants, non-Hispanic black participants [aOR, 0.45 (95% CI, 0.30–0.67)] had lower odds of

TABLE 4. MULTI-VARIABLE RISK FACTORS FOR MEMBERSHIP IN THE SUSTAINED, RAPID INCREASING, AND SLOW INCREASING POLYPHARMACY GROUPS RELATIVE TO NONPOLYPHARMACY GROUP AMONG ALL MULTICENTER AIDS COHORT STUDY (MACS) PARTICIPANTS

	Sustained polypharmacy Odds ratio (95% CI)	Rapidly increasing polypharmacy Odds ratio (95% CI)	Slowly increasing polypharmacy Odds ratio (95% CI)
Age (vs. <50 years)			
≥50 years	2.20 (1.73–2.80)*	2.11 (1.64–2.70)*	1.17 (0.98–1.41)
HIV status (vs. HIV negative)			
Positive	2.24 (1.69–2.96)*	1.19 (0.90–1.58)	1.23 (0.98–1.54)
Race/ethnicity (vs. non-Hispanic white)			
Non-Hispanic black	0.45 (0.30–0.67)*	0.42 (0.28–0.63)*	0.59 (0.43–0.81)
Other race/ethnicity	1.05 (0.65–1.69)	0.69 (0.40–1.18)	0.70 (0.48–1.02)
Geographic location (vs. Baltimore, MD/Washington, DC)			
Chicago, IL	0.82 (0.56–1.19)	1.13 (0.74–1.71)	1.20 (0.86–1.67)
Pittsburgh, PA	0.65 (0.45–0.92)*	1.48 (1.02–2.14)*	0.92 (0.68–1.26)
Los Angeles, CA	0.33 (0.23–0.48)*	0.55 (0.36–0.82)*	0.81 (0.60–1.10)
Educational attainment (vs. high school education)			
<High school	0.66 (0.43–0.99)*	0.89 (0.60–1.31)	0.93 (0.69–1.25)
≥College degree	1.62 (1.20–2.17)*	1.56 (1.14–2.15)*	1.31 (1.01–1.69)*
Enrollment period (vs. later recruitment)			
Early recruitment (1987–1991)	2.97 (2.13–4.16)*	1.33 (0.95–1.85)	1.51 (1.15–2.00)*
Private insurance (vs. no)			
Yes	0.90 (0.69–1.19)	1.09 (0.82–1.44)	1.01 (0.81–1.26)
Public insurance (vs. no)			
Yes	2.00 (1.57–2.56)*	1.54 (1.20–1.98)*	1.01 (0.81–1.26)
Other type of insurance (vs. no)			
Yes	0.87 (0.66–1.15)	1.00 (0.77–1.31)	1.00 (0.80–1.24)
Medication insurance coverage (vs. no)			
Yes	1.45 (1.11–1.89)*	1.33 (0.94–1.89)	1.11 (0.90–1.37)
Health care visits (per unit increase)	1.11 (1.09–1.13)*	1.10 (1.08–1.12)*	1.08 (1.06–1.10)*
Death (vs. no)			
Yes	2.41 (1.44–4.03)*	1.64 (0.86–3.15)	1.29 (0.81–2.06)
Lost to follow-up (vs. no)			
Yes	0.68 (0.47–0.99)*	0.69 (0.44–1.06)	0.70 (0.52–0.94)*

*Statistically significant at $p < 0.05$.
CI, confidence interval.

membership in the sustained polypharmacy group, while those of other races/ethnicities [aOR, 1.05 (95% CI, 0.65–1.69)] had higher odds. Being 50 years of age and older [aOR, 2.20 (95% CI, 1.73–2.80)], having been recruited in the early enrollment period [aOR, 2.97 (95% CI, 2.13–4.16)], having a college degree or higher [aOR, 1.62 (95% CI, 1.20–2.17)], reporting public insurance [aOR, 2.00 (95% CI, 1.57–2.56)], reporting medication insurance coverage [aOR, 1.45 (95% CI, 1.11–1.89)], and having greater health care use [aOR, 1.11 (95% CI, 1.09–1.13)] were associated with greater odds of membership in the sustained polypharmacy group. In comparison with being located in the Baltimore, Maryland/Washington, DC, area, living in Chicago [aOR, 0.82 (95% CI, 0.56–1.19)], Pittsburgh [aOR, 0.65 (95% CI, 0.45–0.92)], and Los Angeles [aOR, 0.33 (95% CI, 0.23–0.48)] presented lower odds of membership in the sustained polypharmacy group. The associations between the co-factors and

membership in rapidly increasing and slowly increasing polypharmacy groups are reported in detail in Table 4.

Factors associated with membership in sustained, rapid, and slow increasing polypharmacy groups among HIV-positive participants

Among HIV-positive participants, reporting public insurance [aOR, 2.39 (95% CI, 1.71–3.34)], being enrolled in the earlier enrollment period [aOR, 2.58 (95% CI, 1.68–3.96)], having a college degree or higher [aOR, 1.99 (95% CI, 1.30–3.06)], and a unit increase in health care use [aOR, 1.11 (95% CI, 1.08–1.14)] were associated with increased likelihood of membership in the sustained polypharmacy group compared with the nonpolypharmacy group (Table 5). Having a detectable VL [aOR, 0.76 (95% CI, 0.62–0.94)] was associated with decreased likelihood of membership in the sustained

TABLE 5. MULTI-VARIABLE RISK FACTORS FOR MEMBERSHIP IN THE SUSTAINED, RAPID INCREASING, AND SLOW INCREASING POLYPHARMACY GROUPS RELATIVE TO NONPOLYPHARMACY GROUP AMONG HIV-POSITIVE MULTICENTER AIDS COHORT STUDY (MACS) PARTICIPANTS

	Sustained polypharmacy Odds ratio (95% CI)	Rapidly increasing polypharmacy Odds ratio (95% CI)	Slowly increasing polypharmacy Odds ratio (95% CI)
Age (vs. <50 years)			
≥50 years	2.23 (1.65–3.01)*	2.42 (1.74–3.39)*	1.45 (1.12–1.86)*
Race/ethnicity (vs. non-Hispanic white)			
Non-Hispanic black	0.28 (0.16–0.48)*	0.27 (0.15–0.48)*	0.74 (0.48–1.14)
Other race/ethnicity	0.81 (0.43–1.55)	0.75 (0.37–1.5)	0.84 (0.49–1.44)
Geographic location (vs. Baltimore, MD/Washington, DC)			
Chicago, IL	1.12 (0.68–1.84)	1.43 (0.79–2.59)	1.51 (0.94–2.43)
Pittsburgh, PA	0.49 (0.28–0.85)*	1.07 (0.61–1.89)	1.14 (0.70–1.84)
Los Angeles, CA	0.52 (0.31–0.87)*	0.84 (0.46–1.55)	1.20 (0.76–1.90)
Educational attainment (vs. high school education)			
<High school	0.72 (0.42–1.25)	1.43 (0.79–2.59)	0.82 (0.55–1.22)
≥College degree	1.99 (1.30–3.06)*	1.07 (0.61–1.89)	1.11 (0.72–1.70)
Enrollment period (vs. later recruitment)			
Early recruitment (1987–1991)	2.58 (1.68–3.96)*	0.92 (0.57–1.48)	1.59 (1.08–2.35)
Private insurance (vs. no)			
Yes	1.11 (0.77–1.58)	1.40 (0.94–2.09)	1.17 (0.88–1.57)
Public insurance (vs. no)			
Yes	2.39 (1.71–3.34)*	1.63 (1.13–2.35)	1.62 (1.21–2.15)*
Other type of insurance (vs. no)			
Yes	1.22 (0.85–1.75)	1.40 (0.94–2.09)	1.04 (0.80–1.36)
Medication insurance coverage (vs. no)			
Yes	1.38 (0.95–2.00)	1.33 (0.93–1.91)	1.29 (0.99–1.69)
Health care visits (per unit increase)	1.11 (1.08–1.14)*	1.10 (1.07–1.13)*	1.08 (1.05–1.11)*
CD4+ count (vs. ≥200 cells/mm³)			
<200 cells/mm³	0.82 (0.51–1.30)	0.87 (0.50–1.54)	0.91 (0.59–1.41)
Viral load (vs. undetectable, <40 copies/mL)			
Detectable (≥40 copies/mL)	0.76 (0.62–0.94)*	1.08 (0.87–1.35)	1.08 (0.90–1.3)
ART medication use (vs. no)			
Yes	1.44 (0.88–2.36)	1.87 (1.11–3.12)*	1.23 (0.88–1.74)
Death (vs. no)			
Yes	2.66 (1.29–5.48)*	3.47 (1.24–9.76)*	1.65 (0.85–3.21)
Lost to follow-up (vs. no)			
Yes	1.11 (1.08–1.14)*	0.51 (0.23–1.15)	0.60 (0.38–0.93)*

*Statistically significant at $p < 0.05$.
ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; IQR, interquartile range.

polypharmacy group. The associations with rapidly increasing and slowly increasing polypharmacy group membership are reported in detail in Table 5.

Discussion

In this large well-characterized cohort of HIV-positive and HIV-negative men, four distinct groups of polypharmacy (overall and among HIV-positive participants only) emerged. Half of all participants (53.9%) and half of HIV-positive participants (51.3%) had membership in one of the three categories of increasing or high polypharmacy groups. Polypharmacy seems to be driven by access care through insurance coverage and health care utilization, particularly among HIV-positive participants.

This novel approach to examining the patterns and associated risk factors of polypharmacy produced results consistent with current published research. Kantor et al. found statistically significant increases in polypharmacy over a 12-year period using data from the National Health and Nutrition Examination Survey.[8] Charlesworth et al. reported the median number of prescribed medications doubling from two to four, and the proportion taking five or more medications tripling over a 22-year period.[9] In a study comparing PLWH and non-PLWH, Moore et al. also found increases in polypharmacy in both populations, with rates increasing among PLWH.[23] Similar to these studies, we found older age, being HIV positive, medication coverage, and increased health care use were strong risk factors for polypharmacy. However, in contrast to Charlesworth et al., we found non-white participants had a decreased risk of being in the higher polypharmacy groups.[9] We also found lower educational attainment to be associated with reduced likelihood of membership in higher polypharmacy groups, which is contrary to published literature that found it to be a risk factor for polypharmacy.[24,25] The positive association between early recruitment and polypharmacy may be explained by early recruited participants being, on average, older than those in the later recruitment period. Among HIV-positive participants, this association may be due to longer duration of infection. The geographic location of participants was associated with group membership. In comparison with the Baltimore, Maryland/Washington, DC, location, participants in Chicago, Pittsburgh, and Los Angeles/San Francisco were less likely to be in the sustained polypharmacy group. The largest employer in the Baltimore, Maryland/Washington, DC, area is the US federal government, which has higher salary and benefits than private sector jobs.[26] With insurance coverage being a key driver of polypharmacy in this cohort, this may explain the increased likelihood of polypharmacy among participants in this location.

Among HIV-positive participants, some associations, such as age and race/ethnicity, were no longer statistically significant. Earlier onset of age-related comorbidities among HIV-positive individuals may have attenuated the association between age and polypharmacy.[3] Surprisingly, the association between CD4 cell count and polypharmacy was not statistically significant, while VL detectability was. The direction of effect for both was the opposite of what would be expected. HIV-positive individuals experience chronically elevated levels of inflammation that contribute to increase incidence of comorbidities.[7] In the overall analysis of this sample, we found HIV-negative participants with slightly higher rates of aging-related comorbidities; however, polypharmacy was found to be significantly higher among HIV-positive participants.[14] HIV-positive participants with medication insurance coverage had higher rates of viral suppression and CD4 cell counts greater than 200 cells/mm^3. Further, rates of medication insurance coverage were higher among HIV-positive participants. This points to higher access to care (i.e., medication insurance coverage) among HIV-positive participants as a driver of polypharmacy rather than comorbidities or virologic or immunologic control. However, care must be taken when considering these implications. Participants in the nonpolypharmacy group had lower medication insurance coverage, fewer health care visits, and, among those who were HIV positive, had lower CD4 cell counts, had lower rates of VL suppression, and reported less ART medication use.

There are several limitations to this study. First, we relied on participants' self-reported medication use, presenting the possibility of recall bias. Short-term medication use, such as antibiotics, may have been underreported. In addition, there is concern that including short-term medication use could impact the results and identification of trajectory groups. However, these medications represent a small percentage (<5% across 12-year period) of polypharmacy and are unlikely to affect group identification. Second, physician bias in prescribing practice may have influenced polypharmacy rates in this cohort, particularly among HIV-positive participants.[27] Third, the probability of polypharmacy within each trajectory group may have been influenced by loss to follow-up or deaths. This was especially true for the sustained polypharmacy group, in which the participants were more likely to be HIV positive and older. To account for possible attrition, we controlled for those factors in the model. Fourth, this study was restricted to HIV-positive and HIV-negative men in four major metropolitan areas; therefore, results may not be generalizable to the general population of HIV-positive and HIV-negative persons. And finally, group assignments were an approximation of real-life behaviors; therefore, care must be taken in applying these trajectories to real-life scenarios. Last, this study did not distinguish between medically appropriate and inappropriate prescribing practices as well as prescribed and nonprescribed medications. Despite these limitations, there were considerable strengths in our evaluation of polypharmacy in this long-term cohort. The MACS undertook standardized collection of medication use over time, which was recorded semiannually, including capture of nonprescription medications and nutritional supplements. To our knowledge, this is the first report using group-based trajectory analysis to ascertain patterns of polypharmacy in a long-term cohort.

More than half of participants belonged to groups that demonstrated a pattern of increasing or sustained polypharmacy. Our study revealed that access to care, through medication insurance coverage and increased health care use, was a key driver of polypharmacy in this cohort, and those in the nonpolypharmacy group had less insurance, had fewer health care visits, and were less immunologically suppressed (HIV positive). Further exploration of medically appropriate and inappropriate prescribing practices in the context of polypharmacy and its impact on health outcomes in this population is warranted.

Additional information

The MACS website is located at http://aidscohortstudy.org/

Author Disclosure Statement

No competing financial interests exist.

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