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Trajectories of Antiretroviral Therapy Adherence and Virologic Failure in Women With HIV in the United States

Abubaker Ibrahim Elbur, PhD,[a] Musie Ghebremichael, PhD,[b] Deborah Konkle-Parker, PhD, FNP,[c] Deborah L. Jones, PhD,[d] Shelby Collins, DNP, NP-C,[e] Adaora A. Adimora, MD, MPH,[f] Michael F. Schneider, MS,[g] Mardge H. Cohen, MD,[h] Bani Tamraz, PharmD, PhD,[i] Michael Plankey, PhD,[j] Tracey Wilson, PhD,[k] Adebola Adedimeji, PhD, MS, MPH, MBA,[l] Jessica Haberer, MD, MPH,[m] and Denise L. Jacobson, PhD, MPH[n]

Background: Women with HIV (WHIV) in the United States face many challenges with adherence to antiretroviral therapy (ART), and suboptimal adherence often leads to virologic failure. This study aimed to determine the association between ART adherence trajectories and the risk of virologic failure.

Methods: We included WHIV (aged 18 years or older) enrolled in the Women's Interagency HIV Study in the United States from April 2014 to September 2019 who had at least 2 consecutive measurements of HIV RNA and ≥3 measurements of self-reported adherence. Group-based trajectory modeling was used to identify adherence trajectories. Cox proportional hazard ratios were used to measure the association.

Main Outcome Measure: Virologic failure was defined as HIV RNA ≥200 copies/mL at 2 consecutive visits.

Results: We included 1437 WHIV (median age 49 years). Of all women, 173 (12.0%) experienced virologic failure. Four adherence trajectories were identified, namely "consistently high" (26.3%), "moderate increasing" (9.5%), "moderate decreasing" (30.6%), and "consistently low" (33.5%). Women in the consistently low adherence group consumed alcohol and experienced depression more than other groups. Compared with the "consistently high" trajectory, the risk of virologic failure was higher among women with "consistently low" [adjusted hazard ratio (aHR) 2.8; 95% confidence interval (CI): 1.6 to 4.9; $P < 0.001$] and "moderate decreasing" adherence trajectories (aHR 1.8; 95% CI: 1.0 to 3.2;

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From the [a]Center for Global Health, Massachusetts General Hospital, Boston, MA; [b]The Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA; [c]Schools of Nursing, Medicine and Population Health, University of Mississippi Medical Center, Jackson, MS; [d]Department of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL; [e]Emory University School of Medicine, Division of Infectious Disease, Atlanta, GA; [f]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC; [g]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore; [h]Department of Medicine, Stroger Hospital of Cook County, Chicago IL; [i]University of California, San Francisco, School of Pharmacy, San Francisco, CA, MA; [j]Georgetown University Medical Center, Department of Medicine, Division of General Internal Medicine, Washington DC; [k]School of Public Health, SUNY Downstate Health Sciences University, Brooklyn, NY; [l]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY; [m]Center for Global Health, Massachusetts General Hospital, Boston, MA; and [n]Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, MA.

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$P = 0.04$), but it was similar to those with "moderate increasing" adherence trajectory (aHR 1.0; 95% CI: 0.4 to 2.5; $P = 0.94$).

Conclusions: Adherence to ART remains a challenge among WHIV. Multilevel behavioral interventions to address poor adherence, alcohol consumption, and depression are needed.

Key Words: medication adherence, antiretroviral therapy, group-based trajectory modeling, virologic failure, women

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INTRODUCTION

In 2019, women accounted for 18% of the 34,800 new cases with HIV diagnosed in the United States,[1] while the Centers for Disease Control and Prevention (CDC) estimated that by the end of 2019, women with HIV (WHIV) will constitute approximately 22% of all people living with HIV (PWHIV) in the United States.[2]

HIV antiretroviral therapy (ART) maintains the health and well-being of an individual and reduces HIV transmission, which can be achieved through viral suppression.[3] Viral suppression among women is sub-optimal, for example, Kassaye et al[4] characterized the long-term HIV viral suppression among nearly 2000 women enrolled in the Women's Interagency HIV Study (WIHS); between 2015 and 2017, only 70% of the women demonstrated sustained viral suppression.

Suboptimal adherence to ART is also high among women when compared with men. For example, an analysis of a large sample of PWHIV data in the United States obtained from the Integrated Dataverse between January 2015 and September 2017 (n = 169,545; 27% female) revealed that female gender was a strong predictor of poor adherence and greater prevalence of drug resistance.[5] Turner et al[6] similarly evaluated the relationship between gender and adherence to ART measured by the proportion of days covered using pharmacy data among people with HIV who use drugs in the United States (1827 female and 3216 male patients); women were found to be significantly less adherent than men (18% vs. 25%, $P < 0.001$). Multiple factors noted in the literature that are associated with a decreased level of adherence among women include alcohol dependence, depression, anxiety, internalized stigma, childcare, other competing life demands, and a history of physical and sexual abuse.[7,8]

Variations in patterns of adherence over time can influence the likelihood of maintaining viral suppression. Most studies have examined the within-subject patterns of adherence over time.[9,10] Static measures, such as the medication possession ratio, are insufficient to capture the dynamic nature of long-term adherence behavior.[11] Group-based trajectory modeling (GBTM) is a novel methodological data-driven approach used for analyzing developmental trajectories (ie, the evolution of an outcome over age or time)[12] and can be used to categorize trajectories of adherence, rather than simply dichotomizing participants as adherent vs. nonadherent. GBTM has increasingly been used to study individuals' adherence to treatment across different disease states.[11] Identifying trajectories may be advantageous in the customization of targeted interventions to increase adherence and improve treatment outcomes because interventions focusing on patients at risk of poor adherence rather than on all patients can produce better outcomes.[13]

Few studies to date have examined the relationship between medication adherence trajectories and healthcare events and/or treatment outcomes.[14–16] We hypothesized that GBTM analysis will delineate different latent trajectories of adherence to ART, and WIHS women who follow a low adherence trajectory over time are at an increased risk of experiencing virologic failure compared with those with moderate or high adherence patterns.

METHODS

Study Design

We conducted a retrospective analysis of longitudinal data among WHIV enrolled in the WIHS, which was the oldest and largest prospective cohort of WHIV or women living without HIV (assigned the female sex at birth) in the United States[17,18]; the WIHS in 2019 combined with the Multicenter AIDS Cohort Study (MACS) to form the MACS/WIHS Combined Cohort Study (MWCCS). WIHS recruited women during 4 waves (1994–1995, 2001–2002, 2011–2012, and 2013–2015) from the Bronx and Brooklyn, NY; WA, DC; Los Angeles and San Francisco, CA; and Chicago, IL. More participants were enrolled during the fourth wave from other research sites in Atlanta, GA; Chapel Hill, NC; Miami, FL; Birmingham, AL; and Jackson, MS.[19] WIHS was approved by the Institutional Review Board at each study site's institution.

WIHS Data

At each semiannual study visit, data collection included clinical examinations, blood samples, and interviewer-administered questionnaires to collect basic sociodemographic data, substance use, non-HIV and HIV medication use, HIV viral load, and CD4 count. At these visits data were collected on sociodemographic characteristics, including age (years), race and ethnicity (non-Hispanic White, non-Hispanic African American, and Hispanic of any race), educational level (below secondary, completed secondary, and some college/completed college), household income (in this study categorized as <$24,000 vs. ≥$24,000), employment status (employed vs. unemployed), estimated or self-reported time since diagnosis with HIV (years), smoking status (never smoker, current smoker, and former smoker), alcohol intake (abstainer, >0–7 drinks/week, >7–12 drinks/wk, and >12 drinks/wk), substance use (marijuana or hash, crack, cocaine, heroin, illicit methadone, methamphetamines, amphetamines, narcotics, hallucinogens, and other drugs), and depression status (measured by the Center for Epidemiological Studies Depression scale with a score of ≥16 indicating the presence of depressive symptoms and <16 indicating no depressive symptoms.[20] The type of ART regimen used at the last visit was also recorded (in this study,

categorized as integrase strand transfer inhibitors without protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor without PIs, PIs alone, no therapy, and others).

Self-reported data on adherence to ART over the past six months were also collected at each visit. Response options included the following: "100% of the time," "95%–99% of the time," "75%–94% of the time," "<75% of the time," and "I have not taken any of my prescribed medications."

Study Participants

The sample population for the current analysis consisted of WHIV enrolled in the WIHS from April 2014 to September 2019. Our analysis included all WHIV aged 18 years or older who were taking ART and had at least 2 consecutive measurements of HIV RNA. In addition, we excluded women with fewer than 3 measurements of adherence because of the minimum requirements for fitting trajectory models. The index visit was defined as the first visit between the above-mentioned dates.

Data Analysis

Main Outcome Measure

The main outcome measure was virologic failure, defined as HIV RNA ≥200 copies/mL at 2 consecutive visits.[21]

Primary Exposure

Adherence to ART trajectories as categorized by GBTM.

Statistical Analysis

Group-Based Trajectory Modeling

We used GBTM to identify latent adherence groups using a censored normal finite mixture model.[22] The analysis process involved 2 steps. First, we started by sequentially fitting several models to identify the appropriate number of trajectory groups. The second step involved the identification of trajectory shapes considering constant, linear, quadratic, and cubic specifications, together with visual inspections. Model fit was determined by considering a combination of criteria, namely (1) Bayesian information criteria with smaller values indicating better model fit, (2) the mean posterior probability of membership within each group (entropy) with values >0.70 generally indicating acceptable classification, (3) the smallest group with at least 5% of the sample, (4) a tight confidence interval (CI) around estimated group membership probabilities and statistically significant groups ($P < 0.05$), and (5) parsimony in the model with few classes and parameters probabilities.[12] In addition to the statistical steps, the model selection process was based on subject matter knowledge about the patterns of adherence to medications and the interpretability of the model. We assumed that missing data were missing completely at random. With this approach, GBTM accommodates missing data by fitting the model using maximum likelihood estimation and generating asymptotically unbiased parameter estimates.[12]

Descriptive Statistics

Categorical variables were presented as numbers and percentages, and continuous variables were summarized as median and interquartile ranges (IQRs) within each adherence trajectory group. We used the χ^2 test to compare age, race, education, employment status, annual income, alcohol intake, smoking, presence of depression symptoms at baseline, type of regimen at the last visit, and an episode of detectable viremia during the entire study period between the identified trajectories.

Adherence Trajectories and Virologic Failure

The association between adherence trajectory groups (defined earlier) and time to virologic failure was assessed using the Kaplan–Meier method, and a log-rank test was used to test for differences between the 4 adherence trajectory groups. Univariate and multivariate Cox proportional hazards models were used to estimate the hazard ratio as the measure of association between adherence trajectory group and virologic failure. The 95% CI was used as a measure of precision. Based on literature and expert knowledge, we selected as potential confounders variables that may have a

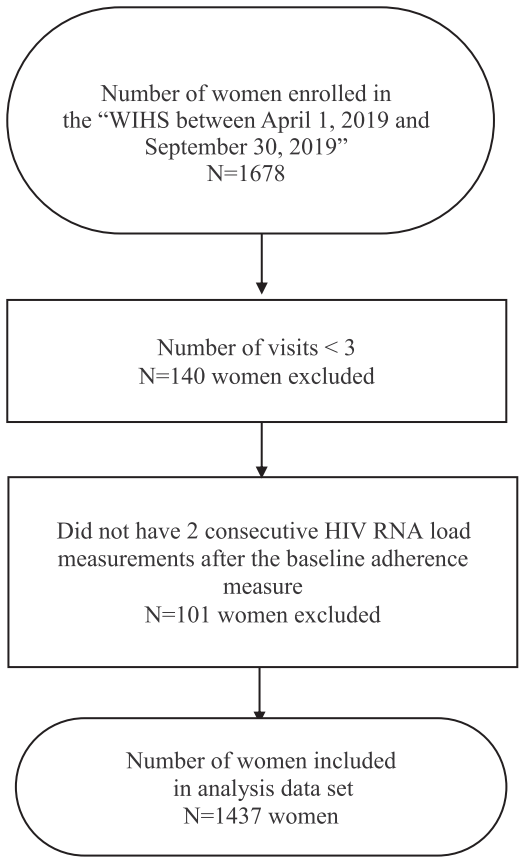

FIGURE 1. Sample selection process.

direct effect on viremia not mediated through adherence. Specifically, we included the type of ART regimen at the last visit and duration of prior viral suppression (estimated from episodes of detectable viremia), which may influence the threshold for viral replication[23,24] as well as alcohol intake, smoking, and depression which may have direct inflammatory effect.[25–27] Detectable viremia was defined as any detectable HIV RNA above the limit of detection (≥20 copies/mL).[28] Episodes of detectable viremia were classified as "never" if women presented with viremia below the limit of detection at all their visits, "infrequent" if women presented with detectable viremia in ≤50% of their total visits, and "frequently" if women presented with detectable viremia in >50% of their total visits.[29] Statistical analyses were performed using Stata

TABLE 1. Baseline Sociodemographic and Clinical Characteristics of Women With HIV in the WIHS Cohort by Adherence Trajectories

	Adherence Trajectories					
Characteristic	**Consistently High (n = 378)**	**Moderate Increasing (n = 137)**	**Moderate Decreasing (n = 440)**	**Consistently Low (n = 482)**	**Total (n = 1437)**	***P***
Age groups						0.1
<50 yrs	193 (51.0)	63 (46.0)	229 (52.0)	274 (56.8)	678 (47.2)	
>50 yrs	185 (49.0)	74 (54.0)	211 (48.0)	208 (43.2)	759 (52.8)	
Race						0.19
African American	274 (72.5)	93 (67.9)	323 (73.4)	369 (76.6)	1059 (73.7)	
Others	104 (27.5)	44 (32.1)	117 (26.6)	113 (23.4)	378 (26.3)	
Education						0.03
Below secondary	141 (37.4)	48 (35.0)	134 (30.5)	146 (30.4)	469 (32.7)	
Completed secondary	130 (34.5)	37 (27.0)	149 (33.9)	149 (31.1)	465 (32.4)	
Some college/completed college	106 (28.1)	52 (38.0)	157 (35.6)	185 (38.5)	500 (34.9)	
Employment status						0.54
No	253 (66.9)	92 (68.1)	284 (64.8)	301 (62.6)	930 (64.9)	
Yes	125 (33.1)	45 (32.9)	154 (35.2)	180 (37.4)	504 (35.2)	
Annual income						0.03
<=$24,000	307 (81.2)	106 (77.4)	322 (73.2)	357 (74.2)	1092 (76.0)	
>$24,000	71 (18.8)	31 (22.6)	118 (26.8)	124 (25.8)	344 (24.0)	
Alcohol categories (%)						<0.001
0 drinks/wk	249 (66.2)	88 (64.2)	242 (55.0)	212 (44.0)	791 (55.1)	
>0–7 drinks/wk	97 (25.8)	43 (31.4)	158 (35.9)	194 (40.2)	492 (34.3)	
>7–12 drinks/wk	15 (4.0)	2 (1.4)	15 (3.4)	29 (6.0)	61 (4.2)	
>12 drinks/wk	15 (4.0)	4 (2.9)	25 (5.7)	47 (9.8)	91 (6.3)	
History of smoking status (%)						0.49
Never smoker	140 (37.0)	48 (35.0)	147 (33.4)	168 (34.9)	503 (35.0)	
Current smoker	125 (33.1)	46 (33.6)	176 (40.0)	183 (37.9)	530 (36.9)	
Former smoker	113 (29.9)	43 (31.4)	117 (26.6)	131 (27.2)	404 (28.1)	
Depression symptoms (%)						<0.001
Yes	77 (20.4)	39 (28.5)	130 (29.5)	192 (39.8)	999 (69.5)	
No	301 (79.6)	98 (71.5)	310 (70.5)	290 (60.2)	438 (30.5)	
Regimen type at the last visit						<0.001
INSTI (without PI/NNRTI)	234 (61.9)	84 (61.3)	239 (54.3)	252 (52.3)	809 (56.3)	
NNRTI (without PI)	72 (19.0)	30 (21.9)	84 (19.0)	71 (14.7)	257 (17.9)	
PI	65 (17.2)	19 (13.9))	89 (20.2)	93 (19.3)	266 (18.5)	
No therapy	1 (0.3)	0	18 (4.1)	54 (11.2)	73 (5.1)	
Others	6 (1.6)	4 (2.9)	10 (2.3)	12 (2.5)	32 (2.2)	
Episodes of detectable Viremia						<0.001
Never	61 (16.1)	10 (7.3)	61 (13.9)	31 (6.4)	163 (11.3)	
Infrequent	208 (55.0)	73 (53.3)	220 (50.0)	207 (42.9)	708 (49.3)	
Frequent	109 (28.8)	54 (39.4)	159 (36.1)	244 (50.6)	566 (39.4)	

INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

software, version 16 (Stata Corp LLC, College Station, TX), and Stata Plugin was used to estimate GBTM parameters.

RESULTS

Participant Characteristics

Of the 1678 women who were active in the WIHS during the study period, 1437 (86%) satisfied the inclusion criteria; they contributed a total of 13,056 participant visits with a median follow-up time of approximately 53.6 (IQR 47–55) months (Fig. 1). During the study period, HIV RNA was measured at 11,649 (89%) participant visits, and women self-reported adherence to ART at 12,389 (95%) participant visits. Among all women in the study sample, the median age was 49 (IQR 42–54) years with most of them (1059; 74%) self-identifying as African American. A total of 930 (65%) were unemployed, nearly three-quarters (76%) had annual income ≤$24,000, and 1376 (96%) had medical insurance. Most women (1122; 78%) were diagnosed with HIV at least 20 years before the baseline visit. See Table 1 for detailed participants' characteristics overall and by adherence trajectory group.

Trajectories of ART Adherence and Characteristics Across Groups

Overall, 67% of participants reported at least a 95% level of adherence to ART. GBTM revealed 4 latent trajectories of adherence to ART, namely "consistently high" (N = 378, 26.3%), "moderate increasing" (N = 137, 9.5%), "moderate decreasing" (N = 440, 30.6%), and "consistently low" (N = 482, 33.5%), as depicted in Figure 2. Race, employment status, and a history of smoking status at the baseline visit were similar across groups (Table 1). A higher percentage of women in the consistently low adherence group used alcohol and experienced depression symptoms at the baseline visit compared with the other groups. In addition, women in the consistently low adherence group were likely to be prescribed integrase strand transfer inhibitors and PI-based regimens, not taking therapy at the last visit, and frequently presented with detectable viremia during the whole study period.

Viral load was consistently not detected in 161 (11.3%) participants in all study visits, of whom 61 (16.1%) were in the consistently high group, 61 (13.9%) in the moderate decreasing, 10 (7.3%) in the moderate increasing, and 31 (6.4%) in the consistently low adherence groups. Viral load was detectable in 5030 (43.2%) visits. Of the women who experienced frequent episodes of viremia, 109 (28.8%) were members of the consistently high adherence group, compared with 159 (36.1%) in the moderate decreasing, 54 (39.4%) in the moderate increasing, and 244 (50.6%) in the consistently low adherence group. Of the women who experienced infrequent viremia, 208 (55.0%) were in the consistently high adherence trajectory, compared with 73 (53.3%), 220 (50.0%), and 207 (49.3%) in the moderate increasing, moderate decreasing, and the consistently low trajectories, respectively ($P < 0.001$).

While the moderate increasing and the moderate decreasing groups started at approximately the same level of adherence at baseline, they began to diverge at the 12-month visit. We found no significant differences in background characteristics between women in the 2 groups at baseline and visit number 3, as summarized in Table 2.

Adherence Trajectories and Time to Virologic Failure

Virologic failure occurred among 173 of 1437 (12.0%) women. Women classified in the consistently low adherence trajectory experienced more virologic failure (103; 21.4%) compared with participants in the moderate decreasing (46; 10.2%), moderate increasing (7; 5.1%), and consistently high (17; 4.5%) trajectories by the end of follow-up, ($P < 0.001$). Figure 3 depicts time to virologic failure among the 4 adherence trajectories.

Risk of Virologic Failure by Adherence Trajectories

Table 3 summarizes unadjusted and adjusted estimates of the risk of virologic failure by adherence trajectories from the Cox proportional hazards model. Compared with the consistently high trajectory, the adjusted hazard ratio (aHR) for the risk of virologic failure was highest among patients classified in the consistently low adherence trajectory (aHR 2.8; 95% CI: 1.6 to 4.9; $P < 0.001$) followed by the moderate decreasing group (aHR 1.8; 95% CI: 1.02 to 3.2; $P = 0.04$). The risk of virologic failure in the moderate increasing group was similar to that in the consistently high trajectory (aHR 1.0; 95% CI: 0.4 to 2.5; $P < 0.94$).

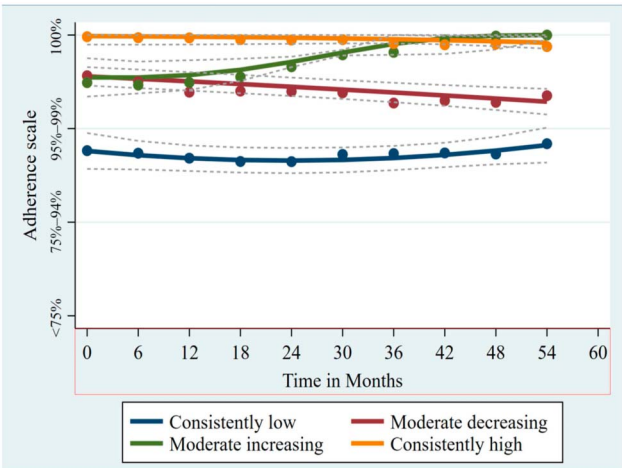

FIGURE 2. Trajectories of ART adherence.

DISCUSSION

Throughout the five-year study period, 12.0% of women included in this analysis experienced virologic failure. GBTM revealed 4 latent trajectories of adherence to ART, with approximately one-third of women in the consistently low adherence group and one-quarter of the women classified in the consistently high group. The rest of the women were grouped into moderate decreasing and moderate increasing

TABLE 2. Characteristics of Women With HIV in Moderate Increasing and Moderate Decreasing Adherence Groups at Baseline and Visit Three in the WIHS Cohort

	Baseline Visit				Third Study Visit			
	Adherence Trajectory				Adherence Trajectory			
Characteristic	Moderate Decreasing n (%) N = 440	Moderate Increasing n (%) N = 137	Total 577	*P*	Moderate Decreasing n (%) N = 440	Moderate Increasing n (%) N = 137	Total 577	*P*
Age groups				0.21				
<50 yrs	229 (78.4)	63 (21.6)	292					
>50 yrs	211 (74.0)	74 (26.0)	285					
Race				0.20				
African American	323 (77.6)	93 (22.4)	416					
Others	117 (72.7)	44 (27.3)	161					
Education				0.30				
Below secondary	134 (73.6)	48 (26.4)	182					
Completed secondary	149 (80.0)	37 (20)	186					
Some college/completed college	157 (75.1)	52 (24.9)	209					
Employment				0.61				0.45
No	284 (75.5)	92 (24.5)	376		260 (75.4)	85 (24.6)	345	
Yes	154 (77.4)	45 (22.6)	199		144 (78.3)	40 (21.7)	184	
Missing					36 (75.0)	12 (25.0)	48	
Annual income				0.32				0.25
≤$ 24,000	322 (75.2)	106 (24.8)	428		298 (75.4)	79 (24.6)	395	
>$24,000	118 (79.2)	31 (20.8)	149		102 (80.3)	25 (19.7)	127	
Missing					40 (72.7)	15 (27.3)	55	
Alcohol categories				0.35				0.18
0 drinks/wk	242 (73.3)	88 (26.7)	330		230 (73.3)	84 (26.7)	314	
>0–7 drinks/wk	158 (78.6)	43 (21.4)	201		139 (79.9)	35 (20.1)	174	
>7–12 drinks/wk	15 (88.2)	2 (11.8)	17		12 (80.0)	3 (20.0)	15	
>12 drinks/wk	25 (86.1)	4 (13.8)	29		22 (88.0)	3 (12.0)	25	
Missing	—				37 (75.5)	12 (24.5)	49	
History of smoking status				0.35				0.83
Never smoker	147 (75.4)	48 (24.6)	195		134 (75.3)	44 (24.7)	178	
Current smoker	176 (79.3)	46 (20.7)	222		154 (77.8)	44 (22.2)	198	
Former smoker	117 (73.1)	43 (26.9)	160		116 (75.8)	37 (24.2)	153	
Missing	—	—	—		36 (75.0)	12 (25.0)	48	
Depression symptoms				0.80				0.60
No	310 (76.)	98 (24.0)	408		288 (75.6)	93 (24.4)	381	
Yes	130 (76.9)	39 (23.1)	169		112 (77.8)	32 (22.2)	144	
Missing					40 (76.9)	12 (23.1)	52	
Substance use				0.55				0.45
No	129 (74.6)	44 (25.4)	173		121 (74.2)	42 (25.8)	163	
Yes	309 (76.9)	93 (23.1)	402		282 (77.2)	83 (22.8)	365	
Missing	2	—	2		37 (75.5)	12 (24.5)	49	

trajectories. The consistently low and moderate decreasing trajectories had higher hazard ratios of experiencing virologic failure compared with women who followed the consistently high and moderate increasing trajectories.

Our observed rate of virologic failure (12.0%) among women followed up between 2014 and 2019 indicates a substantially lower rate of failure compared with that in a previous analysis of the WIHS by McFall et al[30] who found that nearly half of the women enrolled in the WIHS between 2006 and 2011 experienced virologic failure. Notably, the adherence levels were similar between the 2 studies; 68% of the women reported at least a 95% level of adherence to ART in the study conducted by McFall et al compared with 67% of the women in the current analysis. The difference in the rate of virologic failure may be attributed to the advancements made in the development of modern antiretroviral medications with low toxicities, coupled with the changes in the recommendations in 2012 regarding the initiation of ART irrespective of CD4 count compared with starting the treatment at prespecified cutoff points in the previous guidelines.[31]

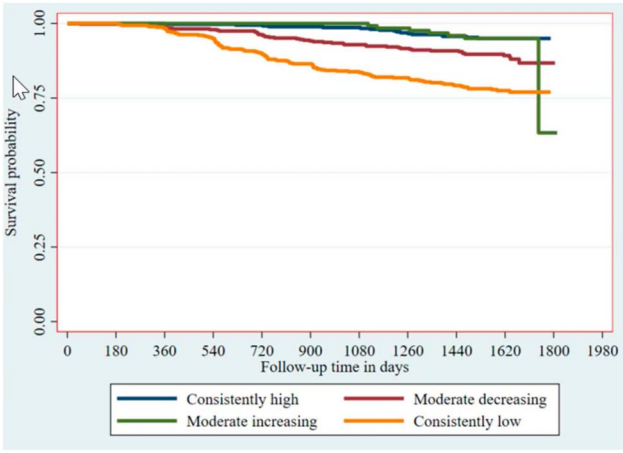

FIGURE 3. Kaplan–Meier plot of time to virologic failure by adherence trajectories.

In this study, GBTM provided a novel insight into the dynamic nature of adherence behavior among WHIV in the United States where we identified 4 categories of adherence over time. Previous studies have generally used the conventional approach of dichotomizing adherence or a maximum grouping into 3 levels of adherence.[32] In contrast to our findings, Storholm et al[33] analyzed electronically monitored adherence using the Medication Event Monitoring System in approximately 240 Black PWHIV in the United States at 3 points in time using GBTM. In that analysis, the model revealed 3 adherence trajectories, namely highly stable (40%), moderately low stable (35%), and low decreasing adherence (25%). The difference in the number of trajectories may be attributed to the difference in the sample size, the method of adherence measurement, and the time points at which adherence was measured. Of interest, the percentages of the consistently high, consistently moderate, and consistently low adherence trajectories in our analysis supported the findings of the study conducted by Kassaye et al[4] who used GBTM to delineate the long-term HIV viral suppression trajectories among women in WIHS. In their analysis, the women were grouped into 3 trajectories based on the probability of viremia above 200 copies/mL as low (28.6%), intermediate (39.4%), and high (32.0%).

TABLE 3. Unadjusted and Adjusted Cox Proportional Hazards Estimates of the Risk of Virologic Failure by Trajectories of Adherence

Covariates	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Adherence trajectories				
Consistently high	1.0		1.0	
Moderate decreasing	2.5 (1.4 to 4.3)	0.002	1.8 (1.02 to 3.2)	0.04
Moderate increasing	1.0 (0.5 to 2.7)	0.81	1.0 (0.4 to 2.5)	0.94
Consistently low	5.3 (3.2 to 8.9)	<0.001	2.8 (1.6 to 4.9)	<0.001

One potential advantage of GBTM in our analysis was seen in identifying latent moderate increasing and moderate decreasing groups; these trajectories started at similar levels of adherence but diverged at 12 months of follow-up. Our results showed no significant difference in the baseline characteristics at the start of the study or later during divergence that would explain the observed change in the trajectory path of the 2 groups. However, given the complexity of the factors that affect adherence, qualitative in-depth studies are needed to explore the underlying reasons that led to the observed divergence.[34] Of interest, the women who followed the moderate increasing trajectory compared with the moderate decreasing had an aHR of virologic failure identical to those who were classified in the consistently high group. The experience of the women in the moderate increasing trajectory deserves further investigation to identify the factors that improved their adherence behavior; such data could be useful for developing adherence interventions for other women in similar circumstances.

The well-known relationship between adherence and viral suppression could be confounded by other factors with alternate, direct effects on viral suppression. In this analysis, we adjusted for such factors that were available in our data set. Specifically, we controlled for the type of regimen at the last visit because of the variations in drug half-lives that influence the extent to which patterns of adherence results in viral suppression.[23] In addition, we adjusted for the frequency of experiencing viremia during the whole study period; the duration of prior viral suppression has a major effect on the level of adherence required to maintain suppression.[24] Furthermore, in the model, we accounted for the role of inflammation by controlling for the following variables: age, smoking, alcohol consumption, and depression,[25–27] which could potentially affect the pharmacokinetics of ART and therefore viral suppression[35] (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C26). We considered the many other individual, interpersonal, community, health system, and structural factors relevant to viral suppression; however, they all operate through adherence and were thus not added individually to the model.[36]

Based on the results of this study, we identified several clinical recommendations that may improve nonadherence and decrease the rate of virologic failure. First, future interventions should focus on women who follow low and moderate decreasing trajectories. Second, behavioral interventions to address the problem of heavy alcohol consumption among women who followed a consistently low trajectory are critical for increasing adherence and improving biological markers.[37] Last, among the same group of women, adherence may be improved by implementing cognitive behavioral therapy that concomitantly addresses both depression and poor adherence.[38]

The major strengths of this analysis are the large sample size of participants who were followed up for sufficient time to observe the outcome of interest. In addition, data were nearly complete, and there was only a slight difference between the number of viral load measurements and the number of self-reported adherence measurements. At the same time, we recognize that women who miss 1 or multiple visits may be exposed to social determinants of health that increase their risk of virologic failure. However, this analysis was not without

limitations. First, women self-reported their adherence to ART during the last month every 6 months, a method subject to recall bias and social desirability.[39] However, the self-report method can still provide useful information about adherence behavior, as demonstrated in this analysis. In this respect, nearly 5% of the women classified in the consistently high trajectory experienced treatment failure, which may indicate misclassification bias in their adherence reporting or potentially use of suboptimal ART regimens (eg, with drug resistance). In the future, objective measures of adherence such as measuring the levels of ART in hair or blood could provide less biased results about the association between adherence trajectories and treatment outcomes.[40] Second, we did not audit the prescribing practice of ART against the treatment guidelines to ensure conformity. Third, although the WIHS recruited women from different geographical locations in the country, our result may not be generalizable to all WHIV. Future studies can use combined data from multiple databases. Last, we cannot exclude the impact of unmeasured residual confounding.

In conclusion, our study emphasizes that adherence to ART remains a challenge among WHIV because approximately one-third of the women were found to be in the consistently low adherence category. Grouping women based on their adherence to multiple trajectories rather than using the conventional method of dichotomizing them into adherent and nonadherent could be of great value to help in designing multilevel behavioral interventions that concomitantly address poor adherence, alcohol consumption, and depression, such interventions are urgently needed.

REFERENCES

1. Bosh KA, Hall HI, Eastham L, et al. Estimated annual number of HIV infections—United States, 1981–2019. *MMWR Morb Mortal Wkly Rep.* 2021;70:801–806.
2. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2015–2019. *HIV Surveill Supplemental Rep.* 2021;26. Available at: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed April 12, 2022.
3. Thaker HK, Snow MH. HIV viral suppression in the era of antiretroviral therapy. *Postgrad Med J.* 2003;79:36–42.
4. Kassaye SG, Wang C, Ocampo JMF, et al. Viremia trajectories of HIV in HIV-Positive women in the United States, 1994–2017. *JAMA Netw Open*. 2019;3:e193822. Available at: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2733428. Accessed August 5, 2022.
5. Benson C, Wang X, Dunn KJ, et al. Antiretroviral adherence, drug resistance, and the impact of social determinants of health in HIV-1 patients in the US. *AIDS Behav.* 2020;24:3562–3573.
6. Turner BJ, Laine C, Cosler L, et al. Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected drug users. *J Gen Intern Med.* 2003;18:248–257.
7. Applebaum AJ, Richardson MA, Brady SM, et al. Gender and other psychosocial factors as predictors of adherence to highly active antiretroviral therapy (HAART) in adults with comorbid HIV/AIDS, psychiatric and substance-related disorder. *AIDS Behav.* 2009;13:60–65.
8. Waldron EM, Burnett-Zeigler I, Wee V, et al. Mental health in women living with HIV: the unique and unmet needs. *J Int Assoc Provid AIDS Care.* 2021;20:2325958220985665. Available at: https://journals.sagepub.com/doi/full/10.1177/2325958220985665. Accessed July 2, 2022.
9. Pellowski JA, Price DM, Harrison AD, et al. A systematic review and meta-analysis of antiretroviral therapy (ART) adherence interventions for women living with HIV. *AIDS Behav.* 2019;23:1998–2013.
10. Geter A, Sutton MY, Armon C, et al. Disparities in viral suppression and medication adherence among women in the USA, 2011-2016. *AIDS Behav.* 2019;23:3015–3023.
11. Alhazami M, Pontinha VM, Patterson JA, et al. Medication adherence trajectories: a systematic literature review. *J Manag Care Specialty Pharm.* 2020;26:1138–1152.
12. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol.* 2010;6:109–138.
13. Whiteley LB, Olsen EM, Haubrick KK, et al. A review of interventions to enhance HIV medication adherence. *Curr HIV/AIDS Rep.* 2021;18:443–457.
14. Franklin JM, Krumme AA, Tong AY, et al. Association between trajectories of statin adherence and subsequent cardiovascular events. *Pharmacoepidemiol Drug Saf.* 2015;24:1105–1113.
15. Lo-Ciganic WH, Donohue JM, Jones BL, et al. Trajectories of diabetes medication adherence and hospitalization risk: a retrospective cohort study in a large state Medicaid program. *J Gen Intern Med.* 2016;31:1052–1060.
16. Winn AN, Dusetzina SB. The association between trajectories of endocrine therapy adherence and mortality among women with breast cancer. *Pharmacoepidemiol Drug Saf.* 2016;25:953–959.
17. Bacon MC, von Wyl V, Alden C, et al. The women's interagency HIV Study: an observational cohort brings clinical sciences to the bench. *Clin Vaccin Immunol.* 2005;12:1013–1019.
18. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's interagency HIV study. *Epidemiology*. 1998;9:117–125.
19. Adimora AA, Ramirez C, Benning L, et al. Cohort profile: the Women's interagency HIV study (WIHS). *Int J Epidemiol.* 2018;47:393–394.
20. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977;1:385–401.
21. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. *Department Health Hum Serv.* Available at: http://www.aid.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf. Accessed April 15, 2022.
22. Jones BL, Nagin DS. A note on a Stata plugin for estimating group-based trajectory models. *Sociological Methods Res.* 2013;42:608–613.
23. Haberer JE, Musinguzi N, Boum Y II, et al. Duration of antiretroviral therapy adherence interruption is associated with risk of virologic rebound as determined by real-time adherence monitoring in rural Uganda. *J Acquir Immune Defic Syndr.* 2015;70:386–392.
24. Lima VD, Bangsberg DR, Harrigan PR, et al. Risk of viral failure declines with duration of suppression on highly active antiretroviral therapy irrespective of adherence level. *J Acquir Immune Defic Syndr.* 2010;55:460–465.
25. Carrico AW, Hunt PW, Emenyonu NI, et al. Unhealthy alcohol use is associated with monocyte activation prior to starting antiretroviral therapy. *Alcohol Clin Exp Res.* 2015;39:2422–2426.
26. Rivera-Rivera Y, Vázquez-Santiago FJ, Albino E, et al. Impact of depression and inflammation on the progression of HIV disease. *J Clin Cell Immunol.* 2016;7:423. Available at: https://www.longdom.org/open-access/impact-of-depression-and-inflammation-on-the-progression-of-hiv-disease-50910.html. Accessed August 22, 2022.
27. Valiathan R, Miguez MJ, Patel B, et al. Tobacco smoking increases immune activation and impairs T-cell function in HIV infected patients on antiretrovirals: a cross-sectional pilot study. *PLoS One*. 2014;19:e97698. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0097698. Accessed August 22, 2022.
28. Weld ED. Limits of detection and limits of infection: quantitative HIV measurement in the era of U = U. *J Appl Lab Med.* 2021;6:324–326.
29. Paintsil E, Martin R, Goldenthal A, et al. Frequent episodes of detectable viremia in HIV treatment-experienced children is associated with a decline in CD4+ T-cells over time. *J AIDS Clin Res.* 2016;7:565. Available at: https://www.hilarispublisher.com/open-access/frequent-episodes-of-detectable-viremia-in-hiv-treatmentexperiencedchildren-is-associated-with-a-decline-in-cd4-tcells-over-time-2155-6113-1000565.pdf. Accessed April 18, 2022.
30. McFall AM, Dowdy DW, Zelaya CE, et al. Understanding the disparity: predictors of virologic failure in women using highly active antiretroviral therapy vary by race and/or ethnicity. *J Acquir Immune Defic Syndr.* 2013;64:289–298.
31. Eholié SP, Badje A, Kouame GM, et al. Antiretroviral treatment regardless of CD4 count: the universal answer to a contextual question. *AIDS Res Ther.* 2016;13:27. Available at: https://aidsrestherapy.biomedcentral.com/articles/10.1186/s12981-016-0111-1. Accessed April 15, 2022.

32. Sok P, Mgbere O, Pompeii L, et al. Evaluation of the sociodemographic, behavioral, and clinical influences on complete antiretroviral therapy adherence among HIV-infected adults receiving medical care in Houston, Texas. *HIV AIDS (Auckl)*. 2021;13:539–555. Available at: https://www.dovepress.com/evaluation-of-the-sociodemographic-behavioral-and-clinical-influences–peer-reviewed-fulltext-article-HIV. Accessed April 12, 2022.
33. Storholm ED, Bogart LM, Mutchler MG, et al. Antiretroviral adherence trajectories among Black Americans living with HIV. *AIDS Behav.* 2019;23:1985–1997.
34. Bezabhe WM, Chalmers L, Bereznicki LR, et al. Barriers and facilitators of adherence to antiretroviral drug therapy and retention in care among adult HIV-positive patients: a qualitative study from Ethiopia. *PLoS One*. 2014;9:e97353.Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0097353. Accessed April 12, 2022.
35. Seifert SM, Castillo-Mancilla JR, Erlandson KM, et al. Inflammation and pharmacokinetics: potential implications for HIV-infection. *Expert Opin Drug Metab Toxicol.*; 2017. 67.641–650.
36. Kaufman MR, Cornish F, Zimmerman RS, et al. Health behavior change models for HIV prevention and AIDS care: practical recommendations for a multi-level approach. *J Acquired Immune Deficiency Syndromes*. 2014;66(suppl 3):S250–S258.
37. Parsons JT, Golub SA, Rosof E, et al. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. *J Acquired Immune Deficiency Syndromes*. 2007;46:443–450.
38. Junkins A, Psaros C, Ott C, et al. Feasibility, acceptability, and preliminary impact of telemedicine-administered cognitive behavioral therapy for adherence and depression among African American women living with HIV in the rural South. *J Health Psychol.* 2021;26:2730–2742.
39. Simoni JM, Kurth AE, Pearson CR, et al. Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. *AIDS Behav.* 2006;10:227–245.
40. Spinelli MA, Haberer JE, Chai PR, et al. Approaches to objectively measure antiretroviral medication adherence and drive adherence interventions. *Curr HIV/AIDS Rep.* 2020;17:301–314.