

Use of and Adherence to Antiretroviral Therapy in a Large U.S. Sample of HIV-infected Adults in Care, 2007-2008

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Abstract: *Background:* Antiretroviral therapy (ART) is the cornerstone of HIV clinical care and is increasingly recognized as a key component of HIV prevention. However, the benefits of ART can be realized only if HIV-infected persons maintain high levels of adherence.

Methods: We present interview data (collected from June 2007 through September 2008) from a national HIV surveillance system in the United States—the Medical Monitoring Project (MMP)—to describe persons taking ART. We used multivariate logistic regression to assess behavioral, sociodemographic, and medication regimen factors associated with three measures that capture different dimensions of nonadherence to ART: dose, schedule, and instruction.

Results: The use of ART among HIV-infected adults in care was high (85%), but adherence to ART was suboptimal and varied across the three measures of nonadherence. Of MMP participants currently taking ART, the following reported nonadherence during the past 48 hours: 13% to dose, 27% to schedule, and 30% to instruction. The determinants of the three measures also varied, although younger age and binge drinking were associated with all aspects of nonadherence.

Conclusion: Our results support the measurement of multiple dimensions of medication-taking behavior in order to avoid overestimating adherence to ART.

Keywords: HIV, medication adherence, antiretroviral therapy, Centers for Disease Control and Prevention (U.S.).

INTRODUCTION

A high level of adherence to antiretroviral therapy (ART) is necessary to maintain viral suppression and achieve optimal clinical outcomes for HIV-infected persons [1, 2], though there is little consensus on the minimum threshold of adherence needed for virologic suppression [3, 4]. Medication adherence often accompanies other healthy behaviors such as diet and health care utilization [5]. ART may also improve population health, reduce the number of premature deaths, and lower health care costs, as studies indicate that access and adherence to ART may play an important role in reducing HIV transmission by suppressing HIV viral load (VL) [6, 7]. Successful ART requires clinicians to assess the risks of nonadherence before deciding on a regimen and to accurately monitor and support adherence throughout therapy [8, 9].

Clinical outcomes have been better predicted by measuring multiple dimensions of medication-taking behaviors than by measuring missed doses [10]. Gill and colleagues found the timing of doses to be important for VL suppression [11]. Despite these findings, many studies of ART adherence have been focused on missed doses, not on adherence to medication schedules and special instructions such as dietary restrictions. Failure to inquire about adherence to schedule and instruction may lead to inaccurate estimates of a patient's level of adherence and may thus result in missed opportunities to educate or failure to identify nonadherence as a cause of treatment failure. The few studies that have compared different dimensions of nonadherence have found that their predictors vary [12, 13]. Because multiple measures of nonadherence have proved useful in predicting clinical outcomes and our knowledge of their predictors (and how they may vary across measures) is limited, examination of multiple measures is warranted. Better knowledge of these factors may inform the development of interventions to improve all aspects of adherence.

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The primary objective of our analysis was to describe the use of ART and to assess the various measures of ART nonadherence in a national sample of adult HIV patients. A secondary objective was to explore the factors associated with the various dimensions of medication-taking behavior, which have been incompletely described to date.

METHODS

We performed a cross-sectional analysis of data from the Medical Monitoring Project (MMP), a supplemental surveillance system for collecting clinical and behavioral data on HIV-infected adults receiving care. The methods have been described in detail elsewhere [14, 15]. MMP uses a three-stage sampling design to obtain annual cross-sectional probability samples of HIV-infected adults in care. In the first stage, states are selected to participate, then HIV care facilities in these states are sampled, and finally HIV-infected adults in care at participating facilities are sampled. Face-to-face interviews are conducted to collect information on demographics, adherence to HIV medication regimens, and behavioral risk factors. The data were collected in 19 states and Puerto Rico from June 2007 through September 2008.¹ The Centers for Disease Control and Prevention has determined that MMP is not human subjects research because it is a routine disease surveillance activity. However, participating project areas obtain local Institutional Review Board (IRB) approval to conduct MMP as required locally. We asked participants about their medication-taking behaviors during the 48 hours before interview. *Dose nonadherence* refers to failure to take a prescribed dose or set of pills/spoonfuls/injections of antiretroviral (ARV) medications. *Schedule nonadherence* refers to failure to follow the prescribed schedule for ARV medications, such as “2 times a day” or “every 8 hours.” *Instruction nonadherence* refers to failure to follow special instructions accompanying ARV medication prescriptions, such as “take with food” or “take on an empty stomach.” Instruction nonadherence was asked of only the participants who reported having received special instructions for their ARV medications. Although self-reported measures have generally been found to indicate lower nonadherence than other measures (such as pill counts, Medication Event Monitoring System [MEMS] devices, or pharmacy refill records), no standard exists for measuring nonadherence [16] and self-reported measures have been correlated with clinical outcomes such as VL [17]. We defined nonadherence as failure to take ARV medication exactly as prescribed (i.e., 100% of doses taken for dose adherence, 100% of doses on the prescribed schedule for schedule adherence, and 100% instructions followed for instruction adherence) given that 100% adherence is a common threshold for self-reported measures [18].

After determining the frequencies of selected characteristics to describe participants currently taking ART and those not taking ART, we tested for differences in these characteristics by using chi-square tests. To assess whether

our measures of nonadherence are related to clinical outcomes, we then tested for bivariate associations between each of the three measures of nonadherence and self-reported undetectable VL, using the Mantel-Haenszel chi-square test and binomial logistic regression. In addition, we used these methods to examine the relationship between the total number of reported nonadherence measures (measured as 0 = 100% adherent on all three measures, 1 = nonadherent on one measure, 2 = nonadherent on two measures, 3 = nonadherent on all three measures) and self-reported undetectable VL.

Finally, to explore differences in the factors associated with the measures of nonadherence, we tested for bivariate relationships between dose, schedule, and instruction nonadherence and the factors associated with nonadherence in the scientific literature. Factors associated with each measure of nonadherence (significant at the $p < 0.10$ level) were included in three multivariate regression models. Final models were determined by using backward stepwise regression with a $p < 0.05$ retention criterion. Model fit was assessed by using the Hosmer and Lemeshow goodness-of-fit test.

All independent variables refer to the past 12 months except where otherwise noted. The following independent variables were examined for each of the three models:

- Sociodemographic: gender, age at interview, race/ethnicity, educational attainment (<high school, >high school or equivalent), receipt of public assistance, homelessness (defined as living on the street, in a shelter, a single-room-occupancy hotel, temporarily staying with friends/family, or living in a car), lack of continuous health insurance coverage
- Alcohol and drug use: crack use, amphetamine use, binge drinking in the past 30 days (>4 drinks per day for men, >3 drinks per day for women)
- Mental health: feeling downhearted and depressed in past 4 weeks (5-point Likert scale ranging from 1 = “none of the time” to 5 = “all of the time”)
- HIV-related: not knowing most recent VL test result, number of daily ARV doses (defined as a set of pills/spoonfuls/injections of antiretroviral (ARV) medications), years since HIV diagnosis, having a discussion with a provider about ARV drug resistance

RESULTS

All sampled states and territories agreed to participate in MMP. During January-April 2007, a sample of 10,503 patients was selected from 582 participating HIV care facilities in the 26 participating project areas. The overall median facility participation rate was 91.4% (range across project areas, 65% to 100%). Of the sample, 311 were ineligible, resulting in a total of 10,192 patients. Reasons for ineligibility included: 29 duplicates, 18 less than 18 years of age, 63 HIV-negative, 114 no care during the sample selection period, and 87 ineligible for other reasons. The median patient participation rate was 40% (range across project areas, 3% to 76%). A total of 3,944 standard interviews were conducted from June 2007 through September 2008. For this analysis, the data of 43 participants

¹The 26 participating project areas: California, Chicago (Illinois), Delaware, Florida, Georgia, Houston (Texas), Illinois, Indiana, Los Angeles County (California), Maryland, Massachusetts, Michigan, Mississippi, New Jersey, New York, New York City (New York), North Carolina, Oregon, Pennsylvania, Philadelphia (Pennsylvania), Puerto Rico, San Francisco (California), South Carolina, Texas, Virginia, and Washington.

Table 1. Factors associated with current use of ART—United States, Medical Monitoring Project, 2007-2008

Characteristic	Currently Taking ART (n = 3307)		Not Currently Taking ART (n = 579)		Chi-Square Test for Differences (p Value)
	No.	% of Total	No.	% of Total	
Gender					
Male	2431	74	373	64	20.52
Female	830	25	197	34	(<.0001)
Transgender	45	1	8	1	
Age (years)					
18-24	45	1	33	6	118.82
25-34	280	8	101	17	(<.0001)
35-44	1039	31	214	37	
45-54	1311	40	180	31	
≤55	632	19	51	9	
Race/ethnicity					
Black, non-Hispanic	1254	38	288	50	31.26
Hispanic	663	20	95	16	(<.0001)
White, non-Hispanic	1173	35	156	27	
Other	212	6	39	7	
Education					
< High School	729	22	149	26	3.81
≥ High School or equivalent	2576	78	430	74	(0.05)
Public assistance, past 12 months					
No	1639	50	322	56	7.4
Yes	1667	50	256	44	(0.01)
Lapse in health coverage, past 12 months					
No	2491	75	379	65	24.06
Yes	808	24	197	34	(<.0001)
Homeless, past 12 months					
No	3080	93	500	86	31.22
Yes	227	7	79	14	(<.0001)
Years since HIV diagnosis					
≤ 1	18	1	5	1	57.43
2-5	616	19	189	33	(<.0001)
6-10	764	23	127	22	
11-25	1711	52	226	39	
Knew most recent HIV viral load test result					
No	639	19	162	28	27.41
Yes	2587	78	383	66	(<.0001)
Most recent HIV viral load test result					
Undetectable	2056	62	110	19	482.24
Detectable but <5000	307	9	93	16	(<.0001)
≥5000-<100000	166	5	142	25	
≥100000	58	2	38	7	
Missing	720	22	196	34	

(Table 1) contd.....

Characteristic	Currently Taking ART (n = 3307)		Not Currently Taking ART (n = 579)		Chi-Square Test for Differences (p Value)
	No.	% of Total	No.	% of Total	
CD4 count (self-reported nadir)					
0-199	1511	46	90	16	218.3
200-349	642	19	128	22	(<.0001)
350-499	261	8	112	19	
500+	140	4	102	18	
Missing	753	23	147	25	
Feeling downhearted and depressed, past 4 weeks					
All of the time	140	4	39	7	10.91
Most of the time	315	10	77	13	(0.00)
Some of the time	992	30	155	27	
A little of the time	799	24	153	26	
None of the time	1054	32	154	27	
Crack use, past 12 months					
No	3128	95	521	90	19.45
Yes	167	5	56	10	(<.0001)
Amphetamine use, past 12 months					
No	3142	95	537	93	5.6
Yes	152	5	40	7	(0.02)
Binge drinking, past 30 days					
No	2864	87	459	79	21.19
Yes	426	13	116	20	(<.0001)

Note: ART, antiretroviral therapy; values may not sum to total due to missing data; missing values shown when >10% of total.

were excluded because interviewers were not confident of the validity of the responses (for example, cases where the participant was incoherent or unresponsive to interview questions).

Antiretroviral Therapy Use

Of 3886 participants who provided information about ART, 3307 (85%) were currently taking ART. Roughly equal proportions had never taken ART (8%) or had previously taken ART (7%). Compared to those not currently taking ART, those who were currently taking ART were significantly more likely to be male, older, non-Hispanic white (hereafter referred to as white) or Hispanic, HIV-diagnosed for a longer period of time, and not homeless; to have continuous healthcare coverage for the past year and a lower self-reported nadir CD4+ T-lymphocyte (CD4) count; to report a lower VL and feeling downhearted and depressed (hereafter referred to as depressed) less often; to know the result of their most recent VL test; and not to receive public assistance, not to use crack or amphetamines, and not to binge drink (Table 1).

Nonadherence to Antiretroviral Therapy

Table 2 presents descriptive statistics for participants who reported nonadherence during the past 48 hours. Of

MMP participants currently taking ART, 13% reported nonadherence to dose, 27% to schedule, and 30% to instruction. Considering all measures, nonadherence was reported by 38% of participants: 22% reported nonadherence to one measure, 11% to two measures, and 5% to all three measures.

Association between Self-reported Detectable Viral Load and Nonadherence

Participants were asked about the results of their most recent VL test (see Table 2). Tests of association revealed statistically significant positive relationships between nonadherence and detectable VL test result ($p < 0.0001$ for dose and schedule nonadherence and $p = 0.03$ for instruction nonadherence). In addition, there was a significant and positive association between the number of nonadherence measures reported and detectable VL ($p < 0.0001$). Logistic regression modeling results indicated that the odds of a detectable VL more than doubled for those reporting dose nonadherence (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.7-2.8). Similar analyses yielded an OR of 2.1 for schedule nonadherence (CI, 1.7-2.6) and 1.3 for instruction nonadherence (CI, 1.0-1.7). In addition, nonadherence to multiple measures was associated with increased odds of a detectable VL. In a comparison of participants who reported nonadherence and participants who did not, the odds of

Table 2. Nonadherence to ART During the Past 48 Hours—United States, Medical Monitoring Project, 2007-2008

	Currently Taking ART		Dose ^a Nonadherence			Schedule ^b Nonadherence			Instruction ^c Nonadherence		
	n = 3307		n = 444		Chi-Square Test for Differences (p Value)	n = 893		Chi-Square Test for Differences (p Value)	n = 638		Chi-Square Test for Differences (p Value)
Characteristic	No.	%	No.	%		No.	%		No.	%	
Gender											
Male	2431	74	293	66	15.62	591	66	34.68	462	72	1.60
Female	830	25	145	33	(0.00)	289	32	(<.0001)	167	26	(0.45)
Transgender	45	1	6	1		13	1		9	1	
Age (years)											
18-24	45	1	18	4	11.33	21	2	12.48	17	3	25.85
25-34	280	8	43	10	(0.00)	83	9	(0.00)	68	11	(<.0001)
35-44	1039	31	135	30		300	34		226	35	
45-54	1311	40	182	41		340	38		245	38	
≤55	632	19	66	15		149	17		82	13	
Race/ethnicity											
Black, non-Hispanic	1254	38	208	47	33.14	400	45	64.78	243	38	0.86
Hispanic	663	20	102	23	(<.0001)	219	25	(<.0001)	146	23	(0.83)
White, non-Hispanic	1173	36	105	24		230	26		207	32	
Other	212	6	29	7		44	5		42	7	
Education											
< High School	729	22	111	25	2.68	250	28	25.41	149	23	0.88
≥ High School or equivalent	2576	78	332	75	(0.10)	643	72	(<.0001)	488	77	(0.35)
Public assistance, past 12 months											
No	1639	50	184	41	13.58	380	43	23.85	323	51	0.03
Yes	1667	50	260	59	(0.00)	513	57	(<.0001)	315	49	(0.86)
Lapse in health coverage, past 12 months											
No	2491	76	327	74	0.64	671	75	0.04	453	71	0.94
Yes	808	24	115	26	(0.42)	220	25	(0.84)	185	29	(0.33)
Homeless, past 12 months											
No	3080	93	398	90	9.81	808	90	13.63	581	91	3.47
Yes	227	7	46	10	(0.00)	85	10	(0.00)	57	9	(0.06)
Years since HIV diagnosis											
≤ 1	18	1	<5	<1	6.29	<5	<1	4.00	<5	1	1.03
2-5	616	20	69	17	(0.01)	140	17	(0.05)	131	22	(0.31)
6-10	764	25	93	22		219	26		147	25	
11-25	1711	55	254	61		467	56		315	53	
Knew most recent HIV viral load test result											
No	639	20	108	25	8.14	238	27	44.22	104	17	2.25
Yes	2587	80	326	75	(0.00)	629	73	(<.0001)	513	83	(0.13)

(Table 2) contd.....

	Currently Taking ART		Dose ^a Nonadherence			Schedule ^b Nonadherence			Instruction ^c Nonadherence		
	n = 3307		n = 444		Chi-Square Test for Differences (p Value)	n = 893		Chi-Square Test for Differences (p Value)	n = 638		Chi-Square Test for Differences (p Value)
Characteristic	No.	%	No.	%		No.	%		No.	%	
Most recent HIV viral load test result											
Undetectable	2056	62	218	49	44.11	438	49	49.47	384	60	4.48
Detectable but <5000	307	9	54	12	(<.0001)	104	12	(<.0001)	73	11	(0.03)
≥5000-<100000	166	5	36	8		61	7		41	6	
≥100000	58	2	18	4		26	3		15	2	
Missing	720	22	118	27		264	30		125	20	
Feeling downhearted and depressed, past 4 weeks											
All of the time	140	4	36	8	29.39	39	4	12.11	32	5	14.15
Most of the time	315	10	56	13	(<.0001)	104	12	(0.00)	67	11	(0.00)
Some of the time	992	30	143	32		287	32		212	33	
A little of the time	799	24	97	22		215	24		165	26	
None of the time	1054	32	110	25		245	28		158	25	
Crack use, past 12 months											
No	3128	95	403	91	18.36	829	93	8.00	597	94	4.69
Yes	167	5	41	9	(<.0001)	61	7	(0.00)	39	6	(0.03)
Amphetamine use, past 12 months											
No	3142	95	418	94	1.72	842	95	0.74	601	95	3.30
Yes	152	5	26	6	(0.19)	46	5	(0.39)	34	5	(0.07)
Binge drinking, past 30 days											
No	2864	87	359	81	16.42	745	84	11.41	519	82	29.95
Yes	426	13	84	19	(<.0001)	144	16	(0.00)	115	18	(<.0001)
Discussed resistance with provider, past 12 months											
No	1174	36	128	29	10.12	310	35	0.24	197	31	0.33
Yes	2079	64	309	71	(0.00)	567	65	(0.62)	431	69	(0.56)

Note: ART, antiretroviral therapy; values may not sum to total due to missing data; missing values shown when >10% of total.

^aDose nonadherence refers to not taking a dose or set of pills/spoonfuls/injections of ARV medications.

^bSchedule nonadherence refers to not following a specific schedule for ARV medication, such as "2 times a day" or "every 8 hours."

^cInstruction nonadherence refers to not following special instructions for ARV medication, such as "take with food" or "take on an empty stomach." Dietary instruction adherence is only calculated for those participants reporting having special instructions for their ARV medications.

detectable VL was 1.3 times as high (CI, 1.0-1.7) for those who reported nonadherence to one measure, 2.1 times as high (CI, 1.6-2.8) for those who reported nonadherence to two measures, and 2.9 times as high (CI, 2.0-4.1) for those who reported nonadherence to all three measures.

Factors Associated with Each Measure of Nonadherence

The factors independently associated with dose nonadherence were female gender; per year decrease in age; non-Hispanic black (hereafter referred to as black) and

Hispanic race/ethnicity; receipt of public assistance; feeling depressed all, most, or some of the time; crack use; binge drinking; higher number of years since HIV diagnosis; and higher number of daily ARV doses (Table 3). The factors independently associated with schedule nonadherence were female gender, per year decrease in age, black and Hispanic race/ethnicity, less than high school education, homelessness, receipt of public assistance, binge drinking, higher number of daily ARV doses, and not knowing one's most recent VL test result. The factors independently

Table 3. Logistic Regression Models of Factors Associated with Nonadherence to ART During the Past 48 Hours—United States, Medical Monitoring Project, 2007-2008

Characteristic	Dose ^a Nonadherence (N = 3307)		Schedule ^b Nonadherence (N = 3298)		Instruction ^c Nonadherence (N = 2101)	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Gender						
Male	Ref	Ref	Ref	Ref	NS	
Female	1.55 (1.24-1.92)	1.36 (1.07-1.74)	1.66 (1.40-1.97)	1.46 (1.20-1.76)		
Transgender	1.12 (0.47-2.68)	0.62 (0.21-1.80)	1.26 (0.66-2.42)	0.99 (0.49-2.01)		
Age (years)	0.98 (0.97-0.99)	0.98 (0.96-0.99)	0.99 (0.98-0.99)	0.98 (0.98-0.99)	0.97 (0.96-0.98)	0.98 (0.97-0.99)
Race/ethnicity						
Black, non-Hispanic	2.02 (1.58-2.60)	1.96 (1.48-2.59)	1.93 (1.60-2.32)	1.56 (1.27-1.93)	NS	
Hispanic	1.85 (1.38-2.47)	1.63 (1.18-2.24)	2.03 (1.63-2.52)	1.59 (1.25-2.02)		
White, non-Hispanic	Ref	Ref	Ref	Ref		
Other	1.61 (1.04-2.50)	1.55 (0.96-2.51)	1.07 (0.75-1.54)	0.97 (0.66-1.41)		
Education						
< high school	NS		Ref	Ref	NS	
≥ high school or equivalent			0.64 (0.53-0.76)	0.78 (0.64-0.95)		
Homeless, past 12 months						
No	Ref	-	Ref	Ref	Ref	-
Yes	1.71 (1.22-2.41)	-	1.69 (1.28-2.24)	1.43 (1.05-1.95)	1.38 (0.98-1.94)	-
Public assistance, past 12 months						
No	Ref	Ref	Ref	Ref	NS	
Yes	1.46 (1.19-1.79)	1.31 (1.05-1.65)	1.47 (1.26-1.72)	1.35 (1.14-1.60)		
Feeling downhearted and depressed, past 4 weeks						
All of the time	2.97 (1.94-4.56)	2.63 (1.64-4.22)	1.27 (0.86-1.89)	-	1.81 (1.13-2.89)	1.61 (0.98-2.64)
Most of the time	1.86 (1.31-2.63)	1.81 (1.23-2.66)	1.63 (1.24-2.14)	-	1.63 (1.15-2.30)	1.54 (1.07-2.22)
Some of the time	1.45 (1.11-1.89)	1.37 (1.02-1.83)	1.35 (1.11-1.65)	-	1.56 (1.22-1.99)	1.51 (1.17-1.95)
A little of the time	1.19 (0.89-1.59)	1.20 (0.88-1.64)	1.22 (0.99-1.51)	-	1.50 (1.16-1.94)	1.51 (1.15-1.98)
None of the time	Ref	Ref	Ref	-	Ref	Ref
Crack use, past 12 months						
No	Ref	Ref	Ref	-	Ref	-

(Table 3) contd.....

	Dose ^a Nonadherence (N = 3307)		Schedule ^b Nonadherence (N = 3298)		Instruction ^c Nonadherence (N = 2101)	
Yes	2.19 (1.52-3.17)	1.66 (1.09-2.52)	1.59 (1.15-2.20)	-	1.58 (1.04-2.40)	-
Amphetamine use, past 12 months	NS		NS		Ref	-
No					1.50 (0.97-2.33)	-
Binge drinking, past 30 days	Ref		Ref		Ref	Ref
No					1.71 (1.32-2.23)	1.63 (1.21-2.20)
Years since HIV diagnosis	1.02 (1.00-1.03)	1.02 (1.00-1.04)	NS		0.98 (0.97-1.00)	-
Number of ARV doses per day	1.16 (1.10-1.23)	1.18 (1.10-1.25)	1.13 (1.08-1.19)	1.16 (1.11-1.22)	NS	
Knew most recent HIV viral load test result	1.41 (1.11-1.79)		1.86 (1.55-2.23)		1.48 (1.21-1.82)	
No						
Yes	Ref	-	Ref	Ref	NS	
Discussed resistance with provider, past 12 months	Ref		NS		NS	
No						
Yes	1.43 (1.15-1.78)	-				

Note: ART, antiretroviral therapy; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; Ref, reference category; NS, not significant.

^a Dose nonadherence refers to not taking a dose or set of pills/spoonfuls/injections of ARV medications.

^b Schedule nonadherence refers to not following a specific schedule for ARV medication, such as "2 times a day" or "every 8 hours."

^c Instruction nonadherence refers to not following special instructions for ARV medication, such as "take with food" or "take on an empty stomach." Dietary instruction adherence is only calculated for those participants reporting having special instructions for their ARV medications.

associated with instruction nonadherence were per year decrease in age; feeling depressed most, some, or a little of the time; and binge drinking.

DISCUSSION

Although studies on nonadherence to ART are common, one strength of this analysis is the use of probability sampling methods, which resulted in coverage of patients from 582 medical facilities in 19 U.S. states and Puerto Rico. The use of ART was high among adults in care for HIV. The persons not receiving ART were more likely to be female, to be black, and to report a lapse in health coverage, substance use, higher VL results, higher CD4 count as the nadir, and more frequent feelings of depression. Our findings agree with those in other reports [19-25]. Understanding factors associated with use of ART may inform efforts to increase appropriate ART among HIV-infected persons.

Nonadherence to ART was substantial. Reported nonadherence during the past 48 hours ranged from 13% to 30%, depending on which measure was examined; 38% were nonadherent to at least one measure. We found a direct

relationship between a detectable VL and each of the three measures of nonadherence. The association increased with the number of measures to which a patient was nonadherent, indicating the clinical importance of assessing multiple dimensions of nonadherence. Our findings are consistent with those reported previously [10, 11], but there have been few studies comparing dose, schedule, and instruction nonadherence, so further examination of the impact of different measures of nonadherence on clinical outcomes is warranted.

Although predictors of the three measures of nonadherence varied, younger age and binge drinking were consistently associated with poorer adherence. Like other researchers [26], we found associations between younger age and multiple measures of nonadherence. Lifestyle differences, decreased awareness of mortality and thus motivation to care for one's health, and a survivor effect have been proposed as reasons for poorer adherence among younger HIV-infected persons [27]. Measured in various ways, alcohol use has consistently been associated with nonadherence [28, 29]. We found that binge drinking was

strongly associated with all three measures of nonadherence. Others have found that the quantity of alcohol ingested was more important in predicting nonadherence than was the frequency of use [29, 30]. Taken together, these findings suggest that HIV care providers should ask patients about both the frequency and the quantity of alcohol consumed. When a patient acknowledges binge drinking, the provider should explain how binge drinking affects ART adherence and other health behaviors. Such conversations could help HIV care providers identify patients who need more intensive counseling about adherence and substance use. Few effective interventions have addressed problem drinking among HIV-infected persons [31], and the effects of the small number of trials on adherence among problem drinkers have not been sustained [32, 33]. The limited evidence suggests that adapting adherence interventions to persons with alcohol problems may be challenging [31]. Our results underscore the need to develop effective adherence interventions for problem drinkers, which potentially could have positive effects on all aspects of adherence.

Black and Hispanic race/ethnicity, female gender, receipt of public assistance, feeling depressed, and number of daily ARV doses were also independently associated with poorer adherence for at least two of the three measures of nonadherence. Several recent studies have found that race/ethnicity is independently associated with nonadherence [17, 34, 35]. Race/ethnicity may also be a proxy for factors associated with nonadherence, such as differences in trust of physicians [36] or HIV conspiracy beliefs (e.g., the belief that HIV was created by the U.S. government to perpetrate genocide against blacks) [37]. Recent studies indicate that disparities in health literacy and numeracy skills, which we were not able to measure, may also be important mediators of the relationship between race and medication management [38, 39].

Similar to findings regarding adherence to treatment for chronic diseases such as diabetes [40], published descriptions of the effect of gender on ART adherence in the scientific literature have been mixed; some studies find women more likely to be nonadherent [41, 42], and others find no difference by gender [43]. Our finding suggests gender may influence some, but not all, dimensions of medication-taking behavior (dose and schedule nonadherence, but not instruction nonadherence). Another possible explanation for the observed gender differences is that other factors affecting nonadherence, such as alcohol or drug use, may differ for men and women [44]. Additional factors we were not able to measure, such as numeracy skills [45], may also mediate the relationship between gender and nonadherence.

Our finding that the frequency of feelings of depression was associated with dose and instruction nonadherence to ART is consistent with other studies [46, 47]. This association reinforces the importance of active screening for depression among HIV-infected persons [48]. Studies have suggested that training in stress management [49] and prescription of antidepressant medications [50] may improve adherence in this population.

Our finding that nonadherence increases as the daily ARV dose increases agrees with published results [51, 52]. Airoldi and colleagues found that switching to a single-pill

regimen improved adherence [53]. Although some ART regimens are less susceptible to nonadherence than others [9], our findings suggest that simplifying ART regimens by decreasing dosing frequency would improve adherence.

LIMITATIONS

Although MMP uses population-based sampling methods, due to low patient response rates across data collection sites MMP data are not weighted and thus are not representative of HIV-infected patients in care in the United States. However, probability sampling is advantageous even with low response rates because of the value of unbiased sampling from well-defined populations [54]. States with the lowest patient response rates were not substantially different by region or HIV epidemiology from those with higher response rates. Examination of the patient sampling frame indicates that respondents and nonrespondents did not differ by gender. Participants were slightly older than nonparticipants, and African Americans were somewhat underrepresented. Because we found that younger age and black race are associated with higher nonadherence, as have other studies [17, 26, 34, 35], these relationships may in fact be stronger than those found for our sample. Despite low patient response, the response rates at the project area and facility stages of sampling were high, and the size and breadth of our facility and patient samples are notable.

Because we studied self-reported measures, our findings are subject to the limitations of self-reported information, such as recall and social desirability biases. Because self-reported measures of adherence have underestimated the extent of nonadherence [16, 18], our estimates of nonadherence may in fact be lower than actual levels of nonadherence. In addition, we were not able to verify through medical record review self-reported clinical information such as receipt of ART. However, Wood and colleagues found relatively high correspondence between self-reported and medical record documentation of current use of ART [55], leading us to have confidence in our results. Also, our analysis was restricted to self-reported VL, and the number of missing responses was high because of difficulties with recall. However, for undetectable VL results, the reported agreement between self-report and the medical record has been relatively high [56, 57]. Also, as our data showed a positive association between dose and schedule nonadherence and not knowing one's most recent VL, it is unlikely that missing data would account for the relationship found between higher VL and the number of nonadherence measures reported.

Our analysis of use of ART is limited due to lack of comprehensive clinical information that would allow us to determine need for therapy among those not on ART. Use of self-reported CD4 values to indicate need for ART is insufficient because other clinical factors are also relevant to treatment decisions (e.g. Hepatitis B coinfection, HIV-associated nephropathy). In addition, because recent treatment guidelines [8] suggest that ART should be an option for all patients regardless of CD4, we felt it was important to describe the difference between those on and not on ART for the entire sample.

Our logistic regression models regarding nonadherence to instruction included only the participants who had

received special instructions. However, limiting our analysis of the dose and schedule nonadherence models to those who received special instructions would have introduced bias by restricting the population to those whose regimens require special instructions. To ensure that our findings were not due to differences in the participants included in the models, we ran the dose and schedule models, restricting them to participants who have received special instructions: we did not find substantive differences compared with results that included all respondents.

CONCLUSION

Recent guidelines recommend initiation early in the course of infection (CD4 cell count ≤ 500 cells/ μ L), but caution that patients should be willing to commit to lifelong treatment and should understand the importance of adherence [8]. In this large sample of HIV-infected patients in the United States, the use of ART was high, but adherence to ART was suboptimal. The determinants of nonadherence to dose, schedule, and instruction varied, although younger age and binge drinking were associated with all three measures. Our results support the need to measure multiple dimensions of medication-taking behavior, because focusing on nonadherence to dose may overestimate adherence to ART. Comprehensive assessment of ART nonadherence should include measures of dose, schedule, and instruction, because accurate information is crucial for evaluating both the effectiveness of ART regimens and interventions designed to increase adherence.

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DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

AUTHOR DISCLOSURE

The authors have no institutional or commercial affiliations that might pose a conflict of interest regarding the publication of this manuscript.

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