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.
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 obtained 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 the 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

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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         |                                             |
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

| Characteristic                  | Currently Taking ART n = 3307 | Dose Nonadherence n = 444 | Schedule Nonadherence n = 893 | Instruction Nonadherence n = 638 | Chi-Square Test for Differences (p Value) |
|---------------------------------|-------------------------------|---------------------------|-------------------------------|----------------------------------|-------------------------------------------|
|                                 | No.  %                        | Nonadherence              | Nonadherence                  | Nonadherence                    |                                           |
| Gender                          |                               |                           |                               |                                 |                                           |
| Male                            | 2431  74                      | 293  66                   | 591  66                       | 462  72                      | 15.62                                     |
| Female                          | 830  25                       | 145  33                   | 289  32                       | 167  26                      | 34.68                                     |
| Transgender                     | 45  1                         | 6  1                      | 13  1                         | 9  1                         |                                           |
| Age (years)                     |                               |                           |                               |                                 |                                           |
| 18-24                           | 45  1                         | 18  4                     | 21  2                         | 17  3                         | 11.33                                     |
| 25-34                           | 280  8                        | 43  10                    | 83  9                         | 68  11                        | 0 (0.00)                                  |
| 35-44                           | 1039  31                      | 135  30                   | 300  34                       | 226  35                       | 0 (0.00)                                  |
| 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                   | 400  45                       | 243  38                       | 33.14                                     |
| Hispanic                        | 663  20                       | 102  23                   | 219  25                       | 146  23                       | 23.85                                     |
| White, non-Hispanic             | 1173  36                      | 105  24                   | 230  26                       | 207  32                       | 64.78                                     |
| Other                           | 212  6                        | 29  7                     | 44  5                         | 42  7                         | 0.86                                      |
| Education                       |                               |                           |                               |                                 |                                           |
| < High School                   | 729  22                       | 111  25                   | 250  28                       | 149  23                       | 2.68                                      |
| ≥ High School or equivalent     | 2576  78                      | 332  75                   | 643  72                       | 488  77                       | 25.41                                     |
| Public assistance, past 12 months |                               |                           |                               |                                 |                                           |
| No                              | 1639  50                      | 184  41                   | 380  43                       | 323  51                       | 13.58                                     |
| Yes                             | 1667  50                      | 260  59                   | 513  57                       | 315  49                       | 23.85                                     |
| Lapse in health coverage, past 12 months |                               |                           |                               |                                 |                                           |
| No                              | 2491  76                      | 327  74                   | 671  75                       | 453  71                       | 0.64                                      |
| Yes                             | 808  24                       | 115  26                   | 220  25                       | 185  29                       | 0.42                                      |
| Homeless, past 12 months        |                               |                           |                               |                                 |                                           |
| No                              | 3080  93                      | 398  90                   | 808  90                       | 581  91                       | 9.81                                      |
| Yes                             | 227  7                        | 46  10                    | 85  10                        | 57  9                         | 13.63                                     |
| Years since HIV diagnosis       |                               |                           |                               |                                 |                                           |
| ≤ 1                             | 18  1                         | <5  <1                    | <5  <1                        | <5  1                         | 6.29                                      |
| 2-5                             | 616  20                       | 69  17                    | 140  17                       | 131  22                       | 4.00                                      |
| 6-10                            | 764  25                       | 93  22                    | 219  26                       | 147  25                       | 0.01                                      |
| 11-25                           | 1711  55                      | 254  61                   | 467  56                       | 315  53                       | 0 (0.00)                                  |
| Knew most recent HIV viral load test result |                               |                           |                               |                                 |                                           |
| No                              | 639  20                       | 108  25                   | 238  27                       | 104  17                       | 8.14                                      |
| Yes                             | 2587  80                      | 326  75                   | 629  73                       | 513  83                       | 44.22                                     |
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

| Characteristic | Currently Taking ART n = 3307 | Dose Nonadherence n = 444 | Schedule Nonadherence n = 893 | Instruction Nonadherence n = 638 |
|---------------|--------------------------------|--------------------------|--------------------------------|---------------------------------|
|               | No. %                          | No. %                    | No. %                          | No. %                          |
| Most recent HIV viral load test result |                                |                          |                                |                                |
| Undetectable  | 2056 62                        | 218 49                   | 438 49                         | 384 60                          |
| Detectable but <5000 | 307 9 | 54 12 | 104 12 | 73 11 |
| ≥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 | 39 4 | 32 5 |
| Most of the time | 315 10 | 56 13 | 104 12 | 67 11 |
| 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 | 829 93 | 597 94 |
| Yes | 167 5 | 41 9 | 61 7 | 39 6 |
| Amphetamine use, past 12 months | | | | |
| No | 3142 95 | 418 94 | 842 95 | 601 95 |
| Yes | 152 5 | 26 6 | 46 5 | 34 5 |
| Binge drinking, past 30 days | | | | |
| No | 2864 87 | 359 81 | 745 84 | 519 82 |
| Yes | 426 13 | 84 19 | 144 16 | 115 18 |
| Discussed resistance with provider, past 12 months | | | | |
| No | 1174 36 | 128 29 | 310 35 | 197 31 |
| Yes | 2079 64 | 309 71 | 567 65 | 431 69 |

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

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

*Schedule nonadherence* refers to not following a specific schedule for ARV medication, such as “2 times a day” or “every 8 hours.”

*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.
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 Nonadherence (N = 3307) | Schedule Nonadherence (N = 3298) | Instruction Nonadherence (N = 2101) |
|---------------------------------------|-------------------------------|----------------------------------|-------------------------------------|
|                                       | OR (95% CI)                   | aOR (95% CI)                     | OR (95% CI)                         |
| Gender                                |                               |                                  |                                     |
| Male                                  | Ref                           | Ref                              | Ref                                 |
| Female                                | 1.55 (1.24-1.92)              | 1.36 (1.07-1.74)                 | 1.66 (1.40-1.97)                   |
| Transgender                           | 1.12 (0.47-2.68)              | 0.62 (0.21-1.80)                 | NS                                  |
| Age (years)                           | 0.98 (0.97-0.99)              | 0.98 (0.96-0.99)                 | 0.97 (0.96-0.98)                   |
| Race/ethnicity                        |                               |                                  |                                     |
| Black, non-Hispanic                   | 2.02 (1.58-2.60)              | 1.96 (1.48-2.59)                 | 1.93 (1.60-2.32)                   |
| Hispanic                              | 1.85 (1.38-2.47)              | 1.63 (1.18-2.24)                 | 2.03 (1.63-2.52)                   |
| White, non-Hispanic                   | Ref                           | Ref                              | 1.07 (0.75-1.54)                   |
| Other                                 | 1.61 (1.04-2.50)              | 1.55 (0.96-2.51)                 | 0.97 (0.66-1.41)                   |
| Education                             |                               |                                  |                                     |
| < high school                          | NS                            | 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                                 |
| Yes                                   | 1.71 (1.22-2.41)              | 1.69 (1.28-2.24)                 | 1.43 (1.05-1.95)                   |
| Public assistance, past 12 months     |                               |                                  |                                     |
| No                                    | Ref                           | Ref                              | Ref                                 |
| Yes                                   | 1.46 (1.19-1.79)              | 1.31 (1.05-1.65)                 | 1.35 (1.26-1.72)                   |
| Feeling downhearted and depressed, past 4 weeks | 2.97 (1.94-4.56)              | 2.63 (1.64-4.22)                 | 2.27 (0.86-1.89)                   |
| All of the time                        |                               |                                  |                                     |
| Most of the time                      | 1.86 (1.31-2.63)              | 1.81 (1.23-2.66)                 | 1.63 (1.24-2.14)                   |
| Some of the time                      | 1.45 (1.11-1.89)              | 1.37 (1.02-1.83)                 | 1.35 (1.11-1.65)                   |
| A little of the time                  | 1.19 (0.89-1.59)              | 1.20 (0.88-1.64)                 | 1.22 (0.99-1.51)                   |
| None of the time                      | Ref                           | Ref                              | -                                   |
| Crack use, past 12 months             |                               |                                  |                                     |
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

| 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)                | 1.59 (1.15-2.20)                | 1.58 (1.04-2.40)                |
| No               | 1.66 (1.09-2.52)                | -                               | -                               |
| Amphetamine use, past 12 months | NS                             | NS                             | Ref                             |
| Yes              | 1.50 (0.97-2.33)                | -                               | -                               |
| Binge drinking, past 30 days | Ref                             | Ref                             | Ref                             |
| No               | 1.71 (1.32-2.23)                | 1.45 (1.17-1.81)                | 2.08 (1.60-2.72)                |
| Yes              | 1.63 (1.21-2.20)                | 1.55 (1.23-1.96)                | 1.88 (1.41-2.49)                |
| Years since HIV diagnosis | 1.02 (1.00-1.03)                | NS                             | 0.98 (0.97-1.00)                |
| No               | 1.02 (1.00-1.04)                | -                               | -                               |
| Yes              | 1.16 (1.10-1.23)                | 1.13 (1.08-1.19)                | 1.16 (1.11-1.22)                |
| Number of ARV doses per day | 1.18 (1.10-1.25)                | 1.16 (1.11-1.22)                | NS                             |
| Knew most recent HIV viral load test result | 1.16 (1.10-1.23)                | 1.13 (1.08-1.19)                | NS                             |
| Yes              | 1.41 (1.11-1.79)                | 1.86 (1.55-2.23)                | 1.48 (1.21-1.82)                |
| Discussed resistance with provider, past 12 months | Ref                             | Ref                             | Ref                             |
| No               | 1.30 (1.15-1.78)                | -                               | -                               |
| Yes              | 1.43 (1.16-1.79)                | -                               | -                               |

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.
Airoldi and colleagues found that switching to a single-pill prescription of antidepressant medications [50] may improve adherence in this population. 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 had 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/µL), 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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