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Barriers to Antiretroviral Therapy Adherence and Plasma HIV RNA Suppression Among AIDS Clinical Trials Group Study Participants

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Abstract

We conducted a secondary data analysis of 11 AIDS Clinical Trials Group (ACTG) studies to examine longitudinal associations between 14 self-reported antiretroviral therapy (ART) adherence barriers (at 12 weeks) and plasma HIV RNA (at 24 weeks) and to discern the relative importance of these barriers in explaining virologic detectability. Studies enrolled from 1997 to 2003 and concluded between 2002 and 2012. We included 1496 (54.2% of the original sample) with complete data. The most commonly selected barriers were ''away from home'' (21.9%), ''simply forgot'' (19.6%), ''change in daily routine'' (19.5%), and ''fell asleep/slept through dosing time'' (18.9%). In bivariate analyses, ''too many pills to take'' (OR = 0.43, $p < 0.001$), ''wanted to avoid side effects'' (OR = 0.54, $p = 0.001$), ''felt drug was toxic/harmful'' (OR = 0.44, $p < 0.001$), ''felt sick or ill'' (OR = 0.49, $p < 0.001$), ''felt depressed/overwhelmed'' (OR = 0.58, $p = 0.004$), and ''problem taking pills at specified time'' (OR = 0.71, $p = 0.04$) were associated with a lower odds of an undetectable HIV RNA. ''Too many pills to take,'' ''wanted to avoid side effects,'' ''felt drug was toxic/harmful,'' ''felt sick/ill,'', and ''felt depressed/overwhelmed'' had the highest relative importance in explaining virologic detectability. ''Simply forgot'' was not associated with HIV RNA (OR = 0.99, $p = 0.95$) and was ninth in its relative importance. Adherence interventions should prioritize barriers with highest importance in explaining virologic outcomes rather than focusing on more commonly reported barriers.

Introduction

Optimal adherence to antiretroviral therapy (ART) is a consistent predictor of HIV virologic suppression, improved quality of life, reduced health care costs, slower disease progression, and overall survival.[1–7] Despite the ability to attain virologic suppression with adherence rates as low as 70–80%, depending on the ART regimen,[8–10] ART adherence in North America has been estimated to be as low as 55%[11] and lower mean ART adherence levels of 33–50% have been reported in the US.[12,13] Therefore, it is imperative to understand barriers to adherence and to examine the association between these barriers and HIV treatment goals in order to develop effective ART adherence interventions.

Prior research has heavily focused on commonly reported adherence barriers to determine intervention targets. For example, given that forgetting to take ART has been reported to be one of the most commonly stated adherence barriers,[12–16] many studies have examined the use of reminder devices in improving adherence.[17–20] However, most have not revealed clinically significant changes in adherence. Studies have reported other adherence barriers, including feeling depressed or overwhelmed, fear of disclosure, sleeping through a dose, substance use, regimen complexity, not having medication, change in daily routine, and not wanting to be reminded of HIV infection.[12–16] However, the association between commonly reported adherence barriers and lack of virologic suppression, as well as the relative importance of barriers in predicting plasma HIV RNA, has not been examined. This information is critical in designing future interventions that are more likely to have a positive impact on HIV treatment goals. Therefore, the objectives of our study were: (1) to examine the association between self-reported

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adherence barriers and virologic detectability, and (2) to establish the relative importance of each adherence barrier in explaining virologic detectability.

Methods

Study design

We conducted a secondary analysis of longitudinal data collected as part of AIDS Clinical Trials Group (ACTG) ART studies that were available for analysis at the time of our request (April 2013). We received approval from the University of California, San Francisco Committee on Human Research and the ACTG's Scientific Agenda Steering Committee of the ACTG Executive Committee.

Setting and study population

We included all ACTG ART studies that were conducted in the US, had used the ACTG adherence barriers questionnaire[21] at least at 12 weeks (±4 weeks), and had collected participant demographics (i.e., age, sex, race/ethnicity, and HIV risk behaviors) at baseline and plasma HIV RNA at 24 weeks (±4 weeks). These time points were selected to account for the temporal ordering of adherence barriers and HIV RNA and because these were the time points when all studies had conducted measurements for adherence barriers prior to subsequent HIV RNA levels. If studies were conducted at both US and non-US sites, we only included participants from US sites. Studies were excluded if they examined non-oral ART, assessed the impact of treatment interruption before 24 weeks (±4 weeks), or recruited fewer than 10 participants.

We identified 11 ACTG studies, four of which included ART-naïve participants (ACTG 371[22], ACTG 384[23,24], ACTG 746[25], and A5073[26,27]) and seven that included ART-experienced participants (ACTG 372[28,29], ACTG 398[30], ACTG 400, A5025[31], A5116[32], A5126[33], A5143[34,35]). The range of enrollment was 1997–2003 and studies were concluded between 2002 and 2012 (median = 2009). Each study enrolled an average of 280 participants (range = 25–987) and had a mean duration of 93 weeks (range = 24–220). We included all participants who had completed the ACTG adherence barriers questionnaire.

Variables

HIV RNA at 24 weeks (±4 weeks) constituted our primary outcome and was dichotomized (detectable/undetectable) based on each study's assay cut-off for the lower limit of quantification to designate viral suppression. Adherence barriers were assessed at 12 weeks (±4 weeks) using the ACTG adherence barriers questionnaire[21] in which participants are asked: ''In the past month, how often have you missed taking your medications because you: (1) were away from home; (2) were busy with other things; (3) simply forgot; (4) had too many pills to take; (5) wanted to avoid side effects; (6) did not want others to notice you taking medication; (7) had a change in daily routine; (8) felt like the drug was toxic/harmful; (9) fell asleep/slept through dose time; (10) felt sick or ill; (11) felt depressed/overwhelmed; (12) had problem taking pills at specified times (with meals, on empty stomach, etc.); (13) ran out of pills; and (14) felt good?'' Adherence barriers were dichotomized (yes/no), and summed and categorized based on their distribution (0 = no adherence barriers; 1 = 1–4 barriers; 2 = 5–14 barriers). These categories were determined post hoc and based on the distribution of the data. Potential confounders included: age, sex, race/ethnicity (white, black, latino, other), HIV risk behaviors [men who have sex with men (MSM), heterosexual, needle sharing, transfusion, other/unknown], and study protocol number. Study protocol number represented the data collection context, reflecting timeframe, geography, population, type of study, and study intervention. By controlling for study protocol number, we thus controlled for a summary measure of the data collection context as it relates to antiretroviral regimens, time and geography.

All ACTG trials used a self-administered questionnaire that was completed by the participant in a quiet secluded place. The questionnaire was written at the sixth-grade level, but subjects may have had the questionnaire read to them, if requested. By not having the study nurses read the questions in a one-on-one interview, social desirability concerns were lessened.[36,37] In addition, these self-report adherence questionnaires have been shown in previous studies to predict both viral suppression and overall HIV progression and death.[37,38]

Analysis

After limiting our dataset to participants who had responded to all 14 barriers and had documented plasma HIV RNA results, we described sample characteristics at 12 weeks. Next, we used bivariate logistic regression to examine the association between individual adherence barriers at 12 weeks and virologic detectability at 24 weeks. We also examined the association between total number of reported barriers at 12 weeks (categorized as 0 = no adherence barriers; 1 = 1–4 barriers; 2 = 5–14 barriers) and virologic detectability at 24 weeks to examine the cumulative effect of barriers on adherence. Inference was performed using robust Huber-White standard errors.[39] We used multivariate logistic regression to examine the association between each adherence barrier at 12 weeks and virologic detectability at 24 weeks while adjusting for potential confounders.

Because studies were conducted at different times, geographical locations across the US, and included different ART regimens and study populations, we assessed interaction terms between study protocol number and 14 adherence barriers to ensure that effects of adherence barriers on virologic detectability did not vary by protocol number. These interactions were added to a model containing main effects for study protocol number and the 14 barriers and tested one by one to examine whether the relationships between barriers and virologic detectability varied as a function of study protocol number.

Finally, we used dominance analysis, a technique which rank-ordered the relative importance or contribution of the 14 adherence barriers at 12 weeks in explaining virologic detectability at 24 weeks. This technique is based on the average pseudo R^2 explained by each adherence barrier across all possible subsets regression models.[40,41] To ensure replication of our results and to help interpret the dominance analysis, we calculated the population attributable risk (PAR) of having detectable plasma HIV RNA for each barrier.[42] In a post-hoc analysis, we examined the relative importance of the 14

barriers at 12 weeks using dominance analysis for those who had been ART-naïve at baseline. We used Stata version 13.1 (StatCorp LP, College Station, TX) for our analyses. p Values less than 0.05 were deemed statistically significant.

Results

Of 2759 participants enrolled in the 11 included ACTG trials, 1263 (45.8%) had missing adherence barrier and/or HIV RNA data and were excluded from the analysis. Among those excluded, 806 (63.8%) had no responses to any of the ACTG adherence barriers questions, 353 (27.9%) did not have an HIV RNA reported, and 104 (8.2%) had some missing adherence barrier data. Participants' sex, race/ethnicity, and HIV risk behavior did not differ between those who had a report HIV RNA and those who had missing data. Having a missing HIV RNA was more likely among younger individuals (mean age = 36.8 years among those missing HIV RNA data and mean age = 39.3 years among those who had a reported HIV RNA, $p < 0.001$), as well as in studies with ART-experienced participants (HIV RNA missing in 9% of studies with ART-naïve participants versus 14% of studies with ART-experienced participants, $p < 0.001$). Participants' age, sex, race/ethnicity, and HIV risk behavior did not differ between those missing or not missing all ACTG adherence barrier responses. However, adherence barrier data was missing in 34.3% of studies with ART-naïve participants versus 24.7% of studies with treatment-experienced participant ($p < 0.001$).

Table 1 summarizes characteristics of 1496 (54.2%) individuals at 12 weeks who met all inclusion/exclusion criteria. On average, participants were 39 years old, 85% male, 51% white, 29% black, 18% Latino, and 61% identifying MSM as their HIV risk behavior. Most participants (53%) were treatment naïve, 46.5% had an undetectable HIV RNA at 12 weeks, and 66% had an undetectable HIV RNA at 24 weeks.

Over 56% reported no adherence barriers. The most commonly selected barriers were ''away from home'' (21.9%), ''simply forgot'' (19.6%), ''change in daily routine'' (19.5%), and ''fell asleep/slept through dosing time'' (18.9%). ''Ran out of pills'' (3.2%), ''too many pills to take'' (5.3%), and ''felt drug was toxic/harmful'' (5.5%) were the least common barriers.

In bivariate analyses, ''too many pills to take,'' ''wanted to avoid side effects,'' ''felt drug was toxic/harmful,'' ''felt sick or ill,'' ''felt depressed/overwhelmed,'' and ''problem taking pills at specified time'' were the only barriers that were associated with a lower odds of having an undetectable HIV RNA (Table 2). In multivariate analyses, ''felt sick or ill'' (OR = 0.53, 95% CI = 0.37–0.76, $p < 0.001$) was significantly associated with lower odds of undetectable HIV RNA while adjusting for all confounders. ''Too many pills to take'' (OR = 0.61, 95% CI = 0.37–1.01, $p = 0.06$) and ''felt like the drug was toxic/harmful'' (OR = 0.62, 95% CI = 0.37–1.04, $p = 0.07$) were marginally associated with a lower odds of an undetectable HIV RNA when controlling for all confounders. In comparison to not reporting any adherence barriers, those reporting 1–4 barriers had a 0.85 odds of an undetectable HIV RNA (95% CI = 0.67–1.09, $p = 0.2$) and those reporting ≥ 5 barriers had a 0.64 odds of an undetectable HIV RNA (95% CI = 0.46–0.87, $p = 0.005$). Study protocols ACTG 398, ACTG 746, A5116, and A5126 were also significantly associated with lower odds of undetectable HIV RNA. Among these studies, ACTG 746 was the only study conducted in treatment-naïve individuals. Interactions between study site and adherence barriers were not statistically significant and therefore dropped from analyses.

Table 1. Characteristics of Study Population at Week 12 ($N = 1496$)

Mean age, years (SD)	39.3 (9.2)
Male, N (%)	1275 (85.2)
Race/ethnicity, N (%)	
White	756 (50.5)
Black	426 (28.5)
Latino	264 (17.7)
Other	50 (3.3)
HIV risk behavior, N (%)[b]	
MSM	798 (61.0)
Heterosexual	316 (24.1)
Needle sharing	69 (5.3)
Transfusion	28 (2.1)
Other/do not know	98 (7.5)
Treatment naïve, N (%)	792 (52.9)
Study protocol number, N (%)	
ACTG 371[a]	102 (6.8)
ACTG 372	42 (2.8)
ACTG 384[a]	358 (23.9)
ACTG 398	278 (18.6)
ACTG 400	21 (1.4)
ACTG 746[a]	101 (6.8)
A5025	168 (11.2)
A5073[a]	231 (15.4)
A5116	132 (8.8)
A5126	21 (1.4)
A5143	42 (2.8)
Mean CD4+ cell count, cells/mL (SD)[c]	402.2 (265.2)
Plasma HIV RNA below limit of quantification, N (%)	694 (46.5)
Barriers to adherence, N (%)	
Away from home	328 (21.9)
Simply forgot	293 (19.6)
Change in daily routine	292 (19.5)
Fell asleep/slept through dose time	282 (18.9)
Busy with other things	255 (17.1)
Felt sick or ill	186 (12.4)
Problem taking pills at specified time	181 (12.1)
Wanted to avoid side effects	133 (8.9)
Felt depressed/overwhelmed	127 (8.5)
Felt good	111 (7.4)
Not want others to notice you taking medications	105 (7.0)
Felt like the drug was toxic/harmful	82 (5.5)
Too many pills to take	79 (5.3)
Ran out of pills	48 (3.2)
Summed adherence barriers, N (%)	
0 (no ACTG barriers reported)	845 (56.5)
1 (1–4 ACTG barriers reported)	446 (29.8)
2 (≥ 5 ACTG barriers reported)	205 (13.7)

ACTG, AIDS Clinical Trials Group; ART, antiretroviral therapy; MSM, men who have sex with men; SD, standard deviation.
[a]ACTG ART naïve studies; [b]N = 1309; [c]$N = 1483$.

In dominance analysis, we examined the relative importance of each barrier in its association with virologic detectability. The top five barriers with the most impact on virologic detectability were: 1. ''felt sick or ill,'' 2. ''had too many pills to take,'' 3. ''felt like the drug was toxic/harmful,'' 4. ''wanted to avoid side effects,'' and 5. ''felt depressed/overwhelmed.'' The

Table 2. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the Bivariate Association Between Adherence Barriers at 12 Weeks and Undetectable Plasma HIV RNA at 24 Weeks ($N = 1496$)

	OR (95% CI)	p *Value*
Adherence barriers		
Away from home	0.88 (0.68–1.13)	0.32
Busy with other things	0.95 (0.72–1.26)	0.73
Simply forgot	0.99 (0.76–1.30)	0.95
Too many pills to take	0.43 (0.27–0.68)	<0.001
Wanted to avoid side effects	0.54 (0.38–0.77)	0.001
Not want others to notice you taking medications	0.94 (0.62–1.43)	0.77
Change in daily routine	0.82 (0.63–1.07)	0.14
Felt like the drug was toxic/harmful	0.44 (0.28–0.70)	<0.001
Fell asleep/slept through dose time	0.84 (0.64–1.10)	0.20
Felt sick or ill	0.49 (0.36–0.66)	<0.001
Felt depressed/overwhelmed	0.58 (0.40–0.84)	0.004
Problem taking pills at specified time	0.71 (0.52–0.98)	0.04
Ran out of pills	1.26 (0.67–2.37)	0.48
Felt good	0.80 (0.54–1.19)	0.27
Summed adherence barriers[a]	-	*0.02*[b]
1 (1–4 ACTG barriers reported)	0.85 (0.67–1.09)	0.20
2 (≥5 ACTG barriers reported)	0.64 (0.46–0.87)	0.005

[a]''No adherence barriers'' as reference category; [b]Omnibus Wald test.

PAR resulted in the same top five barriers but ranked them slightly differently from the dominance analysis. The PAR associated with ''felt sick or ill,'' ''wanted to avoid side effects,'' ''felt depressed/overwhelmed,'' ''felt like the drug was toxic/harmful,'' and ''had too many pills to take'' were 6.2%, 3.8%, 3.2%, 3.2%, and 3.2%, respectively. The dominance analysis ranking of the remaining barriers was as follows with the PAR reported in parentheses: 6. ''ran out of pills'' (−0.5), 7. ''were busy with other things'' (0.6), 8. ''had problem taking pills at specified times'' (2.8), 9. ''simply forgot'' (0.1), 10. ''did not want others to notice you taking medication'' (0.3), 11. ''felt good'' (1.1), 12. ''had a change in daily routine'' (2.6), 13. ''fell asleep/slept through dose time'' (2.2), and 14. ''were away from home'' (1.9). In a post-hoc analysis, the relative importance of adherence barriers at 12 weeks in their association with virologic detectability for individuals who were ART-naïve at study entry was generally similar to the overall population with ''felt sick or ill'' as the most important barrier.

Discussion

In our analysis of 11 ACTG studies, individuals reporting a higher number of adherence barriers had lower odds of attaining virologic suppression, but the majority of participants did not endorse any of the listed adherence barriers. Individual barriers were reported at a low frequency, with the highest prevalence at approximately 21.9% (''away from home''). Given the association between adherence barriers and virologic detectability and that 53% of participants were not virologically suppressed at 12 weeks (time point when adherence barriers were assessed), the identification and understanding of adherence barriers are critical.

Specific adherence barriers related to ART regimens, such as pill burden or perceived/actual medication adverse effects, and feeling depressed or overwhelmed were significantly associated with viral detectability. Despite being some of the least frequently reported barriers, dominance analysis ranked these barriers as the highest in their relative importance in predicting virologic detectability. The PARs associated with these barriers were generally small but were higher than other barriers. Unexpectedly, other frequently reported barriers, such as forgetfulness, were not associated with viral suppression and were ranked relatively low in explaining virologic outcome in both dominance analysis and PAR. It may be that forgetfulness is multi-faceted and may include other barriers such as stigma, depression, drug and alcohol use, and lack of social support. We believe these findings challenge the notion that the justification for an intervention to overcome an adherence barrier be based solely on the frequency of reporting that barrier. This type of reasoning may potentially lead investigators in the wrong direction and may result in ineffective interventions and inefficient allocation of time and resources.

The association between depression and non-adherence has been well-documented.[43] Across 95 independent samples, depression was strongly associated with non-adherence, and this relationship was not limited to individuals with clinical depression. Many studies have suggested a 20–50% prevalence of depression and depressive symptoms in HIV-infected patients.[44–46] Our results add to this body of evidence that feeling depressed is highly correlated with viral detectability and ranks high in its relative importance in explaining this outcome. These findings underscore the need for behavioral interventions aimed at reducing clinical and subclinical depression.

Our findings should be viewed in the context of the following limitations. We conducted a secondary analysis of data collected for other purposes and which contained a substantial number of research participants with missing data. We relied on self-reported adherence barriers, which may be prone to recall and social desirability bias and may not have fully captured all adherence barriers (e.g., substance use,[47] trust in HIV care provider, pregnancy,[36,48] etc.). We examined adherence barriers at only one time point early in the ART course. However, these barriers will likely vary during an individual's life; therefore, their assessment over time is critical to address in order to overcome non-adherence. Due to a great deal of heterogeneity within and across studies

with regard to ART regimen type and time on ART, we were unable to fully control for these variables and were unable to estimate their unique effects accurately. Because the effects of these variables are reflected in the different protocols, inclusion of the protocol number in the multivariate analysis partly accounted for their influence. Lastly, our results capture information from a time period preceding newer and better tolerated ART regimens; therefore, our results may be less generalizable to the present ART era.

Based on our findings, we believe that the assessment of adherence barriers in clinical encounters is critical. ART-related barriers such as high pill burden and adverse effects, as well as feeling depressed or overwhelmed are particularly important barriers to inquire about and address. Interventions should focus on barriers that have been associated with poor virologic outcomes rather than focusing on the most commonly reported barriers.

Currently, ART regimens are more potent, require fewer daily pills, and have improved tolerability profiles. However, lifelong adherence to ART is still a prevailing predicament and many studies continue to examine clinical tools, programs, and interventions to achieve and maintain a high level of adherence.[49–51] Therefore, assessing adherence barriers and examining the association between barriers and HIV RNA detectability for newer regimens can be used to design and develop effective interventions to improve HIV treatment outcomes.

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Author Disclosure Statement

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