Published in final edited form as:
AIDS. 2008 January 2; 22(1): 75–82.

Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance

Edward M. Gardner[a], **Shweta Sharma**[b], **Grace Peng**[b], **Katherine Huppler Hullsiek**[b], **William J. Burman**[a], **Rodger D. MacArthur**[c], **Margaret Chesney**[d], **Edward E. Telzak**[e], **Gerald Friedland**[f], and **Sharon B. Mannheimer**[g]

a *Denver Public Health, Denver, Colorado, USA*

b *University of Minnesota, Minneapolis, Minnesota, USA*

c *Wayne State University, Detroit, Michigan, USA*

d *National Center for Complementary and Alternative Medicine, Bethesda, Maryland, USA*

e *Bronx Lebanon Hospital Center, Bronx, New York, New York, USA*

f *Yale University School of Medicine, New Haven, Connecticut, USA*

g *Harlem Hospital, Columbia University College of Physicians and Surgeons, New York, New York, USA*

Abstract

Objectives—To investigate the occurrence of differential adherence to components of combination antiretroviral therapy and assess its predictors and association with virological failure and antiretroviral medication resistance.

Design—A secondary analysis of prospective clinical trial data.

Methods—The Flexible Initial Retrovirus Suppressive Therapies study (Community Programs for Clinical Research on AIDS 058) was a randomized trial comparing non-nucleoside reverse transcriptase inhibitor (NNRTI) versus protease inhibitor (PI) versus NNRTI plus PI-based (three-class) antiretroviral therapy in treatment-naive HIV-1-infected individuals. Adherence was assessed at months 1 and 4, and then every 4 months. Differential adherence, defined as any difference in self-reported level of adherence to individual antiretroviral medications at the same timepoint, was evaluated as a binary time-updated variable in multivariate Cox regression analyses of time to initial virological failure (HIV-RNA >1000 copies/ml) and initial virological failure with genotypic antiretroviral resistance.

Results—Differential adherence was reported at least once by 403 of 1379 participants (29%), over 60 months median follow-up. Differential adherence was more commonly reported by participants randomly assigned to the three-class strategy (35%) than the NNRTI (28%) or PI (25%) strategies ($P = 0.005$), but was not associated with demographic or baseline disease-specific factors. Of those reporting differential adherence, 146 (36%) reported it before initial virological failure. These participants had an increased risk of initial virological failure and initial virological failure with antiretroviral resistance compared with participants without differential adherence before initial virological failure.

Conclusion—Differential adherence was commonly reported and was associated with an increased risk of initial virological failure and initial virological failure with antiretroviral resistance.

Correspondence to Edward M. Gardner, MD, Denver Public Health, 605 Bannock Street, Denver, CO 80204, USA. Tel: +1 303 436 7269; fax:+ 1 303 436 7194; e-mail: edward.gardner@dhha.org.

Conflicts of interest: None.

Keywords

adherence; antiretroviral resistance; differential adherence; HIV; virological failure

Introduction

Antiretroviral medication adherence is an important predictor of virological, immunological, and clinical outcomes in the treatment of HIV-infected individuals [1–4]. Adherence to antiretroviral therapy (ART) has generally been reported as either the level of adherence to a single component of a multidrug regimen or as the average level of adherence to the multiple components [2,3,5]. When prescribed as individual dosage forms, however, adherence to individual components of combination ART may differ. This can lead to periods of single or dual agent exposure. Mono and dual-therapy are known to be associated with earlier regimen failure and the more rapid emergence of antiretroviral resistance [6–8].

Differential antiretroviral medication adherence has not been well studied. One study found that 15% of patients in a public HIV clinic had differential adherence, as assessed using pharmacy refill data [9]. In that study, differential adherence (selective drug taking) was independently associated with a more rapid progression to AIDS and death. The association of differential adherence with virological failure and the development of antiretroviral medication resistance has not been investigated. This study was conducted to assess the frequency of differential adherence, its predictors, and its impact on treatment outcomes including virological failure and the development of antiretroviral medication resistance in previously antiretroviral-naive participants enrolled in the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) Flexible Initial Retrovirus Suppressive Therapies (FIRST, CPCRA 058) trial [10].

Methods

Participants

The CPCRA is a National Institutes of Health-sponsored clinical trials group that conducts community-based HIV/AIDS research targeting underserved populations. The CPCRA FIRST study was a randomized clinical trial assessing different initial treatment strategies for antiretroviral-naive HIV-infected adults [10]. From 1999 to 2002 participants were randomly allocated (1:1:1) to one of three initial strategies: the protease inhibitor (PI) strategy [PI(s) + nucleoside analogues]; the non-nucleoside reverse transcriptase inhibitor strategy (a NNRTI + nucleoside analogues); or the three-class strategy [PI(s) + a NNRTI + nucleoside analogue (s)]. The majority of participants receiving PI received non-boosted regimens [10].

Whereas the antiretroviral strategy was randomized, clinicians could choose individual drugs within the assigned strategy or those drugs may have been randomly assigned for participants who agreed to enroll in class-specific substudies [11]. FIRST was a trial comparing strategies of ART, not three specific regimens, and therefore medications were not generally supplied by the study. For a small subset of participants (13.5%) co-enrolled in a nucleoside reverse transcriptase inhibitor (NRTI) substudy, some NRTI were provided for some time during the study, but in general participants used their usual pharmacy for all prescription medications. All participants in FIRST who had at least one follow-up self-reported adherence assessment at any timepoint during the study were included in this report. Written informed consent was obtained from all participants in order to participate in the FIRST trial.

Data collection and definitions

Participant demographics were obtained at study entry. At baseline, months 1 and 4, and then every 4 months thereafter; data obtained included the following: ART regimen, CD4 lymphocyte count, HIV-1-RNA level, and self-reported ART adherence (except at baseline). Genotypic antiretroviral resistance testing was performed at the time of initial virological failure, defined as an HIV-1-RNA level greater than 1000 copies/ml at or after 4 months of follow-up. Resistance was defined as definite drug resistance by genotype (Trugene HIV-1 Genotyping Kit; Bayer HealthCare Ag, Leverkusen, Germany, and CPCRA interpretive algorithm v4.0). Disease progression events were defined as the occurrence of a confirmed or probable AIDS-defining event (excluding CD4 lymphocyte count criteria) according to modified US Centers for Disease Control criteria [12]. Each participating site reported deaths and AIDS-defining illnesses as soon as this information was available.

In FIRST, adherence was assessed using the 7-day CPCRA adherence self-report form, a global recall asking participants to estimate their level of adherence during the previous week to each individual antiretroviral medication [13]. Participants were asked to complete the statement 'During the last 7 days I took' with one of the following choices:'all my pills every day, most of my pills, about one-half of my pills, very few of my pills or none of my pills'. The five levels of this Likert scale were assigned adherence scores of 100, 80, 50, 20 and 0%, respectively, based on earlier research [4]. Overall adherence was calculated at each visit as the average adherence score for all components of the regimen. Fixed-dose combination formulations were included in adherence calculations once. An individual not on ART was assigned an adherence score of zero for that visit. An adherence report form was considered missing if a protocol-required visit was missed or if a visit was attended but the adherence form was not submitted. Missing forms were not assigned an adherence value. For each participant, we calculated cumulative adherence at each visit as the average of all overall adherence scores up to that time.

At each study visit, differential adherence was defined as any difference in self-reported adherence to individual antiretroviral regimen components. For example, if an individual on an antiretroviral regimen of three separate medications reported taking 'all my pills every day' for two medications and 'most of my pills' for the third, that participant was defined as having differential adherence at that visit. On the other hand, a participant taking three separate antiretroviral medications who reported taking 'most of my pills' for all three medications would not be classified as having differential adherence at that visit.

Statistical analysis

Characteristics at baseline for participants with or without differential adherence at least once during follow-up were evaluated using basic descriptive statistics. Continuous variables are presented as medians with the interquartile range, and categorical variables are presented as proportions. A multivariate logistic regression model with baseline covariates was used to determine predictors of differential adherence.

Cox proportional hazards regression models were used to assess the effect of differential adherence, as a time-updated covariate, on the event of interest. Differential adherence was a dichotomous variable that switched 'on' at the first report of differential adherence and stayed 'on' for the rest of follow-up. Events considered in this report were time to initial virological failure, time to initial virological failure with antiretroviral resistance, time to progression of HIV disease to AIDS or death, and time to a drop in the CD4 lymphocyte count to less than 200 cells/μl (in participants starting with ≥200 CD4 lymphocytes/μl). Results are reported for the overall cohort and by randomized treatment strategy (intent-to-treat). All Cox models were adjusted for baseline variables (age, ethnicity, CD4 lymphocyte count, HIV-RNA level) and

time-updated covariates (cumulative adherence score and binary variables for ART status and the presence of differential adherence).

The effect of repeated reporting of differential adherence over time (referred to as a 'dose effect') was studied by repeating the analyses of time to initial virological failure and time to initial virological failure with antiretroviral resistance using indicators for three time-updated categories of differential adherence: differential adherence only once, differential adherence more than once, and no differential adherence (the reference group). Forty-two participants (3%) had only one adherence assessment and were thus not eligible for the 'differential adherence more than once' category but were included in this analysis.

Statistical analyses were performed using SAS (version 8.2; SAS Institute Inc., Cary, North Carolina, USA). Hazard ratios (HR) are presented with 95% confidence intervals (CI). All *P* values cited are two sided.

Results

The results of the FIRST study have already been reported; the three strategy arms were well balanced in terms of demographic and other baseline characteristics [10]. Of the 1397 participants randomlyassigned in FIRST, 1379 (99%) with at least one adherence assessment during follow-up were included in this analysis. Overall, 85% of the expected adherence self-report forms were completed; there were no differences in completion rates among the three strategies.

During a median follow-up period of 60 months, differential adherence was reported at least once by 403 participants (29%; Fig. 1). It was more commonly reported by participants randomly assigned to the three-class strategy (35%) than the NNRTI (28%) or PI (25%) strategies ($P = 0.005$; Table 1). Not all participants were on their originally randomly assigned treatment strategy at the time that differential adherence was first reported. In the three-class, NNRTI and PI strategies, 61, 78 and 76% of participants were on their initial strategy at the time differential adherence was first reported.

Overall, 134 individuals reported differential adherence on more than one occasion (Table 1 and Fig. 1). This represented 10% of the overall population, and 33% of those individuals reporting differential adherence at any point during the study. By randomized strategy, reporting differential adherence on more than one occasion was more common in participants randomly assigned to the NNRTI (12%) and three-class (11%) strategies than the PI strategy (6%; $P = 0.007$). The maximum number of times that differential adherence was reported was 13 times (72% of follow-up visits for that individual) by a participant randomly assigned to the NNRTI strategy.

Characteristics at baseline for participants who reported differential adherence at least once during follow-up and for those who never reported differential adherence are presented in Table 2. The median age of the overall population was 38 years; 17% were Latino; 54% were black; 21% were women; 61% were men reporting a history of sex with other men; 15% reported a history of injection drug use; and 38% reported an AIDS diagnosis before study enrollment. The median baseline CD4 lymphocyte count was 163 cells/μl and the median baseline HIV-RNA level was 5.1 $\log_{10}$ copies/ml. In multivariate logistic regression models, no baseline demographic or disease-specific factors were significant predictors of differential adherence during follow-up (data not shown).

Of the 403 individuals with differential adherence, 146 (36%) reported it before initial virological failure and 71 (18%) had antiretroviral resistance detected at the time of initial virological failure. A summary of the multivariate Cox proportional hazards regression

analyses is presented in Table 3. For the overall cohort, differential adherence before initial virological failure was associated with an increased risk of initial virological failure compared with those with no differential adherence (HR 1.33, 95% CI 1.10–1.60). Similarly, participants reporting differential adherence before initial virological failure had an increased risk of initial virological failure with antiretroviral resistance (HR 1.34, 95% CI 1.03–1.75) compared with those without differential adherence. By randomized strategy, differential adherence significantly increased the risk of initial virological failure (HR 1.63, 95% CI 1.22–2.19) and initial virological failure with antiretroviral resistance (HR 1.75, 95% CI 1.16–2.64) in the three-class strategy but not in the PI or NNRTI strategies.

Other factors significantly associated with time to initial virological failure in the multivariate model for the overall cohort included mean cumulative adherence (HR 1.24 per 10% decrease), age (HR 0.82, per 10-year increase), black race (HR 1.79 compared with white or other individuals), baseline CD4 lymphocyte count (HR 0.95 per 100 cell increase), baseline $\log_{10}$ HIV-RNA (HR 1.37 per $\log_{10}$ increase), and not being on antiretroviral medications (HR 3.56 compared with those on antiretroviral medications; Table 3). These same factors, except for not being on antiretroviral medications, were significantly associated with time to initial virological failure with antiretroviral resistance (Table 3).

The overall cohort was used to explore a potential ‘dose effect’ for differential adherence using Cox regression models adjusted for the same baseline and time-updated covariates as in Table 3. Compared with participants not reporting any differential adherence, those reporting differential adherence only once before initial virological failure had a significantly increased risk of initial virological failure (HR 1.28, 95% CI 1.04–1.57), whereas those reporting differential adherence more than once had an even greater risk (HR 1.54, 95% CI 1.08–2.20; Fig. 2). Similarly, compared with participants without differential adherence, those who reported differential adherence only once had an increased risk of initial virological failure with antiretroviral resistance (HR 1.22, 95% CI 0.91–1.64), although this finding was not statistically significant. Participants who reported differential adherence more than once had twice the risk of initial virological failure with resistance compared with those without differential adherence (HR 1.93, 95% CI 1.19–3.15).

In adjusted Cox regression models, differential adherence was not associated with the composite endpoint of progression of HIV disease to AIDS or death (HR 1.17, 95% CI 0.86–1.58). Similarly, differential adherence was not associated with the time to first CD4 lymphocyte count of less than 200 cells/μl among the 618 participants with baseline CD4 lymphocyte counts of 200 cells/μl or greater (HR 0.98, 95% CI 0.60–1.60).

Discussion

Differential adherence was commonly reported in this randomized clinical trial of alternative initial ART strategies; 29% of participants self-reported differential adherence on at least one occasion. Neither demographic nor baseline clinical data were predictive of differential adherence. Although differential adherence was common in each randomized strategy, participants randomly assigned to the three-class strategy were more likely to report this behavior. Self-reported differential adherence was independently associated with an increased risk of initial virological failure and initial virological failure with antiretroviral resistance after adjusting for cumulative adherence and other potential confounders. An association between differential adherence and clinical or immunological outcomes was not evident.

In clinical practice, it is not uncommon for individuals to report different levels of adherence to antiretroviral regimen components. Whereas adherence to ART has been extensively studied, the pattern of differential adherence has not been thoroughly evaluated. Two small

studies suggested that different levels of adherence to regimen components was uncommon [14,15]. A third study using pharmacy refill adherence data found that 15% of unselected patients in a clinic cohort exhibited differential adherence during a median follow-up of 2.5 years, and that differential adherence during an initial antiretroviral regimen increased the risk of adverse clinical outcomes [9].

The current study expands the differential adherence literature in several ways. First, it confirms that differential adherence is common. This has previously been shown in an unselected clinic population and now in a broad population of US clinical trial participants, two distinct populations [9]. Second, despite uncertainty in the best way to assess differential adherence, self-reported adherence appears to be an effective measurement tool. Self-reported adherence assessments, like the CPCRA 7-day recall used in this study, are widely available and inexpensive to implement in clinical and research settings. Furthermore, they can assess adherence to all components of a regimen, which has generally not been the case in studies using microelectronic monitoring systems. Third, our study validates the clinical relevance of differential adherence by showing its relationship to the biologically plausible outcomes of virological failure and virological failure with antiretroviral resistance. The lack of an association between differential adherence and clinical outcomes in a treatment-naive population may reflect the prolonged time between virological failure and the occurrence of HIV disease progression events that is expected in this group [16].

A common theme in the antiretroviral adherence literature has been to analyse baseline factors that might predict non-adherence to ART [17–19]. In this report we have taken an initial look at potential predictors of differential adherence to ART. No demographic or baseline disease-specific factors appear to be associated with future report of differential adherence. Notably, we did not have information regarding active substance abuse and active mental illness at baseline, both of which have been associated with antiretroviral non-adherence in general [3, 17]. The significantly higher rate of discontinuation of one or more drugs in the antiretroviral regimen because of toxicity in the three-class strategy, and the greater frequency of differential adherence among these participants, suggest that regimen complexity or tolerability may be a factor in the frequency of differential adherence [20]. Regimen and drug-specific variables that may be risk factors for differential adherence in the FIRST study will be evaluated in subsequent on-treatment analyses.

A chief concern with differential adherence is that, in effect, individuals have periods of treatment with only one or two antiretroviral agents. It is known that mono and dual-therapy for HIV is associated with less durable virological responses and a greater incidence of antiretroviral resistance [6–8]. Therefore, we hypothesized that differential adherence and the extent of this behavior reported over time would be associated with virological failure and virological failure with antiretroviral resistance. The clear association between differential adherence and these two outcomes demonstrates that self-reported differential adherence is a clinically relevant pattern of non-adherence. The ‘dose–response’ association between differential adherence and virological failure with resistance further supports this hypothesis. Why this behavior appears more deleterious in patients randomly assigned to the three-class strategy is unknown. It may have to do with the magnitude of differential adherence or the drugs or drug classes that are less often taken.

Detailed analyses of other antiretroviral adherence patterns may prove useful, and there is ongoing research in this area [21–23]. How descriptions of patterns of non-adherence will influence future adherence research and interventions is unclear. For differential adherence, systematic interventions may be warranted because of the frequency of this behavior and the lack of demographic or clinical factors to predict its occurrence. Many current successful adherence intervention strategies rely on behavioral modification [20,24]. For differential

adherence it may be possible to develop a healthcare system-level intervention. The development and usage of new fixed-dose combination dosage forms containing all regimen components would make differential adherence impossible. Requiring all regimen components to be refilled in sync, with intervention targeting individuals not requesting refills of all regimen components, may also be of benefit. Differential adherence exerts an independent effect on virological outcomes, and therefore future adherence intervention research may need to address both differential adherence and overall non-adherence.

A limitation of this analysis, the lack of an on-treatment assessment, will be addressed in future analyses of this study population. Other important limitations of this study are presented here. First, a Likert scale does not provide the fine detail that would allow a more precise calculation of the magnitude of the difference in the level of adherence between regimen components. We were thus unable to quantify the influence of the level of differential adherence on outcomes. Second, participants in clinical trials may differ from general clinic populations in a number of ways. It is, however, notable that differential adherence has now been documented among both clinical trials participants and a general clinical cohort. Third, differential adherence is not possible with regimens composed of a single fixed-dose combination dosage form, but we were unable to assess the impact of a completely co-formulated regimen in this study. Fourth, for the virological failure with resistance endpoint, the lack of baseline resistance testing for the entire population limited our ability to assess whether resistance mutations at first failure were new. Baseline resistance tests were, however, performed on stored samples for a random subset ($N = 491$) of FIRST participants [25]. Of the 306 participants with genotypic resistance tests at both baseline and virological failure, 18 (6%) had definite drug resistance at baseline. Therefore, it is likely that most of the resistance documented at the time of virological failure among patients in this study was acquired resistance. Finally, previous reports suggest that self-reported adherence overestimates true adherence behavior.

In summary, differential adherence was common among patients starting combination ART and was associated with the clinically relevant outcomes of virological failure and failure with drug resistance. Over longer periods of time this detrimental effect of differential adherence on virological outcomes is likely to translate into worse clinical outcomes, although this remains to be proven. Further research will be required to evaluate interventions to decrease differential adherence.

Acknowledgements

The authors would like to acknowledge and thank the participants in the FIRST study and the dedicated staff at participating CPCRA units.

This study was presented in part at the 2nd International Conference on HIV Treatment Adherence, Jersey City, New Jersey, USA, 28–30 March 2007.

Sponsorship: The National Institute of Allergy and Infectious Diseases, National Institutes of Health grants 5U01AI042170, 5U01AI046362 and 1U01AI068641 provided financial support for this work as part of the FIRST study (CPCRA 058) and INSIGHT Network. E.M.G. is supported by a career development award from the National Institutes of Health, National Institute of Allergy and Infectious Diseases (K01 AI067063).

References

1. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, et al. Nonadherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 2001;15:1181–1183. [PubMed: 11416722]
2. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Adherence to triple therapy and viral load response. J Acquir Immune Defic Syndr 2000;23:360–361. [PubMed: 10836763]

3. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;133:21–30. [PubMed: 10877736]
4. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. Clin Infect Dis 2002;34:1115–1121. [PubMed: 11915001]
5. Bangsberg DR, Hecht FM, Charlebois ED, Zolopa AR, Holodniy M, Sheiner L, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS 2000;14:357–366. [PubMed: 10770537]
6. Jacobsen H, Hanggi M, Ott M, Duncan IB, Owen S, Andreoni M, et al. In vivo resistance to a human immunodeficiency virus type 1 proteinase inhibitor: mutations, kinetics, and frequencies. J Infect Dis 1996;173:1379–1387. [PubMed: 8648209]
7. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853–860. [PubMed: 9516219]
8. Saravolatz LD, Winslow DL, Collins G, Hodges JS, Pettinelli C, Stein DS, et al. Zidovudine alone or in combination with didanosine or zalcitabine in HIV-infected patients with the acquired immunodeficiency syndrome or fewer than 200 CD4 cells per cubic millimeter. N Engl J Med 1996;335:1099–1106. [PubMed: 8813040]
9. Gardner EM, Burman WJ, Maravi ME, Davidson AJ. Selective drug taking during combination antiretroviral therapy in an unselected clinic population. J Acquir Immune Defic Syndr 2005;40:294–300. [PubMed: 16249703]
10. MacArthur RD, Novak RM, Peng G, Chen L, Xiang Y, Hullsiek KH, et al. A comparison of three highly active antiretroviral treatment strategies consisting of nonnucleoside reverse transcriptase inhibitors, protease inhibitors, or both in the presence of nucleoside reverse transcriptase inhibitors as initial therapy (CPCRA 058 FIRST Study):a long-term randomised trial. Lancet 2006;368:2125–2135. [PubMed: 17174704]
11. MacArthur RD, Chen L, Mayers DL, Besch CL, Novak R, Van den Berg-Wolf M, et al. The rationale and design of the CPCRA (Terry Beirn Community Programs for Clinical Research on AIDS) 058 FIRST (Flexible Initial Retrovirus Suppressive Therapies) trial. Control Clin Trials 2001;22:176–190. [PubMed: 11306155]
12. Centers for Disease Control. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep Recomm Rep 1992;41:1–19.
13. Mannheimer S, Thackeray L, Huppler Hullsiek K, Chesney M, Gardner EM, Wu AW, et al. A randomized comparison of two instruments for measuring self-reported antiretroviral adherence. AIDS Care. 2007In press
14. McNabb JJ, Nicolau DP, Stoner JA, Ross J. Patterns of adherence to antiretroviral medications: the value of electronic monitoring. AIDS 2003;17:1763–1767. [PubMed: 12891062]
15. Wilson IB, Tchetgen E, Spiegelman D. Patterns of adherence with antiretroviral medications: an examination of between-medication differences. J Acquir Immune Defic Syndr 2001;28:259–263. [PubMed: 11694833]
16. Lima VD, Hogg RS, Harrigan PR, Moore D, Yip B, Wood E, et al. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. AIDS 2007;21:685–692. [PubMed: 17413689]
17. Chesney MA. Factors affecting adherence to antiretroviral therapy. Clin Infect Dis 2000;30(Suppl 2):S171–S176. [PubMed: 10860902]
18. Gifford AL, Bormann JE, Shively MJ, Wright BC, Richman DD, Bozzette SA. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. J Acquir Immune Defic Syndr 2000;23:386–395. [PubMed: 10866231]
19. Golin CE, Liu H, Hays RD, Miller LG, Beck CK, Ickovics J, et al. A prospective study of predictors of adherence to combination antiretroviral medication. J Gen Intern Med 2002;17:756–765. [PubMed: 12390551]

20. Mannheimer SB, Morse E, Matts JP, Andrews L, Child C, Schmetter B, et al. Sustained benefit from a long-term antiretroviral adherence intervention. Results of a large randomized clinical trial. J Acquir Immune Defic Syndr 2006;43(Suppl 1):S41–S47. [PubMed: 17091022]

21. Catz SL, Kelly JA, Bogart LM, Benotsch EG, McAuliffe TL. Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. Health Psychol 2000;19:124–133. [PubMed: 10762096]

22. Hill Z, Kendall C, Fernandez M. Patterns of adherence to antiretrovirals: why adherence has no simple measure. AIDS Patient Care STDS 2003;17:519–525. [PubMed: 14588092]

23. Vrijens, B.; Lange, AC.; Tousset, E.; Urquhart, J. Key findings from a large database of electronically-computed dosing histories of HIV+ patients prescribed various protease inhibitors. 2nd International Conference on HIV Treatment Adherence; Jersey City, NJ, USA. 28–30 March 2007;

24. Amico KR, Harman JJ, Johnson BT. Efficacy of antiretroviral therapy adherence interventions: a research synthesis of trials, 1996 to 2004. J Acquir Immune Defic Syndr 2006;41:285–297. [PubMed: 16540929]

25. Novak RM, Chen L, MacArthur RD, Baxter JD, Huppler Hullsiek K, Peng G, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. Clin Infect Dis 2005;40:468–474. [PubMed: 15668873]

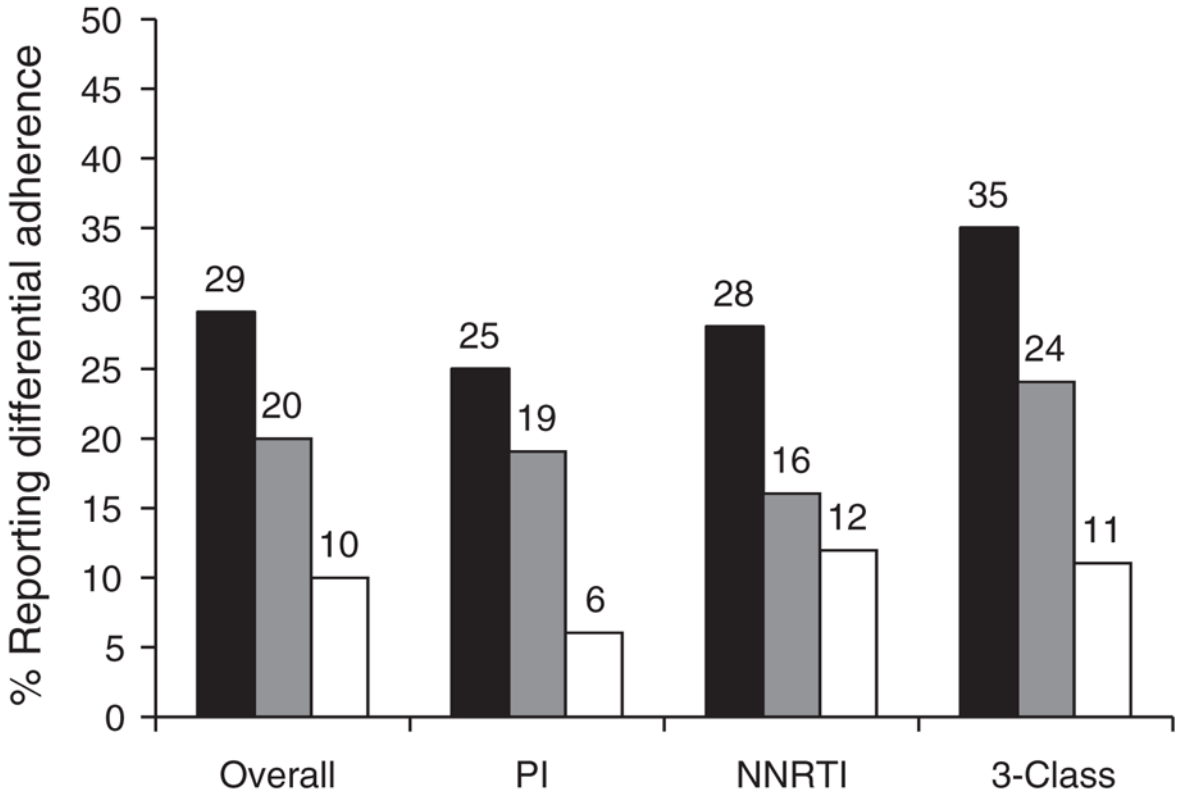

Fig. 1. Percentage of participants reporting differential adherence at any time during follow-up: overall and by randomized strategy

■ Ever reported; ▩ reported once; □ reported more than once. NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

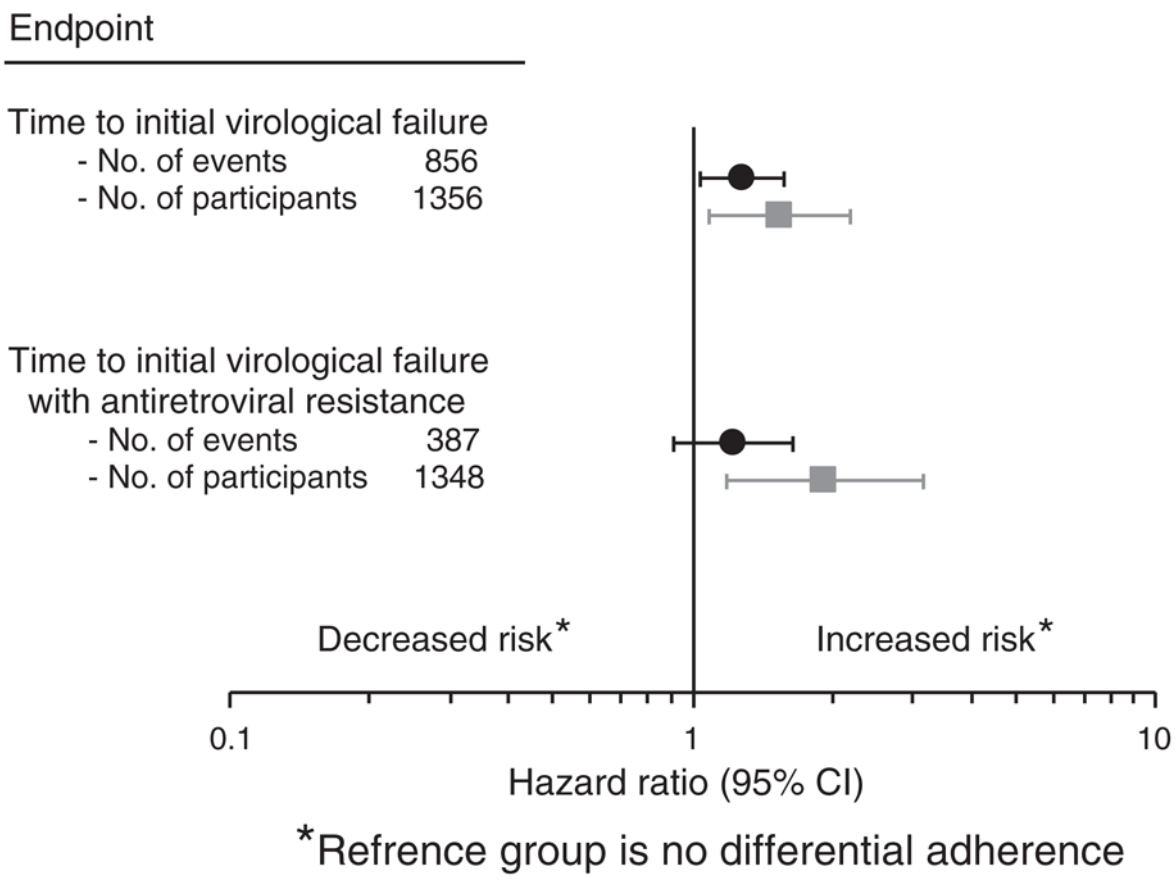

Fig. 2. Evaluation of the 'dose-effect' of differential adherence: adjusted hazard ratios for participants with differential adherence (once or more than once) compared with participants with no differential adherence in the Community Programs for Clinical Research on AIDS Flexible Initial Retro-virus Suppressive Therapies Study

● Differential adherence once; ■differential adherence more than once. CI, Confidence interval; Reference group is no differential adherence.

Table 1

Summary statistics for differential adherence, overall and by randomized strategy

Summary statistic	PI strategy		NNRTI strategy		3-Class strategy		Overall		Strategy comparison *P* Value
	N	%	*N*	%	*N*	%	*N*	%	
Differential adherence at least once	118	25.4	126	27.6	159	34.8	403	29.2	0.005
Differential adherence more than once	29	6.2	54	11.8	51	11.2	134	9.7	0.007
On randomized strategy at time of first differential adherence[a]	90	76.3	98	77.8	97	61.0	285	70.7	0.002
On randomized strategy at time of initial virological failure[b]	221	67.6	166	62.9	125	46.1	512	59.4	<0.0001
No. of participants	465		457		457		1379		

NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a] Limited to participants with differential adherence at least once.

[b] Limited to 862 of the 1379 participants with virological failure.

Table 2

Demographic and baseline factors among participants with and without differential adherence.

Baseline characteristics	Differential adherence during follow-up (*N* = 403)	No differential adherence during follow-up (*N* = 976)	Overall (*N* = 1379)
Median age, years (IQR)	38 (31–44)	38 (32–44)	38 (31–44)
Race			
White, %	25.3	26.9	26.5
Black, %	57.8	52.2	53.8
Latino, %	15.4	17.4	16.8
Other, %	1.5	3.5	2.9
Sex, % female	19.9	20.8	20.5
Male sex with men, %	60.7	60.4	60.5
Previous injection drug use, %	15.1	14.9	15.0
Previous AIDS, %	37.7	37.6	37.6
Median CD4 lymphocyte count,[a] cells/ml (IQR)	155 (42–318)	164 (34–339)	163 (36–332)
Median HIV-RNA,a $\log_{10}$ copies/ml (IQR)	5.2 (4.7–5.6)	5.1 (4.5–5.6)	5.1 (4.6–5.6)

IQR, Interquartile range.

[a] Average of screening and baseline levels.

Table 3

Hazard ratios (95% CI) from multivariate cox regression analyses of time to initial virological failure[a] and time to initial virological failure[a] with antiretroviral resistance: overall and by randomized treatment strategy in the Community Programs for Clinical Research on AIDS Flexible Initial Retrovirus Suppressive Therapies Study.

Variables	Initial virological failure				Initial virological failure with antiretroviral resistance			
	Overall	PI strategy	NNRTI strategy	3-Class strategy	Overall	PI strategy	NNRTI strategy	3-Class strategy
Age (per 10-year increase)	0.82 (0.76–0.89)	0.76 (0.66–0.87)	0.85 (0.74–0.97)	0.86 (0.75–0.99)	0.78 (0.70–0.88)	0.76 (0.63–0.93)	0.73 (0.59–0.89)	0.85 (0.69–1.03)
Latino ethnicity[b]	0.94 (0.75–1.18)	1.06 (0.73–1.52)	0.75 (0.47–1.17)	0.91 (0.61–1.35)	1.09 (0.77–1.54)	0.70 (0.39–1.26)	1.52 (0.78–2.94)	1.12 (0.62–2.01)
Black ethnicity[b]	1.79 (1.52–2.11)	2.08 (1.59–2.73)	2.10 (1.55–2.84)	1.34 (1.01–1.79)	2.18 (1.69–2.82)	1.82 (1.19–2.77)	3.39 (2.04–5.62)	1.75 (1.13–2.71)
Baseline CD4 lymphocyte count (per 100 cells/μl increase)	0.95 (0.92–0.99)	0.88 (0.82–0.94)	1.09 (1.01–1.17)	0.96 (0.90–1.03)	0.86 (0.80–0.92)	0.76 (0.67–0.87)	0.92 (0.81–1.05)	0.89 (0.80–1.00)
Baseline HIV-RNA (per $\log_{10}$ copies/ml increase)	1.37 (1.25–1.51)	1.18 (1.00–1.38)	1.65 (1.38–1.98)	1.48 (1.26–1.74)	1.48 (1.27–1.73)	1.35 (1.05–1.74)	1.72 (1.30–2.28)	1.49 (1.16–1.92)
Mean cumulative adherence score (per 10% decrease)[c]	1.24 (1.21–1.28)	1.21 (1.16–1.27)	1.31 (1.24–1.38)	1.25 (1.19–1.32)	1.25 (1.20–1.31)	1.27 (1.18–1.37)	1.24 (1.15–1.34)	1.26 (1.17–1.36)
Not on ART[c]	3.56 (2.71–4.68)	3.52 (2.18–5.70)	3.65 (2.31–5.77)	4.10 (2.54–6.62)	1.00 (0.58–1.74)	0.13 (0.02–0.99)	1.08 (0.41–2.83)	1.90 (0.85–4.22)
Differential adherence[c]	1.33 (1.10–1.60)	1.26 (0.89–1.79)	1.02 (0.72–1.44)	1.63 (1.22–2.19)	1.34 (1.03–1.75)	1.12 (0.67–1.89)	1.12 (0.69–1.83)	1.75 (1.16–2.64)
No. of events (no. of participants)	856 (1356)	322 (459)	263 (448)	271 (449)	387 (1348)	134 (457)	126 (446)	127 (445)

ART, Antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a] Time to HIV-RNA level >1000 copies/ml at or after month 4.

[b] Reference group is white or other.

[c] Time-updated variable.