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Durability of Adherence to Antiretroviral Therapy on Initial and Subsequent Regimens

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Abstract

There is uncertainty regarding the durability of adherence to antiretroviral therapy. This study is a retrospective review of previously antiretroviral naïve patients initiating therapy between 1997 and 2002. Antiretroviral adherence was calculated using prescription refill data and was analyzed over time on an initial regimen and on sequential antiretroviral regimens. Three hundred forty-four patients were included. The median lengths of the first, second, and third regimens were stable at 1.7 years, 1.2 years, and 1.5 years, respectively ($p = 0.10$). In multivariate analysis the factor most significantly associated with earlier initial regimen termination was poor adherence. On an initial regimen, adherence decreased over time and declined most rapidly in patients with the shortest regimens (4 to <16 months, −43% per year), followed by patients with intermediate regimen duration (16 to <28 months, −19% per year), and then patients with longer regimens (≥28 months, −5% per year). In patients progressing to a third regimen, there was a trend toward decreasing adherence over successive regimens. In conclusion, sequential antiretroviral regimens are of similar lengths, with adherence being highly associated with first regimen duration. Adherence decreases during an initial regimen and on sequential antiretroviral regimens. Effective and durable interventions to prevent declining adherence are needed.

INTRODUCTION

COMBINATION ANTIRETROVIRAL THERAPY has revolutionized the treatment of HIV, but sub-optimal adherence, toxicity, and the development of resistance may limit available therapy.[1,2] Because there are a limited number of antiretroviral drug classes and cross resistance may limit the potency of other members of a class once resistance has developed, it is critical to identify ways to prolong the success of existing combination regimens. Adherence to therapy is an important determinant of the initial success of antiretroviral therapy, but there are uncertainties about the durability of adherence behavior. Some studies have found adherence to be stable, while others have shown decreasing adherence over time.[3–9] Most of these studies were carried out in prospective or clinical trial cohorts with 1 to 2 years of follow-up.

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We conducted a retrospective study to determine the durability of adherence to combination antiretroviral therapy in two ways. First, we evaluated the changes in adherence over the course of an initial antiretroviral regimen. We then evaluated adherence over successive antiretroviral regimens.

MATERIALS AND METHODS

Setting and population

Denver Health is an integrated public health care system serving 1400 HIV-infected individuals yearly. We identified antiretroviralnaïve patients initiating therapy between January 1997 and December 2002 using an administrative pharmacy refill database and the local database of the Adult and Adolescent Spectrum of Disease (ASD) project.[10] Approximately 90% of Denver Health patients use the Denver Health pharmacy system for their antiretroviral prescriptions.[11] Treatment-naïve status was confirmed by chart review. Patients were excluded if they initiated therapy at an outside facility or through an outside pharmacy, had no verifiable antiretroviral use, or received any antiretroviral medications through a clinical trial. Up to three regimens per person were analyzed. Duration of followup spanned from the date of dispensing of the first antiretroviral regimen until death, loss to follow-up, or March 2004. The Colorado Multiple Institutional Review Board approved the study.

Definitions

All unique antiretroviral medications initiated within 60 days of each other constituted a regimen. A modification was defined as a single intraclass antiretroviral medication switch. Other changes, additions, or deletions of medications signified termination of that regimen, as did sequential modifications or a gap in refills of 180 days or more. The termination date was the date of the final refill of the regimen, or the date of pick-up of the new regimen if regimens overlapped. Regimens were censored if ongoing at loss to follow-up or if an outside prescription source was identified. To evaluate whether gaps in pharmacy refills might result from the use of an outside pharmacy, the medical records (including telephone encounters and refill requests) were reviewed for the corresponding time period of all gaps in refills lasting greater than 30 days. A lapse in care was defined as a concomitant gap in antiretroviral refills and clinical care lasting at least 180 days.

Any antiretroviral medication use for one or more days constituted a regimen. For most adherence analyses, regimens shorter than 31 days were excluded. Most prescriptions were dispensed in 30-day supplies, thus adherence on regimens shorter than 31 days was usually 100%. Reasons for modifications and terminations were obtained by chart review. Significant adverse drug events were defined as any adverse event that led to discontinuation of an antiretroviral medication.

Adherence was determined based on pharmacy refill data and calculated by individual drug as doses obtained divided by doses prescribed. Regimen-specific adherence was calculated as the average adherence for medications included in that regimen over the entire duration of that regimen. Our pharmacy refill adherence measure has been validated by demonstrating a close association between adherence and HIV viral suppression (<400 copies per milliliter) during the first 6-months of therapy.[11]

Patients were defined as having active psychiatric disease (ICD-9 codes 295.X and 296.X) or active substance abuse (including alcohol, ICD-9 codes 304.X and 305.X) if these diagnoses were coded at least once from 6 months prior to 6 months after initiation of the first regimen. Baseline CD4 count and HIV viral loads were within 6 months prior to therapy initiation. All regimen-specific variables were obtained through the pharmacy refill database. Highly active

antiretroviral therapy (HAART) was defined as any regimen containing three or more antiretroviral medications or containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) and a protease inhibitor (PI).

Data analysis

Regimen durations were assessed using Kaplan-Meier analysis, time to regimen termination. Any regimen continuing at the end of follow-up was censored on the date of the last refill. Sequential regimen durations were compared using the log-rank test. To compare our data with a previous report,[12] we reanalyzed regimen durations with modifications equaling terminations and excluding non-HAART regimens and regimens lasting less than 14 days.

Regimen characteristics for initial versus subsequent regimens were compared using an independent sample *t* test or the χ^2 test. Bivariate proportional hazards regression analysis was performed to assess for a relationship between baseline characteristics (including first regimen adherence) and first regimen duration. Multivariate proportional hazards regression was performed using all variables with significance $p < 0.20$ in bivariate analysis. Because adherence was included in this model, only regimens lasting longer than 30 days were assessed. To assure that excluding shorter regimens (<31 days) did not affect our conclusions, a second multivariate proportional hazards regression analysis was performed including all regimens.

Adherence over time on an initial regimen was determined by analyzing sequential 120-day periods of adherence. This duration was selected to allow analysis of at least three sequential time periods in regimens that lasted more than 1 year. To assure that all adherence periods contained a full 120 days of data, we excluded regimens shorter than 120 days and we ignored the terminal adherence period if less than 120 days. The adherence periods were compared using a mixed effects model to account for correlated data. Adherence on sequential regimens was compared using the Friedman test, a nonparametric test that accounts for correlated data.[13] The Friedman test was performed using all regimens (i.e., including regimens <31 days) because missing data from a single regimen would exclude a patient from the overall analysis. Data analyses were performed using SAS statistical software version 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

Three hundred forty-four (83%) of 415 previously antiretroviral naïve patients initiating therapy between 1997 and 2002 were included. Exclusions included the following: 31 (44%) of the 71 excluded patients received medications through a clinical trial, 18 (25%) initiated therapy in an outside facility, 12 (17%) solely used an outside pharmacy, and 10 (14%) had no verifiable antiretroviral use. There were no significant differences between included and excluded patients (Table 1). Forty-seven (14%) of 344 included patients were participants in clinical trials. There were no differences between clinical trial and nonclinical trial patients with regards to baseline demographics, initial regimen duration, initial regimen adherence, or proportion progressing past their initial regimen (data not shown). These patients were retained in the remainder of the analyses.

Overall, 530 regimens were evaluated over a median follow-up of 2.2 years (interquartile range [IQR] 1.2−3.8). One hundred thirty-three (39%) of 344 patients progressed to a second regimen and 53 (15%) progressed to a third regimen. Four hundred ninety-six (94%) of 530 regimens consisted of at least three antiretroviral medications. 255 (48%) of 530 regimens consisted of a PI and nucleoside reverse transcriptase inhibitors (NRTIs), 187 (35%) contained an NNRTI and NRTIs, 44(8%) contained both a PI and an NNRTI, and 44(8%) contained only NRTIs.

There were significant differences in regimen characteristics of initial versus subsequent regimens. One hundred eighty-seven (54%) of 344 initial regimens and 68 (37%) of 186 subsequent regimens were PI based ($p < 0.001$). Correspondingly, initial regimens were less likely to be NNRTI based (33% versus 39%) or to contain both an NNRTI and a PI (5% versus 15%). Compared to subsequent regimens, initial regimens used more pills per day (mean 9.4 versus 8.2, $p = 0.001$) and more doses per day (mean 2.1 versus 2.0, $p < 0.001$) but were less likely to include medications with different dosing schedules (31% versus 43%, $p = 0.005$) and contained fewer individual regimen components (mean 3.0 versus 3.2, $p < 0.001$).

The durability of sequential antiretroviral regimens

The median lengths of the first, second, and third regimens were 1.7 years (IQR 0.5−4.6), 1.2 years (IQR 0.3−2.6), and 1.5 years (IQR 0.6th−75th percentile not yet reached) respectively (Fig. 1). Overall, there were no significant differences between lengths of regimens ($p = 0.10$). However, first regimens were significantly longer than second regimens ($p = 0.04$, not adjusted for multiple comparisons). There was no significant difference in the proportion of censored regimens, occurring in 45%, 46%, and 55% of first, second, and third regimens, respectively ($p = 0.40$). In noncensored regimens, significant adverse drug events were the most common reason for regimen termination (96/286; 34%) followed by regimen failure (41/286; 14%), and lapses in care (36/286; 13%). Reanalyzing regimen duration data in which modification equaled termination and excluding non-HAART regimens and regimens shorter than 14 days revealed median durations of first, second, and third regimens of 1.6 years (IQR 0.4−4.0), 0.7 years (IQR 0.2−2.6), and 1.6 years (IQR 0.6th−75th percentile not yet reached), respectively ($p = 0.02$).

Among first regimens lasting longer than 30 days ($n = 304$), baseline factors were assessed for association with earlier first regimen termination (Table 2). Multivariate Cox regression revealed an association between poor adherence, psychiatric comorbidity, and the use of a non-HAART first regimen with an increased hazard of first regimen termination. For every 10% decrement in first regimen adherence the hazard of first regimen termination increased by 17% (hazard ratio [HR] 1.2, 95% confidence interval [CI]: 1.1−1.3). Patients with psychiatric comorbidity had 1.5 times (95% CI: 1.1−2.2) the hazard of earlier first regimen termination compared to patients without this comorbidity. Patients receiving a non-HAART first regimen had 2.1 times (95% CI: 1.1−3.9) the hazard of earlier first regimen termination compared to patients receiving a HAART regimen.

Two further analyses confirmed these associations. First, in an adjusted Cox regression model including regimens less than 31 days in duration, both psychiatric comorbidity and use of a non-HAART regimen remained significantly associated with shorter initial regimen duration (data not shown). Second, inclusion of significant adverse events in the final model did not change the multivariate results, despite their strong association with initial regimen duration. Because, by definition, a significant adverse event led to a medication change, we did not include it in the model presented.

The durability of adherence on an initial antiretroviral regimen

Two hundred fifty-four (74%) of 344 total patients had an initial regimen lasting at least 120 days. Overall, this cohort appeared to have slowly declining adherence over time at a rate of 2.6% per year ($p = 0.004$) (Fig. 2. However, because adherence is associated with regimen duration, this analysis was potentially biased because patients remaining in the analysis at later time points had better adherence. For this reason, we divided our cohort by first regimen duration. The groups were selected in order to include 3, 6, and 9 analyzable sequential adherence periods: 4 to less than 16 months ($n = 114$), 16 to less than 28 months ($n = 62$), and 28 months or more ($n = 79$) (Fig. 2). All three of these groups had adherence that decreased

significantly over time. Patients with the shortest regimens had the most rapid decline in adherence at a rate of 43% per year ($p < 0.001$). In the group with regimens lasting 16 to less than 28 months, the rate of decline was 19% per year ($p < 0.001$). For patients with regimens longer than 28 months, the rate of decline was 5% per year ($p < 0.001$). In each group, the significance levels indicate that the rate of change in adherence was significantly different from zero.

The durability of adherence over sequential antiretroviral regimens

The median adherence on the first regimen was 90.4% (IQR 78.8%–97.9%), on the second regimen it was 86.3% (IQR 71.0%–96.8%), and on the third regimen it was 79.5% (IQR 67.7%–98.7%) (Fig. 3). However, because patients with excellent adherence were less likely to progress to a second or third regimen, such patients may bias the overall adherence of earlier regimens. To account for this potential bias we reanalyzed median regimen adherence for first and second regimens in patients with two regimens ($n = 80$). In this population, median first and second regimen adherence was 90.3% (IQR 78.6%–97.0%) and 87.3% (IQR 69.5%–96.4%), respectively ($p = 0.41$). Similarly, we analyzed sequential regimen adherence for the first three regimens in patients with three regimens ($n = 53$). In this population, median adherence decreased from 88.2% (IQR 71.4%–99.5%) to 83.6% (IQR 72.1%–97.8%) to 79.5% (IQR 67.7%–98.7%) on the first, second, and third regimens, respectively ($p = 0.06$).

DISCUSSION

We report the durability of antiretroviral adherence in an unselected, previously antiretroviral-naïve, clinic population. The duration of consecutive antiretroviral regimens was stable. Antiretroviral adherence was closely associated with initial regimen duration but decreased over time during that regimen. The rate of decline varied and was greatest in patients with the shortest regimens, although even in patients with the most durable regimens, there was a significant decline in adherence during the initial regimen. Adherence trended downward on sequential antiretroviral regimens. These findings suggest that declining adherence is common and may have a significant impact on the durability of combination antiretroviral therapy.

Our data regarding the duration of sequential regimen duration are different than previously published.[12,14] In prior reports there was a significant trend toward progressively shorter sequential regimens. The reasons for the differences are unclear but may be due to the inclusion of non-naïve individuals[14] or to different inclusion dates and regimen characteristics.[12] There is little prior data on the association of adherence with regimen duration. Moss et al.[5] found that poor early adherence was a major predictor of therapy discontinuation. This is not surprising because poor adherence is associated with the most common reasons for therapy discontinuation in this and other studies, adverse events and virologic failure.[15,16]

The durability of adherence has been previously assessed but with conflicting results, some showing that adherence decreases over time and others finding it to be stable.[3–9] Most of these analyses have been limited by small numbers, short duration of follow-up, or inclusion of primarily patients enrolled in prospective studies. In a study involving a cohort of homeless persons in San Francisco, California, adherence decreased rapidly in patients who discontinued therapy within the first year of follow-up.[5] Our data support that adherence decreases over time, even in very adherent patients. For example, the median adherence among those with regimen lengths greater than 2 years was 96%, but there was a clear decrease in adherence over time in this group. We are unaware of a prior analysis of adherence on sequential regimens. Although our analyses were limited by small numbers, we feel that the trend toward lower adherence on sequential regimens supports the hypothesis that adherence decreases over time. This information has implications for the need to develop sustainable adherence interventions in the future.

Inclusion of all patients in all adherence analyses limits the ability to assess the durability of adherence. We are not the first to suggest that within a population there are subpopulations of patients with different adherence characteristics.[3] Patients with excellent adherence have the longest first regimens and thus raise population adherence levels at later time points when looking at an individual regimen. Similarly, patients with excellent adherence are less likely to progress to a second or third regimen, which can artificially inflate first regimen adherence, compared to subsequent regimens. However, when analyzed carefully, adherence decreased over time in each sub-population assessed.

These data support that adherence fatigue is a valid and troubling concern as we look for ways to extend the long-term effectiveness of existing antiretroviral therapies. Adherence fatigue (declining adherence over time) was seen in our patients despite, as in most settings, the consistent system-wide messages to patients on the critical importance of antiretroviral adherence. More concerning is the lack of proven interventions to prevent declining adherence. Possible interventions include better adverse event management, regimen simplification, treatment interruption, and sustainable adherence interventions. These are avenues that need continued intensive investigation.

One contradictory finding in our analysis remains unexplained. Adherence tended to decrease on sequential regimens yet regimen durations remained stable. There are several potential explanations. More second and third regimens were NNRTI based and recent evidence suggests that rates of viral suppression with NNRTIs may be adequate at lower adherence levels.[17, 18] Also, the potency of PIs used on second and third regimens was likely greater as more were ritonavir boosted. Whether or not more salvage regimens might be continued in the face of virologic failure is unknown. Finally, second and third regimens were started somewhat later during the study period and thus were more often chosen using resistance testing, which was uncommonly performed before initial antiretroviral regimens during the study period.

Our study is limited in several ways. All of our data are retrospective. However, in adherence research, retrospective data may be advantageous in that no intervention is required. Thus, pharmacy refill data allow the evaluation of a high percentage of a clinic population and should not have any effect on adherence behavior itself. Some analyses were limited by small numbers of patients; particularly the analyses of adherence on sequential regimens, and these observations need to be assessed in larger populations. Our data are from a single institution and its applicability in other settings is unknown. However, the ability to assess adherence among more than 80% of the patients provides assurance that we characterized adherence behavior in our system. The use of ICD diagnosis codes to identify active substance abuse and psychiatric disorders may not accurately or completely define these groups. Finally, because we were unable to ascertain data on adverse events that did not lead to a medication change, we have likely underestimated the overall frequency of these events.

This research should assist clinicians and researchers by giving a better understanding of the dynamic process of antiretroviral regimens, antiretroviral adherence, and the interaction between them. The development of sustainable adherence interventions to prevent or decrease adherence fatigue will be paramount in extending the useful life of available antiretroviral medications. Our data also underscore the important interaction between adverse events, poor adherence, and shorter antiretroviral regimen durations. Future research is necessary to define the association and contribution of these factors to successful treatment of HIV-infected patients.

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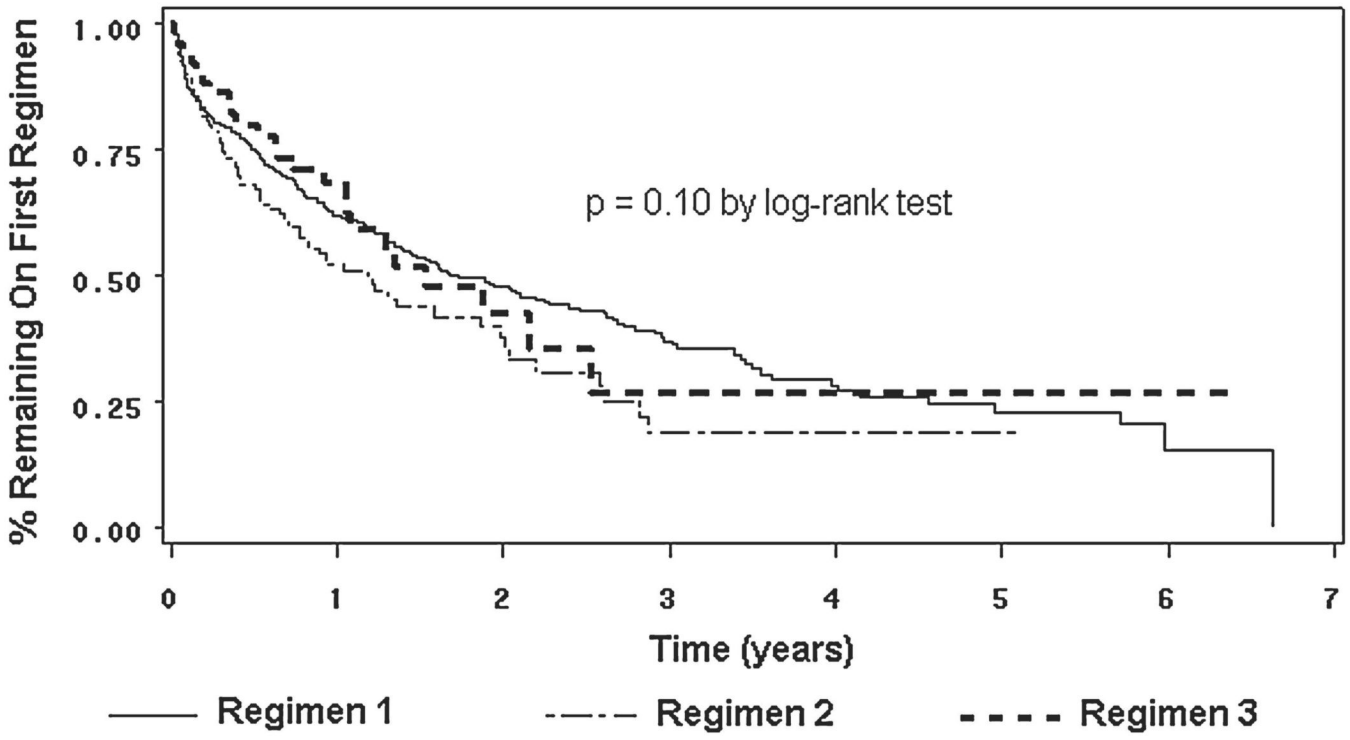

FIG 1.
Duration of first, second, and third antiretroviral regimens in a cohort of patients previously antiretroviral naïve (Kaplan-Meier analysis), Denver Health, 1997 through 2002.

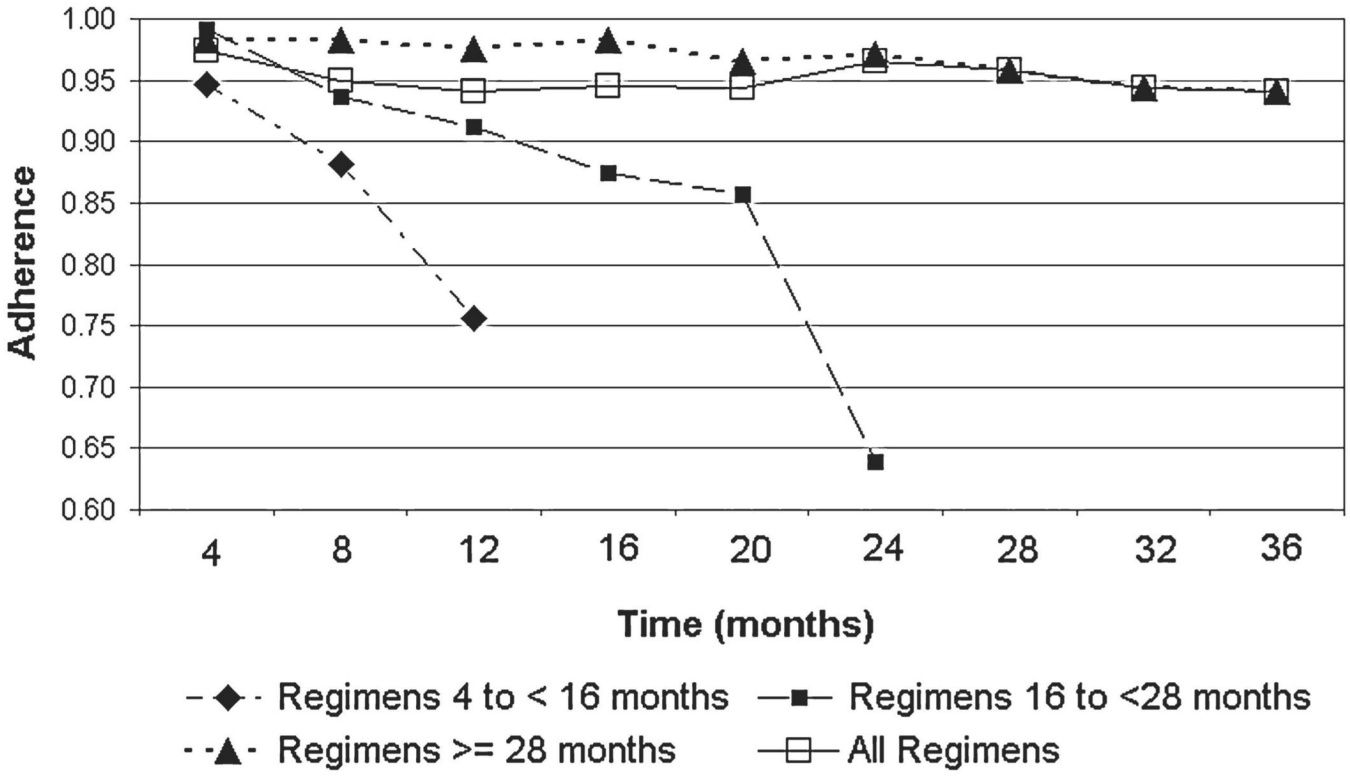

FIG 2.
Median adherence over time on an initial antiretroviral regimen as measured by sequential 4-month adherence blocks in patients with initial regimens of various durations.

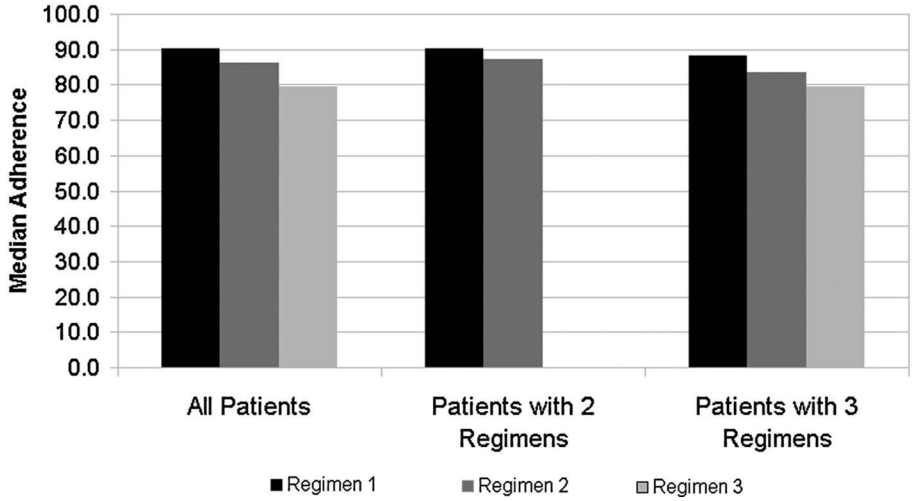

FIG 3.
Median adherence on sequential antiretroviral regimens in the entire cohort, in patients with two regimens (n = 80), and in patients with three regimens (n = 53).

Table 1

Baseline Demographics and Disease-Specific Characteristics of Previous Antiretroviral-Naïve Patients Initating Therapy at Denver Health, 1997 through 2002

	Included (n = *344*)	*Excluded* (n = *71*)	p *value*
Age (years)[a]	37 (32–42)	38 (32–44)	0.53
Gender[b]			
Female	41 (12%)	10 (14%)	0.61
Race[b]			
White	159 (46%)	24 (34%)	0.23
Black	72 (21%)	18 (25%)	—
Hispanic	105 (31%)	28 (39%)	—
Other/Unknown	8 (2%)	1 (1%)	—
HIV Transmission Mode[b]			
MSM	188 (55%)	36 (51%)	0.53
IDU	27 (8%)	7 (10%)	—
MSM/IDU	44 (13%)	14 (20%)	—
Heterosexual	27 (8%)	5 (7%)	—
Other/unknown	58 (17%)	9 (13%)	—
Primary Language[b]			
English	248 (72%)	49 (69%)	0.74
Spanish	32 (9%)	6 (8%)	—
Other/Unknown	64 (19%)	16 (23%)	—
Psychiatric Comorbidity[b]	100 (29%)	18 (25%)	0.53
Active Substance Use[b]	116 (34%)	21 (30%)	0.50
Baseline CD4 cell count (cells/ul)[a]	168 (47–305)	123 (37–305)	0.35
Baseline HIV RNA (log copies/ml)	5.1 (4.5–5.6)	5.1 (4.3–5.8)	0.73

MSM, men who have sex with men; IDU injection drug users.

[a] Median (interquartile range) comparisons made using the Wilcoxon rank-sum test.

[b] *n* (%) comparisons made using the χ^2 test

Table 2

Association of Baseline Factors with Time to First Regimen Termination in Previously Antiretroviral-Naïve Individuals Initiating Therapy at Denver Health, 1997 through 2002

	Bivariate hazard ratio (95% CI)	*Multivariate hazard ratio (95% CI)*	*Multivariate* p *value*
Age (per 10-year increase)	0.86 (0.72−1.03)	0.87 (0.72−1.04)	0.12
Gender (female)	1.10 (0.68−1.79)	—	—
Race (African American)[a]	1.17 (0.79−1.73)	—	—
Mode of transmission (MSM)[a]	1.13 (0.72−1.78)	—	—
Primary language (English)[a]	0.99 (0.56−1.76)	—	—
Psychiatric comorbidity	1.68 (1.20−2.37)	1.53 (1.06−2.20)	0.02
Active substance use	1.33 (0.95−1.86)	1.13 (0.79−1.62)	0.49
Baseline CD4 count (per 100 cell decrease)	1.01 (0.92−1.10)	—	—
Baseline HIV RNA (per 1 log increase)	0.94 (0.76−1.17)	—	—
Participant in clinical trial	0.98 (0.63−1.53)	—	—
Pills per day (per 1 pill increase)	1.01 (0.97−1.05)	—	—
Doses per day (per 1 dose increase)	0.99 (0.65−1.52)	—	—
Non-HAART 1st regimen	2.66 (1.47−4.81)	2.09 (1.12−3.91)	0.02
Different dosing schedules[b]	0.91(0.65−1.29)	—	—
PI-based vs. non-PI based	1.04 (0.75−1.44)	—	—
Regimen adherence (per 10% decrease)	1.23 (1.12−1.35)	1.17 (1.06−1.29)	0.002

MSM, men who have sex with men; CI, confidence interval; HAART, highly active antiretroviral therapy.

[a] Statistical comparison excludes patients with missing data.

[b] Having individual medications with different dosing schedules on the same regimen.