JAIDS Journal of Acquired Immune Deficiency Syndromes
29:495–503 © 2002 Lippincott Williams & Wilkins, Inc., Philadelphia

Prevalence and Correlates of Highly Active Antiretroviral Therapy Switching in the Women's Interagency HIV Study

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Objective: The purpose of this study was to describe the variability in highly active antiretroviral therapy (HAART) regimens over time, the extent to which individuals switch, and the characteristics of those who are switching.

Methods: We evaluated data collected between 1994 and 2000 from 1056 HIV-positive women enrolled in the Women's Interagency HIV Study (WIHS) who reported initiating HAART. We described the variability and prevalence of changes in HAART regimens between semiannual visits, estimated time to switch using Kaplan-Meier methods, investigated factors associated with a first switch using Cox proportional hazards models, and compared disease markers among women switching or remaining on unchanged HAART regimens.

Results: We demonstrated a 13-fold increase in the number of unique HAART regimens reported since mid-1996 and showed that the amount of time spent on the first, second, or third regimen is similar, with an 8-month median time to switching or discontinuing the initial HAART regimen. Women who switched had a lower mean CD4 cell count and were more likely to have HIV RNA levels greater than 400 copies/mL. Overall, the percentage of women switching decreased over the course of follow-up (to 37% in September 2000), although the percentage discontinuing therapy altogether increased 2-fold.

Conclusion: Our findings on the relatively high rate of HAART switching emphasize the complexity of managing and evaluating these therapies.

Key Words: HAART—Antiretroviral therapy—Switching—Modification—Discontinuation.

The current era of highly active antiretroviral therapy (HAART) has led to dramatic progress in the ability to suppress HIV replication and slow the progression of HIV-associated disease (1–8). Prospective cohort studies, by their longitudinal nature, offer the opportunity to quantify and characterize changes in therapy and to describe therapy patterns across time. Few data have yet emerged describing the amount of therapy switching that is occurring in populations such as women and minorities—populations that now make up an increasing proportion of HIV-infected individuals.

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Manuscript received June 22, 2001; accepted December 18, 2001.

Smaller studies have documented the frequency of discontinuing and switching therapy regimens in these cohorts. Saag et al. (9) described the increasing number of unique antiretroviral regimens over time in a group of 120 male patients and showed that the median duration of a specific regimen within this group was approximately 4 months. Van Roon et al. (10) reported that 25% of their AIDS clinic patients ($n = 99$; 82% male) discontinued HAART within 1 year of initiating therapy. The Italian Cohort of Antiretroviral-Naïve Patients found that 36% of men who began a HAART regimen ($n = 862$) modified or discontinued their initial regimen over a median follow-up time of 11 months (11). Finally, Mocroft et al. (12) estimated that 26% of their patients initiating HAART ($n = 556$; 81% male) modified or discontinued their regimen within 6 months of initiation and that 45% had modified or discontinued their regimen after a median follow-up time of 14 months. Studies of therapy have also reported that the use of viral load monitoring (9), higher viral levels of HIV RNA (12,13), baseline $CD4^+$ cell count (10), and no prior therapy use (10) were associated with switching or discontinuing a HAART regimen and that participants in clinical trials were less likely to switch their HAART regimens (12). Toxicities were often the main reason cited for discontinuation of therapy (11,13), and one study reported that women were twice as likely as men to discontinue HAART because of toxicities (11).

With some exceptions, these studies characterize regimen changes predominantly among white men. By June 2000, women and individuals of color represented 68% of all HIV infection cases and 61% of all AIDS cases (14,15). Based on possible differences by race and gender in adherence and ability to manage drug toxicities (16–18), it is critical to document the trends in switching and discontinuation of HAART regimens in populations of women as well as in minority populations.

The aims of this study are threefold. First, we provide a comprehensive description of the variability in HAART regimens among a cohort of women through 2000. Second, we describe the prevalence of and calendar time associated with reported changes in HAART regimens between semiannual visits. We estimate time to switch and investigate factors associated with a first switch. Finally, we compare disease markers among women switching or discontinuing HAART with those of women remaining on unchanged HAART regimens. We use data through September 2000 from participants enrolled in the Women's Interagency HIV Study (WIHS), a unique cohort of HIV-infected women across five major urban areas in the United States.

METHODS

Study Cohort and Follow-Up

Between October 1994 and November 1995, 2059 HIV-positive women aged 13 years or older were enrolled in the WIHS. Recruitment occurred in five major urban areas across the United States: New York, Chicago, Los Angeles, San Francisco, and Washington, DC. Women were recruited through HIV primary care sites, drug treatment facilities, and community-based outreach centers. WIHS participants returned semiannually for a physical examination, collection of specimens, and series of interviewer-administered questionnaires eliciting information that included their use of antiretroviral medication. Participants were asked to identify each antiretroviral medication they had taken since their prior study visit and whether they were currently taking each medication on the day of their study visit. To help participants correctly recall and identify their antiretroviral medication use, photo-medication cards that identified all medications by brand and generic drug name were used. Although participants were compensated for attending visits, medications were not provided by the study itself. Plasma viral loads were measured using the isothermal nucleic acid sequence–based amplification (Nuclisens) method (Organon Teknika Corp., Durham, NC, U.S.A.). The lower limit of quantification was 400 copies/mL. T-cell subsets were determined using standard flow cytometry techniques. From October 1994 through October 1999, the retention rate of participants was approximately 81% (19). Further details of the study methods and cohort demographics are reported elsewhere (20).

Definitions of Therapy

Women reporting use of one of the following combinations at the time of their study visit were considered to be on HAART: 1) two or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor (PI) or one nonnucleoside reverse transcriptase inhibitor (NNRTI), 2) one NRTI in combination with at least one PI and at least one NNRTI, 3) a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTIs, or 4) an abacavir-containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs. Combinations of zidovudine and stavudine with either a PI or an NNRTI were not considered to represent HAART because of their contraindication (21). These definitions were guided by the Department of Health and Human Services/Kaiser and the International AIDS Society–U.S.A. Panel guidelines (21,22).

Study Population and Data Analysis

Data from the 1056 women who reported using antiretroviral medication combinations consistent with our HAART definition at one or more follow-up visits through September 2000 were used to describe the number of unique HAART combinations over time. HAART regimens were categorized as 1) PIs with no NNRTIs, 2) NNRTIs with no PIs, 3) both PIs and NNRTIs, or 4) neither PIs nor NNRTIs (e.g., HAART defined by abacavir).

To describe the extent and timing of HAART switching, we restricted all further analyses to the 994 women (94% of the 1056 HAART initiators) who contributed study visits after HAART initiation which were at most 12 months apart. Data from participants who missed a period of 12 months or greater between study visits were censored at the last visit seen. Using longitudinal data, the date of HAART initiation was calculated by taking the midpoint between the

date of the last visit the participant was seen HAART-free and the date of the first visit the participant was seen on HAART. We defined a switch as any change in reported medication use since the time of a participant's last visit compared with the medications reported at that individual's prior visit. This included participants who discontinued or switched to a less intense therapy regimen as well as those switching to a different HAART regimen. We then identified time of the first, second, and third changes in HAART regimen after initiation. Time of switch was estimated as the midpoint between visits at which the switch was identified, and time on HAART was calculated as time from initiation to switch. Participants who missed one 6-month study visit were treated similarly; time of switch was estimated to be the midpoint between the two nonconsecutive visits.

We used Kaplan-Meier (KM) estimates to examine the timing of regimen changes in two ways. First, we evaluated time on the first, second, and third regimens, censoring times at a participant's last visit if no switch occurred. The percentage of women switching 1 year after starting their first, second, or third HAART regimen was estimated. Second, we evaluated time from incident HAART use to the first, second, and third reported regimen switches and reported median time to switch.

We evaluated heterogeneity in time to first regimen switch in two ways. First, we used univariate and multivariate Cox proportional hazards models to determine the association of factors with time to any regimen switch. Women reporting stable HAART regimens were censored at their last follow-up visit. Second, we used similar methods to investigate factors associated with time to first HAART regimen switch. Women who reported stable HAART regimens, switching to less intense regimens, or discontinuation were censored. Factors included in the models were disease markers (pre-HAART $CD4^+$ lymphocyte counts, HIV RNA levels, and clinical AIDS status), ethnicity, clinical site, education (less than high school versus high school graduate or greater), and pre-HAART characteristics (depression [Center for Epidemiologic Studies Depression Scale score <21 versus ≥ 21]), household income [<$12,000 per year versus ≥$12,000 per year], use of recreational drugs or alcohol [4 or more drinks per day], and report of insurance [yes/no]).

We also compared $CD4^+$ cell counts and HIV RNA levels of participants who switched between consecutive visits with those of participants who could have switched but remained on the same regimen. For each visit, the Student t test and χ^2 test were used to detect differences in mean $CD4^+$ lymphocyte levels and in the proportion of women with HIV RNA below 400 copies/mL between the two groups.

To characterize further the amount and type of switching in women, we calculated the proportion of women on HAART who reported 1) remaining on HAART but switching at least one antiretroviral drug within their regimen, 2) discontinuing HAART for a less intensive regimen (e.g., monotherapy or non-HAART combination therapy), or 3) discontinuing antiretroviral therapy altogether. We then plotted these proportions by calendar time to depict the longitudinal trends in regimen switching.

RESULTS

Longitudinal Patterns of HAART Regimens

Figure 1 presents the trends in the reported use of individual antiretroviral medications by calendar time among the 2059 HIV-positive women in the WIHS. Trends among the three drug classes reflect the timing of drug approval by the U.S. Food and Drug Administration as well as preferential use of certain medications after their approval dates. As of September 2000, the most commonly reported NRTI, PI, and NNRTI were lamivudine, nelfinavir, and nevirapine, respectively.

Figure 2 presents the number of unique HAART regimens and the cumulative incidence of HAART among the 1056 women reporting HAART through September 2000. In parallel to the increase in U.S. Food and Drug Administration–approved antiretroviral medications, there was a striking increase in the number of unique HAART regimens reported in the WIHS cohort since April 1996. There were 13 unique HAART regimens reported between April 1996 and September 1996. Zidovudine/lamivudine/indinavir was the most common regimen during this time, and it was reported by 25% of the women on HAART. In contrast, between April 2000 and September 2000, the number of unique HAART regimens reported by women in the WIHS had increased to 171. The most common regimen reported at this later time was stavudine/lamivudine/nelfinavir, which was reported by 11.1% of the women on HAART.

Marked changes also occurred in the components comprising the HAART regimens. The most common type of HAART regimen reported during the early months of HAART availability was one containing a PI and two or more NRTIs but no NNRTIs (92.9%). Over the course of this study, there was a substantial increase in the number of PI-sparing regimens. Of these non-PI regimens, there was a small but notable increase in the number of HAART regimens containing abacavir in combination with other NRTIs. Additionally, there was an increase in the number of regimens containing both a PI and an NNRTI (13.8% by September 2000). These regimens are most likely multidrug salvage regimens rather than the first line of therapy. This notion is supported by the fact that only 3.8% of the incident HAART regimens reported by September 2000 included both a PI and an NNRTI (data not shown).

Timing and Characteristics of Switching

Figure 3 displays the KM curves for evaluating differences in time on the first, second, and third HAART regimens. Of the 994 women initiating HAART, 754 women (75.9%) reported at least one change to their HAART regimen during the time of this study. The median time to switching or discontinuing an initial HAART regimen was 8 months (see Fig. 3A). One year after initiation, the percentage of women estimated to

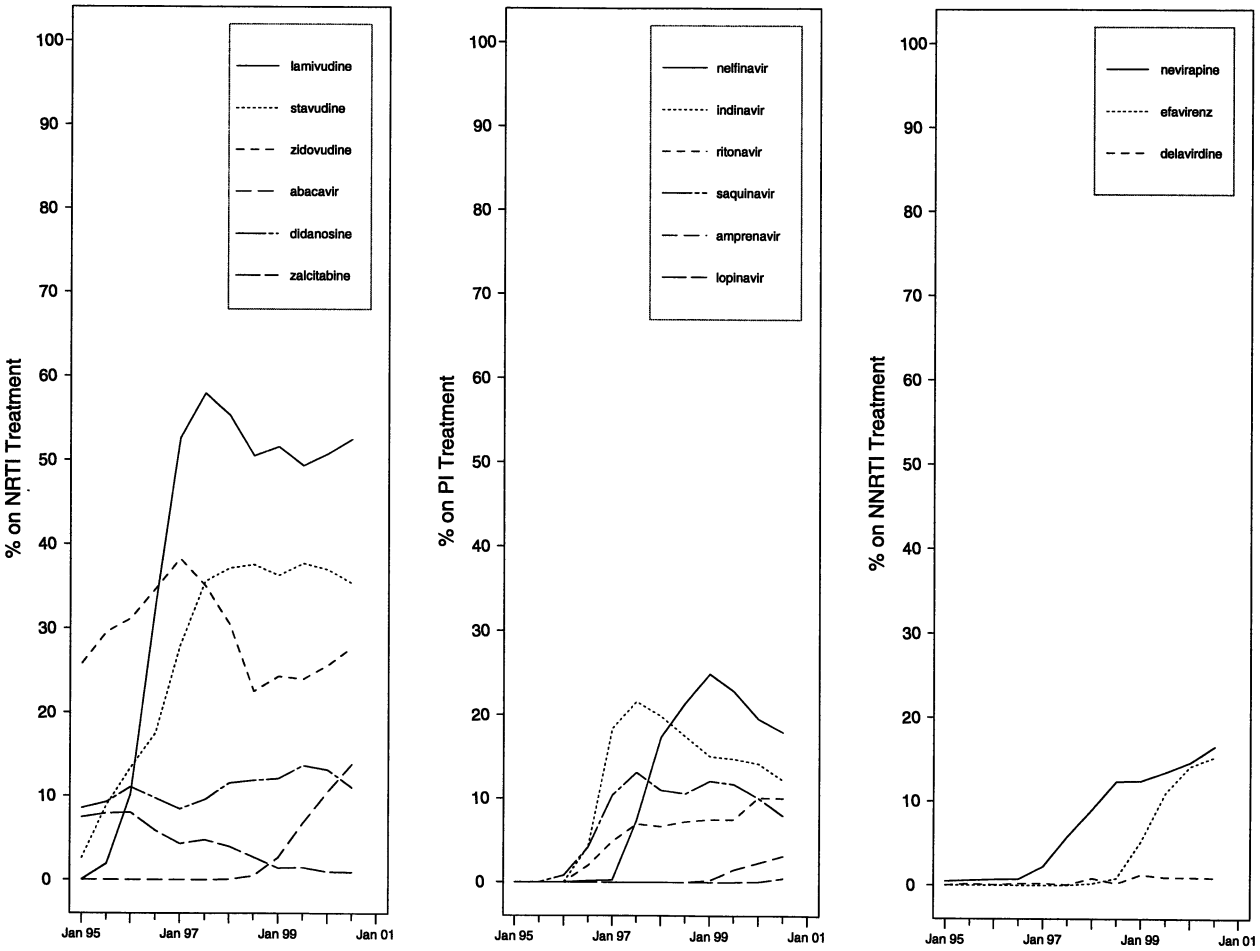

FIG. 1. Antiretroviral therapy trends among HIV-positive women enrolled in the Women's Interagency HIV Study. The proportion of women using each medication was plotted at the midpoint of the semiannual visit at which the medication was reported.

have switched their initial HAART regimen was 65% (95% confidence interval [CI]: 62%, 68%). This estimate did not differ from the percentage of women switching 1 year after starting their second HAART regimen (62%; CI: 58%, 66%) or from the percentage switching 1 year after starting their third HAART regimen (62%; CI: 55%, 67%).

Figure 3B shows the KM estimates for time to switch using the date of HAART initiation (i.e., date of first regimen) as the origin rather than the date of each new HAART regimen as in Figure 3A. Median time to first, second, and third HAART regimen switches from HAART initiation were estimated to be at 8, 26, and 36 months, respectively. Notably, time between the first and second HAART switches (18 months) was longer than time between the second and third HAART switches (10 months), despite the results from Figure 3A indicating that time on each HAART regimen was similar.

To evaluate factors associated with switching, we limited our analysis to time from HAART initiation to the first switch. Univariate models indicated that a $\log_{10}$ increase in pre-HAART viral load (relative risk [RR] = 1.15; CI: 1.08, 1.23), African-American ethnicity (RR = 1.12; CI: 1.01, 1.24), Hispanic ethnicity (RR = 1.24; CI: 1.11, 1.38), and having less than a high school education (RR = 1.20; CI: 1.03, 1.39) increased the risk of switching from an initial HAART regimen. The only variables that remained statistically significant in the multivariate model were pre-HAART $\log_{10}$ HIV RNA and ethnicity. In a reduced multivariate model, a $\log_{10}$ increase in pre-HAART viral load led to a 1.16 increase in the risk of switching an initial HAART regimen (CI: 1.09, 1.24). Hispanic (RR = 1.24; CI: 1.11, 1.40) and black patients (RR = 1.13; CI: 1.02, 1.26) were more likely than white patients to make a change in their initial HAART regimen.

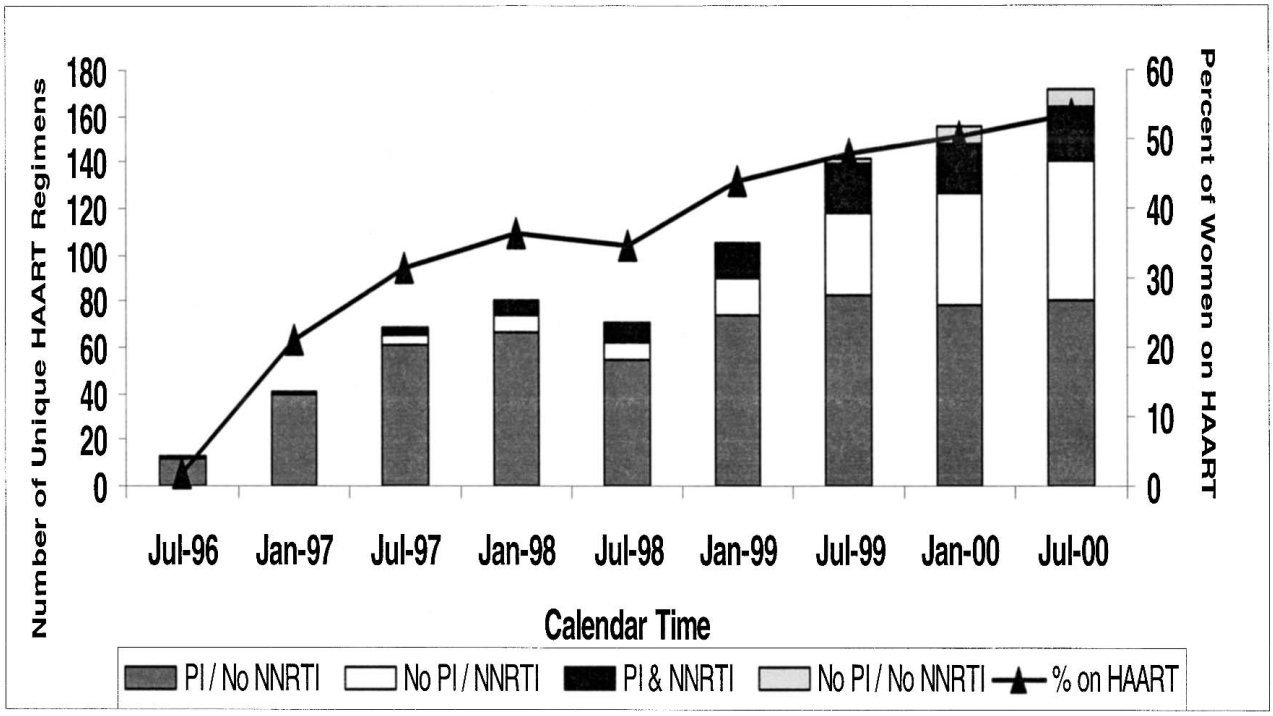

FIG. 2. Cumulative incidence of HIV-positive women reporting highly active antiretroviral therapy (HAART) (*solid line*) and the number of unique HAART regimens (*histograms*) stratified by regimen composition. Data were plotted at the midpoint of the semiannual visit at which the regimen was reported.

The results from our time to first HAART regimen switch model (i.e., the model censoring women who remained on a stable HAART regimen, switched to a less intensive regimen, or discontinued) had interesting differences from the previously discussed model. Increasing pre-HAART viral load remained predictive of shorter time to first switch (RR = 1.16; CI: 1.04, 1.28). In contrast to the previous model, ethnicity was not a significant factor in the time to first HAART regimen switch model. Drug and alcohol use, which was not significant in the previous model, was associated with an increased time to first HAART regimen switch (RR = 0.75; CI: 0.57, 0.98).

The mean $CD4^+$ lymphocyte count and proportion of women with HIV RNA less than 400 copies/mL of those women who switched their HAART regimen at a subsequent visit compared with those who did not switch is shown in Figure 4. During each semiannual period, participants who switched their regimen in the next period had lower mean $CD4^+$ cell counts compared with participants who remained on a stable HAART regimen in the next period. The difference in mean $CD4^+$ cell counts increased over time between switchers and nonswitchers and was significantly different ($p < .05$) beginning in July 1997. Furthermore, women who switched were more likely to have a level of HIV RNA greater than 400 copies/mL compared with women who did not switch ($p < .05$ for all time periods).

Longitudinal Patterns of HAART Switching

Figure 5 illustrates the longitudinal trends in the proportion of women who make a change to their HAART regimen, switch to a less intense regimen, or discontinue antiretroviral therapy altogether. Of the 944 women contributing consecutive study visits, 33 reported using HAART between April 1996 and September 1997. Of those 33 women, 17 (51.5%) remained on HAART but reported a modified regimen, 2 (6.1%) reported a less intense regimen, and 2 (6.1%) reported no antiretroviral therapy between October 1996 and March 1997. The remaining women (12 women [36.4%]) reported the same HAART regimen between October 1996 and March 1997. Between April 1997 and September 1997, when a larger number of women had initiated HAART, 45.6% switched their HAART regimen, and 18% reported discontinuing HAART (13% switched to a less intense regimen, 5% discontinued antiretroviral therapy). Three years later, in September 2000, the percentage of women switching their HAART regimen had

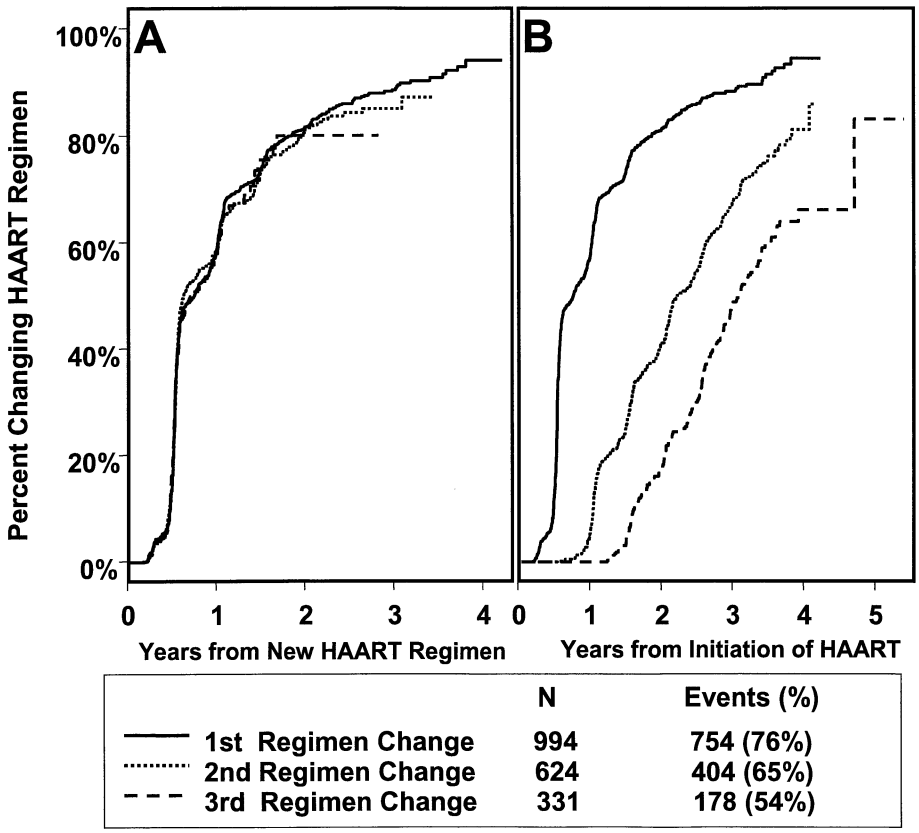

FIG. 3. Kaplan-Meier estimates for time to first, second, and third highly active antiretroviral therapy (HAART) switches. **(A)** Time relative to initiation of the respective HAART regimen is depicted. **(B)** Time relative to first HAART regimen is depicted.

decreased considerably to 36.7% (21.4% switching their HAART regimen, 3.9% switching to a less intense regimen, 11.4% discontinuing therapy). Importantly, the percentage of women discontinuing therapy altogether increased 2.3-fold, from 5% to 11.4%.

DISCUSSION

Previous analyses of the patterns of antiretroviral therapy use have focused mainly on predictors of initiation to (23,24), response to (25–29), or discontinuation of

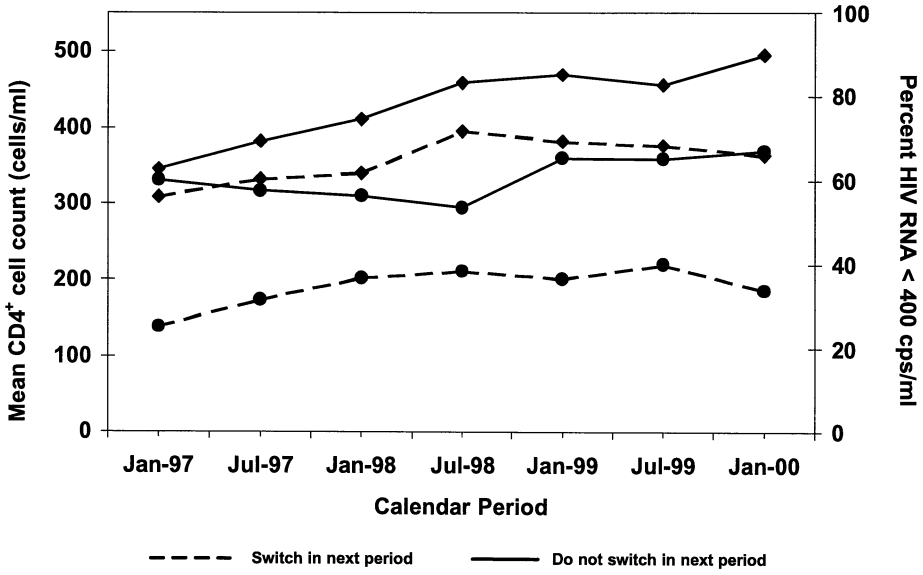

FIG. 4. Longitudinal trends in mean $CD4^+$ lymphocyte counts (left axis, ♦) and the proportion of women with HIV RNA levels less than 400 copies/mL (right axis, ●) among women who switch between consecutive visits (*solid lines*) compared with those who remain on the same HAART regimen (*dashed lines*).

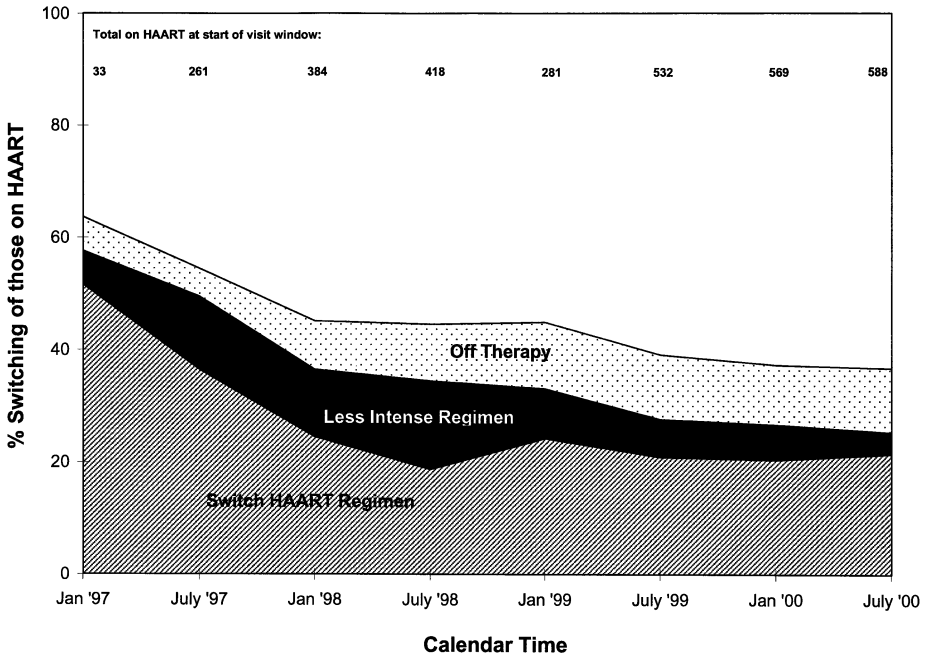

FIG. 5. Longitudinal trends in the proportion of women on highly active antiretroviral therapy (HAART) who make a switch in their HAART regimen (*hatched area*), switch to a less intense regimen (*black area*), or discontinue therapy altogether (*dotted area*). Proportions are plotted relative to the calendar time of the visit at which the switch was reported.

HAART (11–13). However, the extent to which individuals switch their antiretroviral regimens and the characteristics of those who switch have not been investigated in large population-based studies of women and minorities. Both the International AIDS Society–U.S.A. Panel (21) and DHHS/Kaiser (22) treatment guidelines caution against prematurely switching an individual's antiretroviral regimen because of the limitations placed on future treatment alternatives. The implications of regimen switches can be highly significant on the clinical level, because exposure to the limited number of antiretroviral medications available can diminish the efficacy of related drugs in future therapeutic regimens.

It is important to quantify the frequency of switching specific regimens while remaining continuously on HAART, because this provides a rough estimate of the rate at which HAART regimens are failing or not tolerated. This use of switching remains an important marker of unsuccessful therapies whether they are unsuccessful because of their inability to control the virus or because of their intolerable obtrusiveness in a patient's life. In this article, we have not focused on reasons for switching or on the consequences of switching—this is the subject of ongoing investigation. Instead, we have documented the amount and type of switching that is occurring in the WIHS and have given an epidemiologic characterization of those who are switching. We describe for the first time the complexity associated with the 13-fold increase in regimen combinations over 3 years. This complexity is likely to increase as new drugs are approved within the already existing antiretroviral classes and within new classes. With more drugs and more drug classes in development, it is crucial to be able to summarize in a meaningful way a patient's antiretroviral therapy history as well as population-level antiretroviral therapy use.

The individual components comprising HAART have changed significantly across time. Although regimens consisting of a PI and two or more NNRTIs were common in the WIHS in 1996, the use of NNRTI regimens and triple NRTI regimens has increased. This temporal change in therapy patterns largely reflects the approach that clinicians now take in an attempt to prescribe easier regimens with lower pill burdens as well as to preserve future regimen options. Despite the rapid introduction of new medications over the past several years, we have shown that time spent on a first, second, or third regimen is unchanged.

We estimated the degree of switching by calendar time and showed that the percentage of women reporting a change in their HAART regimen decreased between early 1997 and mid-1999, when 21% reported a modification in their HAART regimen, 4% switched to a less intense regimen, and 11% discontinued therapy altogether. Our estimates of the degree of regimen switching are likely to be conservative, because multiple regimen changes may have occurred during the 6-month interval between WIHS visits, which would be labeled as a single regimen change in our analyses.

Lastly, in the WIHS cohort, we found that women switching or discontinuing their HAART regimen were

more likely to have advanced HIV disease—as defined by lower $CD4^+$ cell counts and higher levels of HIV RNA—than women who reported an unchanged HAART regimen. Our findings complement those of others (12,13) showing that higher HIV RNA levels predict switching and HAART discontinuation. One limitation of our study is the fact that medication use and switching are entirely self-reported in the WIHS. The use of semiannual self-reported therapy data required that we estimate the timing of therapy initiation and switching. The study only began collecting start and stop dates of therapy use beginning in October 1998.

In conclusion, our findings on the relatively high rate of antiretroviral regimen switching emphasize the complexity of managing and evaluating these therapies. Clinicians must cope with limits on the number of therapeutic options, a fact largely the result of potential cross-resistance among drugs of a single class. The occurrence of side effects, patient nonadherence, and virologic failure may result in more frequent regimen switching, but this needs future study. As HIV infection becomes more of a chronic disease, it is increasingly important to take a long-term strategic approach to both initial and subsequent decisions regarding antiretroviral therapy. In general, clinical trials cannot examine switching, because change in regimen is often an end point. Prospective follow-up of the women enrolled in the WIHS, in addition to cohorts of men and injection drug users, should be invaluable for quantifying the dynamics in the use of antiretroviral therapy over time. Furthermore, these observational studies have a key role in evaluating optimal switching strategies and the long-term effects of switching in a setting complementary to clinical trials (30).

Acknowledgments: The authors thank the WIHS participants for their dedication. Data used in this study were collected by the WIHS Collaborative Study Group with centers (Principal Investigators) at the New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington DC Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); and Data Coordinating Center (Alvaro Muñoz, Stephen J. Gange).

The WIHS is funded by the National Institute of Allergy and Infectious Diseases, with supplemental funding from the National Cancer Institute, the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Dental and Craniofacial Research, the Agency for Health Care Policy and Research, the National Center for Research Resources, and the Centers for Disease Control and Prevention (U01-AI-35004, U01-AI-31834, U01-AI-34994, U01-AI-34989, U01-HD-32632, U01-AI-34993, U01-AI-42590, M01-RR00079, and M01-RR00083).

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