

# Alternation of Antiretroviral Drug Regimens for HIV Infection

## A Randomized, Controlled Trial

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**Background:** Mathematical modeling has suggested that alternating antiretroviral regimens while patients' viral load remains suppressed would minimize HIV resistance mutations.

**Objective:** To compare alternation of antiretroviral regimens with the current standard of switching regimens after viral load rebound.

**Design:** Randomized, multicenter, open-label, pilot trial.

**Setting:** 15 outpatient HIV clinics in Spain and Argentina.

**Patients:** 161 HIV-1–infected, antiretroviral-naive persons.

**Intervention:** Patients were assigned to continuously receive stavudine, didanosine, and efavirenz (standard of care, regimen A) or zidovudine, lamivudine, and nelfinavir (standard of care, regimen B) until virologic failure, or to alternate between those two regimens every 3 months while viral load was suppressed (regimen C).

**Measurements:** Time to virologic failure, percentage of patients with undetectable plasma viremia over 48 weeks, CD4 and CD8 cell counts, adverse events, emergence of drug resistance, drug adherence, and quality of life.

**Results:** Patients receiving standard-of-care regimens A and B did not differ. Virologic failure over 48 weeks was delayed in the alternating therapy group compared with the pooled standard-of-care group (incidence rate, 1.2 events/1000 person-weeks [95% CI, 0.3 to 3.6 events/1000 person-weeks] vs. 4.8 events/1000 person-weeks [CI, 2.9 to 7.4 events/1000 person-weeks];  $P = 0.01$ ). Genotypic drug resistance emerged in 79% of patients in the standard-of-care group who experienced on-therapy treatment failure. Patients in the standard-of-care and alternating therapy groups had similar CD4 cell counts, frequency of adverse events, reported drug adherence, and quality of life.

**Conclusions:** Virologic outcome was better with alternating therapy than with the current standard of care, while adverse events and adherence were similar. The strategy of alternating therapy merits further investigation.

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See editorial comment on pp 148-149.

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The use of triple-drug antiretroviral therapies for HIV-1 infection can markedly reduce viral load and slow clinical progression (1–4). The goals of therapy are maximal, durable suppression of viral load; restoration or preservation of immunologic function; improved quality of life; and reduced HIV-related morbidity and mortality (5). Although as many as 70% to 90% of antiretroviral drug-naive patients achieve maximal viral load suppression in clinical trials, results can vary and may be less favorable in practice settings (6). Therapy fails because of complex interactions among several factors, including incomplete adherence, inadequate anti-HIV activity or drug exposure, and viral resistance. In standard care, an antiretroviral drug regimen is changed only after it fails. This allows viral replication under the selection pressure of the failing regimen, potentially for prolonged periods, regardless of how failure was initiated.

New treatment strategies are being studied to maximize and prolong benefits of current drugs, and improved therapies are under development. Simultaneous use of four or more antiretroviral drugs has been explored (7), but this method may cause greater toxicity and has not yet proved better than standard three-drug regimens (8). Two-drug maintenance regimens following triple-drug induction therapy have not yet been successful (9, 10). In addition,

repeated supervised interruptions of antiretroviral treatment, which are intended to bolster immune control of HIV-1, have not yet achieved that goal in most persons with chronic HIV infection (11–15).

Analyses of the optimum time to change drug therapy have suggested another strategy (16). Mathematical modeling has been used to evaluate laboratory monitoring methods as triggers for a regimen change. Simulations have indicated that proactively switching regimens while patients' viral load remains suppressed could more effectively shorten the period of virus replication under the selection pressure of a failing regimen and decrease accumulation of resistance mutations compared with changing the regimen after viral load rebound is detected or resistance emerges. This method would also theoretically allow repeated use of drugs ("recycling," or drug regimen alternation) and a shorter continuous period of exposure to the same drugs, which may diminish cumulative long-term toxicity. However, changing well-tolerated, successful drugs may increase risk for poor tolerability of and adherence to the next regimen. Our trial, SWATCH (SWitching Antiviral Therapy Combination against HIV-1), was designed to compare proactively alternating two triple-drug regimens every 3 months with continuous administration of either of the same regimens until viral load rebound.

**Context**

Although combination antiretroviral therapy slows the clinical progression of HIV-1 infection, drug resistance remains a vexing problem. Some have speculated that alternating between drug regimens on a fixed schedule might forestall drug failure.

**Contribution**

This pilot study randomly assigned patients to receive one of two triple-drug regimens (stavudine, didanosine, and efavirenz or zidovudine, lamivudine, and nelfinavir) or to alternate between the two regimens every 3 months. Alternating the regimens delayed virologic failure.

**Implications**

Alternating antiretroviral drug regimens may be a promising strategy for delaying failure of therapy for HIV-1 infection. However, this study was small, and improved antiretroviral regimens have become available since the investigators conducted this study.

—The Editors

**METHODS****Study Participants**

This randomized, multicenter, open-label trial compared two strategies for switching antiretroviral drug regimens among HIV-infected patients beginning antiretroviral treatment. Study participants were recruited from 15 hospital-based outpatient HIV clinics in Spain and Argentina (Appendix, available at [www.annals.org](http://www.annals.org)). Institutional review boards at all participating hospitals approved the study, and all eligible patients who presented to the clinics for initial treatment were asked to participate.

The inclusion criteria were age of at least 18 years, no previous antiretroviral therapy, and a baseline plasma HIV-1 RNA level of more than 400 copies/mL within 4 weeks before randomization. CD4 cell count was not an entry criterion. Women were required to have a negative result on a urine pregnancy test within 72 hours before the start of therapy with the study medication. Prophylaxis against *Pneumocystis carinii* was permitted in patients with CD4 cells counts of less than  $0.200 \text{ cells} \times 10^9 \text{ cells/L}$  or a previous event.

**Interventions**

Patients were randomly assigned to one of two strategies for switching antiretroviral regimens: the standard-of-care approach, involving a switch triggered by viral load rebound, or alternation of regimens every 3 months while viral load remained suppressed. Two groups of patients who received different initial regimens were treated with the standard-of-care approach. Regimen A consisted of 400 mg of didanosine once daily (1 hour before or 2 hours after eating), 40 mg of stavudine every 12 hours (30 mg for patients weighing <60 kg), and 600 mg of efavirenz once daily. Regimen B consisted of 300 mg of zidovudine every

12 hours, 150 mg of lamivudine every 12 hours, and 1250 mg of nelfinavir every 12 hours with a meal or light snack. Regimens A and B were each continued until viral load rebounded. Patients who received the alternating regimen (regimen C) alternated between regimens A and B every 3 months, beginning with regimen A. Each regimen was used twice in the alternating therapy group. Use of efavirenz in this group was extended 1 extra week after patients switched to regimen B, and use of nelfinavir was extended 1 extra week after patients switched back to regimen A. The rationale was to maintain antiviral effect during regimen changes until the new drugs reached steady-state levels in the blood. Patients were assessed at enrollment and at weeks 12, 24, 36, and 48.

**Objectives**

We wanted to determine whether alternation of two antiretroviral regimens prolonged time to virologic failure of initial treatment compared with the standard-of-care approach. We also tested whether regimen alternation differed from standard of care in adverse events, treatment discontinuations, resistance at time of virologic failure, CD4 cell counts, adherence, perceived effort of therapy, and quality of life. Another aim was to assess whether virologic failure differed when patients began therapy with one rather than the other of the two regimens given using the standard-of-care approach.

**Outcome Measures**

The primary outcome measure was time to virologic failure, defined as the first plasma HIV-1 RNA level of 400 copies/mL or greater between weeks 24 and 48 after viral load had decreased to less than 400 copies/mL by week 24. Secondary outcome measures included the percentage of patients in whom viral load was suppressed to undetectable levels over 48 weeks of treatment, using a viral load cutoff of 400 copies/mL or 50 copies/mL. Other secondary outcome measures included time to treatment discontinuation due to all causes, due to causes other than virologic failure, and due to adverse events.

Levels of HIV-1 RNA were assessed at each center by using the Amplicor HIV-1 Monitor test (Roche Diagnostics, Indianapolis, Indiana). A level of 400 copies/mL or greater triggered confirmatory testing of a second aliquot of plasma from the same time point. The Amplicor HIV-1 Monitor UltraSensitive test (Roche Diagnostics) was used retrospectively to also detect as few as 50 copies/mL.

Absolute counts of CD4 and CD8 cells, as assessed by flow cytometry at 48 weeks, and changes in cell counts between weeks 12 and 48 were also secondary outcome measures. Results of resistance tests performed at virologic failure were compared across groups. Resistance genotyping (Viro-Seq, Applied Biosystems, Barcelona, Spain) was performed on all failure specimens and matching baseline specimens to identify amino acid differences in HIV-1 *pol* from the reference wild-type sequence, NL4-3. Phenotypic resistance testing with a recombinant virus assay (Antiviro-

gram, Virco, Mechelen, Belgium) determined 50% inhibitory concentrations (17, 18).

We assessed adverse events (signs, symptoms, or laboratory abnormalities) that were defined as severe according to World Health Organization guidelines and required discontinuation of treatment. Adherence was self-reported, as described elsewhere (19), and appropriate adherence was defined as consumption of at least 95% of the medication prescribed (20). The perceived effort required to follow study treatment properly was assessed with a 100-mm visual analogue scale effort index (19, 21), ranging from 0 (no effort) to 10 (maximum effort). For self-assessment of quality of life over the 4 weeks preceding each visit, a 5-point scale adapted from the Medical Outcomes Study–HIV questionnaire was used (22). Compared with the previous visit, a score of 1 reflected the greatest reduction in quality of life, a score of 3 indicated no change, and a score of 5 indicated the best possible improvement. A score of 3 was used as the arbitrary baseline value.

All patients taking each of the three study regimens received the same supportive instruction at each visit. Patients who discontinued using study medications or withdrew from the protocol for any reason were followed, if possible, for adverse events, clinical outcome, and all protocol testing. The protocol recommended that patients who had viral load rebound or adverse effects while receiving regimen A should be offered regimen B after leaving the study, and vice versa. For patients who had treatment failure with the alternating regimen (regimen C), we provided results of the drug resistance tests to their physicians to assist them in selecting the next treatment.

### Sample Size

We estimated that a sample size of 162 (54 patients for each regimen) would allow 85% power at a two-sided significance level of 5%. This estimate was based on comparison of expected failure rates of 45% versus 15% between two groups (standard-of-care regimen A or B vs. alternating regimen C) and an anticipated loss to follow-up of 10%.

### Randomization

After giving informed consent, patients were randomly assigned to receive one of the three regimens. Randomization was performed by using computer-generated random numbers stratified by study center to balance distribution of centers across treatment groups. Administrative personnel, who were blinded to trial design, conduct, and evaluation, provided treatment assignment.

### Blinding

Neither patients nor investigators were blinded to regimen assignment because of the prohibitive cost of placebo medications and the diminished generalizability likely to result from the greater adherence challenge of multiple placebos. Measurements of outcome were objective, were not performed by the study clinicians, and were analyzed by separate investigators who did not interact with the patients.

### Statistical Analysis

Patients' characteristics at baseline were compared across the three treatment regimens by using the Kruskal–Wallis test (for non-Gaussian continuous variables) or one-way analysis of variance (for Gaussian variables). The chi-square test or the Fisher exact test was used to compare proportions of dichotomous variables across groups. We planned to first compare virologic failure for regimen A versus regimen B to exclude a difference based on initial regimen. Pooling of regimens A and B as the standard-of-care group was planned only if patients receiving the two regimens did not differ. Time to treatment failure, treatment discontinuation, and adverse events were compared by using the exact log-rank test, and cumulative probability of events was presented by using the Kaplan–Meier method. Overall incidence rates of events were determined with Clopper–Pearson exact 95% CIs. Intention-to-treat analyses of time to virologic failure (the primary outcome measure) counted all viral load increases to 400 copies/mL or more between weeks 24 and 48 as failure, regardless of whether they occurred while the patient was receiving study-assigned therapy. On-treatment analyses censored patients at time of treatment discontinuation for reasons other than virologic failure.

Cochran–Mantel–Haenszel tests were used to compare proportions of patients who continued to receive study treatment at each visit over 48 weeks and had suppression of plasma HIV-1 RNA levels to less than 400 copies/mL or less than 50 copies/mL. Changes in CD4 and CD8 cell counts were assessed by using mixed models (23), and self-reported adherence was analyzed by using chi-square tests. Effort index and quality of life were compared at each time point by using the Mann–Whitney U test; changes in these scores between 24 and 48 weeks were analyzed within each group by using the Wilcoxon signed-rank test. Statistical analyses were performed by using SPSS, version 10 (SPSS, Inc., Chicago, Illinois), or SAS, version 8.02 (SAS Institute, Inc., Cary, North Carolina), with two-tailed significance levels of 5%.

### Role of the Funding Sources

The authors had complete control over data collection and analysis. The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

### RESULTS

One hundred sixty-one treatment-naive HIV-infected patients were enrolled in the study between June 1999 and April 2000. Patients receiving each regimen did not differ significantly in age, sex, AIDS status, plasma viremia, or CD4 and CD8 cell counts (Table 1). Approximately one fourth of the patients enrolled had baseline HIV RNA levels greater than 100 000 copies/mL, and one fourth had CD4 cell counts less than  $0.200 \times 10^9$  cells/L. The pattern of missing visits did not differ across study groups. Eight

**Table 1. Baseline Characteristics of the Study Patients\***

Characteristic	Regimen A	Regimen B	Regimen C
Patients, <i>n</i>	52	54	55
Sex, %			
Male	86	70	79
Female	14	30	21
Mean age ± SD, y	36 ± 8	39 ± 6	34 ± 8
Infection route, %			
Heterosexual exposure	29	22	33
Male homosexual risk	17	24	20
Intravenous drug use	38	41	35
Unknown	15	13	13
AIDS, <i>n</i>	7	7	8
Plasma viral load, log <sub>10</sub> HIV-1 RNA copies/mL			
Median	4.5	4.8	4.7
Interquartile range	4.1–5.0	4.2–5.0	4.3–5.2
Range	3.1–5.8	3.5–6.2	3.2–5.9
CD4 cell count, ×10 <sup>9</sup> cells/L			
Median	0.329	0.360	0.316
Interquartile range	0.220–0.444	0.137–0.515	0.151–0.503
Range	0.005–1.045	0.016–1.211	0.007–1.711
CD8 cell count, ×10 <sup>9</sup> cells/L			
Median	0.863	0.910	0.828
Interquartile range	0.659–1.32	0.686–1.473	0.588–1.218
Range	0.380–2.421	0.099–3.104	0.245–5.146

\* Regimen A = efavirenz, stavudine, and didanosine; regimen B = nelfinavir, zidovudine, and lamivudine; regimen C = alternating regimens. No significant difference was observed across the groups for the factors listed.

patients were excluded from time-to-event analyses because a viral load decrease to less than 400 copies/mL by week 24 was not documented. Of these 8 patients, 2 had been assigned to regimen A, 5 had been assigned to regimen B, and 1 had been assigned to regimen C.

**Table 2. Time-to-Event Analyses\***

Regimen	Description	Patients in Analysis	Virologic Failure in Intention-To-Treat Analysis	Virologic Failure in On-Treatment Analysis	Adverse Events†	Premature Discontinuation for All Causes Other Than Virologic Failure
A	Continuous therapy with efavirenz, stavudine, and didanosine	50	10 (20)	8 (16)	5 (10)‡	11 (22)
B	Continuous therapy with nelfinavir, zidovudine, and lamivudine	49	10 (20)	7 (14)	7 (14)§	10 (20)
<i>P</i> value for A vs. B			>0.2	>0.2	>0.2	>0.2
A + B	Standard-of-care group	99	20 (20)	15 (15)	11 (11)	21 (21)
C	Alternating therapy group (proactively switching regimens A and B)	54	3 (6)	0 (0)	9 (17)	16 (30)
<i>P</i> value for A + B vs. C			0.014	0.002	>0.2	>0.2
Total		153	23 (15)	15 (10)	20 (13)	45 (29)

\* Discontinuations are during the first 48 weeks of therapy. Exact log-rank tests were used for analyses, including *P* values. For intention-to-treat analysis of time to virologic failure, patients were censored only after the final follow-up visit. For on-treatment analysis of time to virologic failure, patients were also censored after study treatment discontinuation for reasons other than virologic failure as well as after final follow-up visit. Patients were censored at virologic failure for time to premature discontinuation analysis and were censored at both virologic failure and the last follow-up visit for time to adverse event analysis.

† Treatment changed because of adverse event, not virologic failure.

‡ Peripheral neuropathy (*n* = 3), anemia (*n* = 1), hepatitis (*n* = 1).

§ Anemia (*n* = 3), diarrhea (*n* = 3), rash (*n* = 1).

|| Diarrhea (*n* = 3), central nervous system symptoms (*n* = 2), hepatitis (*n* = 2), anemia (*n* = 1), rash (*n* = 1).

**Measures of Efficacy**

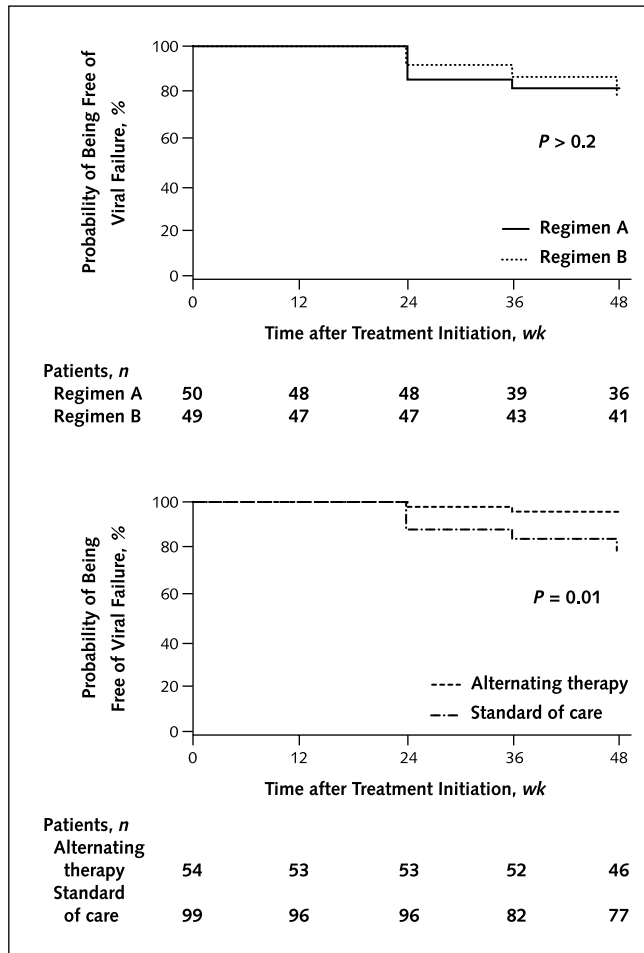
**Comparison between Regimens A and B**

No difference in primary or secondary end points was observed between patients receiving regimens A and B. Distribution of time to virologic failure was similar between both regimens over 12 months in intention-to-treat analyses (Table 2 and Figure 1, top) and on-treatment analyses (Table 2). Incidence rates in the intention-to-treat analyses were 4.9 events/1000 person-weeks (95% CI, 2.3 to 9 events/1000 person-weeks) for regimen A and 4.7 events/1000 person-weeks (CI, 2.2 to 8.6 events/1000 person-weeks) for regimen B. Time to premature treatment discontinuation due to adverse events or causes other than virologic failure did not differ (Table 2). Over 48 weeks, regimens A and B did not differ in the proportion of patients with viral load less than 400 copies/mL (odds ratio, 1.01 [CI, 0.9 to 1.2]; *P* > 0.2) (Figure 2, top) or less than 50 copies/mL (odds ratio, 1.04 [CI, 0.9 to 1.2]; *P* > 0.2). CD4 cell counts increased from baseline over 48 weeks by 2.3 cells per week (CI, 0.8 to 3.9; *P* = 0.003); this increase did not differ between regimens A and B. Marginal decreases in CD8 cell counts were observed over 48 weeks (2.7 cells/wk [CI, -0.24 to 5.61 cells/wk]; *P* = 0.07), but patients receiving regimens A and B did not differ. Therefore, regimens A and B were pooled as the standard-of-care group to be compared with regimen C, the alternating therapy group.

**Comparisons between Standard of Care and Alternating Therapy**

Virologic failure of initial study-assigned therapy was significantly delayed in the alternating therapy group compared with the standard-of-care group. The incidence rate

Figure 1. Kaplan–Meier plots.



Top. Time to first plasma HIV-1 RNA level above 400 copies/mL in the standard-of-care group during the first 48 weeks. Bottom. Time to first plasma HIV-1 RNA level above 400 copies/mL in the alternating therapy group compared with the standard-of-care group during the first 48 weeks.

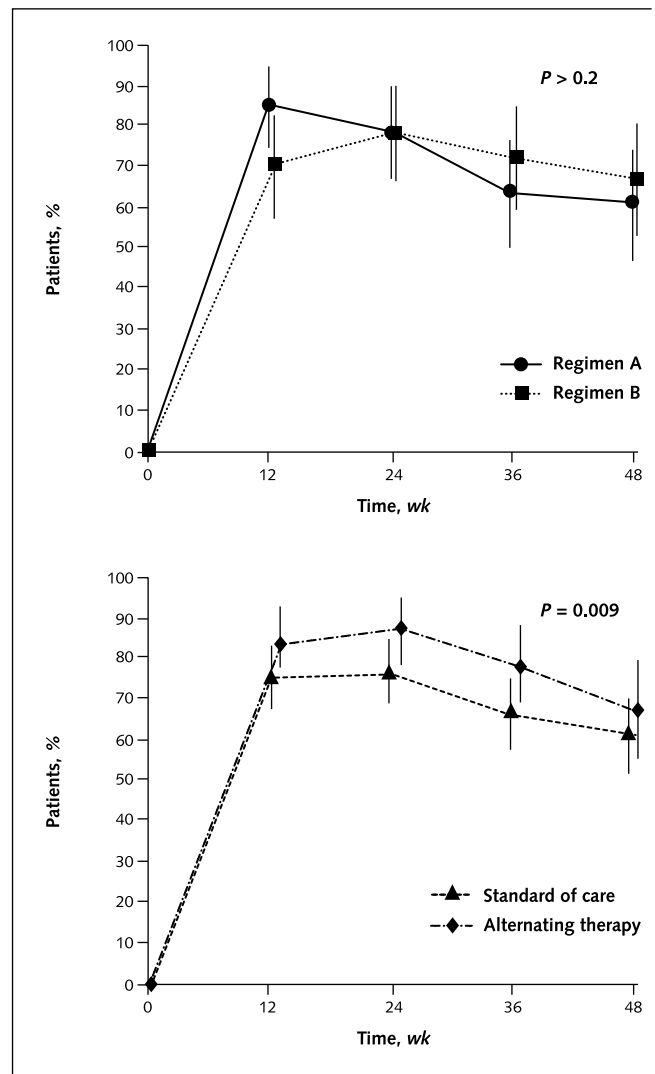
was 1.2 events/1000 person-weeks (CI, 0.3 to 3.6 events/1000 person-weeks) for the former and 4.8 events/1000 person-weeks (CI, 2.9 to 7.4 events/1000 person-weeks) for the latter (Table 2 and Figure 1, bottom). In the intention-to-treat analysis, virologic failure occurred in three patients in the alternating therapy group and 20 patients in the standard-of-care group (10 receiving regimen A and 10 receiving regimen B). On-treatment analysis also favored alternation: The incidence rate was 0 virologic failures/1000 person-weeks (CI, 0 to 1.5 virologic failures/1000 person-weeks) for the alternating therapy group and 3.7 virologic failures/1000 person-weeks (CI, 2 to 6 virologic failures/1000 person-weeks) for the standard-of-care group (Table 2).

Significantly more patients in the alternating therapy group than in the standard-of-care group had plasma HIV-1 RNA levels less than 400 copies/mL while receiving treatment. As shown in Figure 2, the odds ratio for a viral load less than 400 copies/mL over 48 weeks in the alter-

nating therapy group was 1.2 (CI, 1.1 to 1.4;  $P = 0.009$ ). A similar advantage for alternating therapy was also observed in the proportion of patients who achieved a viral load less than 50 copies/mL while receiving treatment (48 patients [87%] vs. 76 patients [72%] at week 24, 37 patients [67%] vs. 61 patients [58%] at week 48; odds ratio at week 48, 1.2 [CI, 1.0 to 1.3];  $P = 0.03$ ). Both the standard-of-care and alternating therapy groups had significant increases in absolute CD4 cell count (1.9 cells/wk [CI, 0.7 to 3.1 cells/wk];  $P = 0.002$ ) and decreases in absolute CD8 cell count over 48 weeks (2.7 cells/wk [CI, 0.3 to 5.0 cells/wk];  $P = 0.03$ ). The rates of increase in CD4 cell counts and decrease in CD8 cell counts were similar between groups (Figure 3).

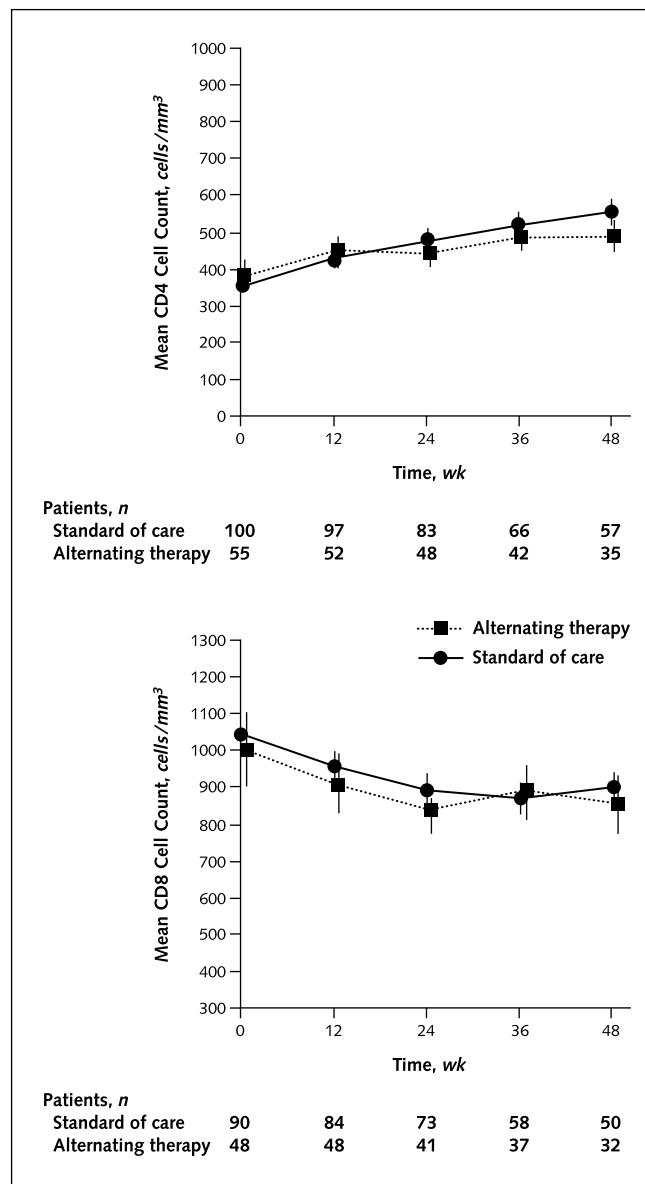
Treatment-limiting adverse events or laboratory ab-

Figure 2. Proportion of patients with plasma HIV-1 RNA levels less than 400 copies/mL during 48-week follow-up.



Top. Regimen A (efavirenz, didanosine, stavudine) versus regimen B (nelfinavir, zidovudine, lamivudine). Bottom. Alternating therapy group versus the standard-of-care group (regimens A and B combined). Error bars represent 95% CIs.

**Figure 3.** Change in mean CD4 cell counts (top) and mean CD8 cell counts (bottom) during 48-week follow-up in the alternating therapy group versus the standard-of-care group.



Error bars represent standard error. To convert CD4 and CD8 cell counts to  $\times 10^9$  cells/L, multiply by 0.001.

normalities occurred at similar frequencies in the alternating therapy and standard-of-care groups. Main side effects were rash and central nervous system symptoms in patients receiving the stavudine, didanosine, and efavirenz regimen and diarrhea and anemia in those receiving the zidovudine, lamivudine, and nelfinavir regimen. Among patients in the alternating therapy group, drug-related side effects that occurred at the beginning of a regimen generally did not recur, or were less severe, when the same regimen was reinitiated 24 weeks later. Time to premature treatment discontinuation due to adverse events did not differ between groups (incidence rate, 3.8 events/1000 person-

weeks [CI, 1.7 to 7.1 events/1000 person-weeks] for the alternation group and 2.7 events/1000 person-weeks [CI, 1.3 to 4.8 events/1000 person-weeks] for the standard-of-care group;  $P > 0.2$ ). As shown in Table 2, adverse events and unexplained loss to follow-up (all causes of discontinuation other than virologic failure) also did not differ (incidence rate of treatment discontinuation at 48 weeks, 6.7 events/1000 person-weeks [CI, 3.8 to 10.8 events/1000 person-weeks] for the alternating therapy group and 5.1 events/1000 person-weeks [CI, 3.2 to 7.8 events/1000 person-weeks] for the standard-of-care group;  $P > 0.2$ ).

### Drug Resistance

All 15 patients in the standard-of-care group who had viral load rebound while receiving study treatment had plasma samples collected at baseline and at the time of confirmed treatment failure. Results of baseline resistance tests were available for 14 patients. Only two viruses had resistance at baseline to a study drug to which they were exposed. One of these two viruses, and 10 of the other 12 evaluable viruses, evolved to be more drug resistant at treatment failure.

Seven of eight viruses in patients who had treatment failure with stavudine, didanosine, and efavirenz (regimen A) developed efavirenz-selected resistance mutations and high-level efavirenz resistance (Appendix Table 1, available at [www.annals.org](http://www.annals.org)). One of these viruses also developed RT L74V, which is associated with low-level didanosine resistance, although an increased 50% inhibitory concentration for didanosine was not measured. The eighth patient in this group (patient 052) experienced treatment failure without any detectable viral resistance (Appendix Table 1, available at [www.annals.org](http://www.annals.org)). In four of seven patients who had treatment failure with nelfinavir, zidovudine, and lamivudine (regimen B), the lamivudine-selected RT M184V resistant mutation with more than 30-fold reduction in lamivudine susceptibility emerged from a wild-type baseline population. Two of seven patients (patients 351 and 207) had no new detectable resistance (Appendix Table 2, available at [www.annals.org](http://www.annals.org)).

### Drug Adherence, Effort Index, and Quality of Life

Both groups maintained good adherence during follow-up. No significant differences were observed over time in either group, between groups, or among regimens (data not shown). The mean effort index ( $\pm$ SD) did not vary between patients in the alternating and standard-of-care groups who received the same therapy (at week 24,  $3.8 \pm 2.9$  vs.  $4.1 \pm 2.3$  [ $P > 0.2$ ]; at week 48,  $4.7 \pm 2.3$  vs.  $4.4 \pm 3.2$  [ $P > 0.2$ ]). The effort index did not increase significantly from baseline in either group. Self-reported quality of life increased slightly in all patients. In the standard-of-care group, mean quality-of-life score ( $\pm$ SD) was  $4.3 \pm 1.7$  at week 24 and  $4.7 \pm 1.9$  at week 48 ( $P < 0.001$ ). Patients in the alternating therapy group reported a mean quality-of-life score ( $\pm$ SD) of  $4.1 \pm 1.1$  at week 24 and  $4.5 \pm 1.5$  at week 48 ( $P < 0.001$ ). There was no sig-

nificant difference in quality-of-life scores between groups at any time point.

## DISCUSSION

Our results support the efficacy and safety of proactive switching and alternation of antiretroviral drug regimens, which differs from the current standard practice of changing drug therapy only after viral load rebound. Earlier analyses predicted that this new approach would minimize emergence of drug-resistant virus better than frequent monitoring for viral load rebound or drug-resistant virus (16). In our pilot trial, compared with the standard-of-care group, virologic failure was significantly delayed in the group that alternated antiretroviral regimens while viral load was suppressed.

The primary (intention-to-treat) and secondary (on-treatment) analyses of time to virologic failure, as well as comparison of the proportion of patients who continued to receive study treatment and achieved a viral load less than 400 copies/mL or less than 50 copies/mL, support the virologic advantage of the alternating regimen strategy. CD4 and CD8 cell count responses did not differ significantly between groups. Of importance, premature discontinuation of therapy for causes other than virologic failure (adverse events and loss to follow-up), measures of adherence, and quality-of-life scores were not worse among patients in the alternating therapy group. During standard-of-care failure, a single new resistance mutation emerged in 5 patients and many new resistance mutations were detected early in the plasma HIV RNA of 6 of 15 patients (**Appendix Tables 1 and 2**, available at [www.annals.org](http://www.annals.org)). These findings are consistent with the hypothesis that more resistance mutations accumulate during standard care than during alternating therapy. Moreover, the similar virologic effectiveness of regimens A and B during standard care indicated that initiation of therapy with regimen A was not responsible for the decreased virologic failures in the alternating therapy group. The similarity of regimens A and B in our study is supported by results of a larger randomized trial (24). That and other recent studies have found response rates for initial triple-drug combination regimens that are similar to those reported here and better than those expected when our study was designed (8, 24, 25).

Although other trials have used a definition of virologic failure that requires confirmation of an increased viral load on two consecutive visits, our definition required viral load to rise above 400 copies/mL on only a single visit, ensuring early switching in the standard-of-care group. However, the difference between the standard-of-care and alternating strategies was not due to our definition of failure. For example, 14 of 15 patients who had on-treatment failure in the standard-of-care group had viral loads above 400 copies/mL on subsequent visits after meeting the failure criterion. We did not apply criteria for virologic failure until 6 months after therapy started, both to allow ade-

quate time for a response and because the alternating therapy group first switched therapy at month 3 and continued that regimen until month 6. Patients with earlier virologic failure, as well as nonresponders, were excluded from analyses; their inclusion, however, would have further strengthened the observed advantage of treatment alternation. Analyses of time to failure that included all available follow-up (beyond 48 weeks) also supported the advantage of alternating therapy (data not shown).

We chose 12 weeks as the time for a proactive switch because visits and new prescriptions commonly occur every 12 weeks. This differs from the timing of 1 to 2 years suggested in earlier modeling (16) and increased the likelihood that a treatment switch would precede emergence of an undetected mutant subpopulation that might preclude successful regimen “recycling.” To maximize antiviral effect while newly started drugs reached steady-state blood levels, we continued a drug from the earlier regimen (either efavirenz or nelfinavir) for the first week after each proactive switch. Given other recent reports (8), it seems unlikely that use of four drugs for 1 week every 3 months accounted for the observed better responses in the alternating therapy group.

Only 0.6% of clinic visits were missed before assigned therapy was discontinued. The patterns of missing visits (data not shown) and measures of adherence did not differ significantly across the three regimens, suggesting that the lack of clinician blinding did not introduce bias. However, the lack of placebo controls, as well as the small sample size and limited geographic locations of study sites, suggests that clinicians should use caution before generalizing our results. In addition, our formal follow-up was short, given the increasing duration of response to antiretroviral regimens. These limitations suggest that larger trials of this novel strategy should be done before standard practice is changed. Moreover, the hypothesis that viral resistance occurs less frequently with alternating regimens (16) remains to be proven.

Previous studies have assessed the benefits of alternating antiretroviral regimens (26–29), but none examined highly active antiretroviral therapy. In addition, none changed regimens while viral load remained suppressed. Each of the previously tested alternating regimens would therefore have been likely to select resistant mutations. Nevertheless, previous studies of alternating therapy demonstrated a reduction in emergence of resistance compared with continuous monotherapy (27, 29). Fixed cycles of different drugs with nonoverlapping toxicity profiles and resistance patterns are also used in chemotherapy for cancer (30).

It is clear that strict adherence to highly active antiretroviral therapy is of paramount importance for long-term viral suppression (31–33). However, the percentage of our patients who reported taking fewer than 95% of prescribed pills was low and was consistent with previous studies (19, 21). Moreover, adherence was not worse in the alternating therapy group ( $P > 0.2$ ). The alternation of two triple-

drug combination regimens every 3 months did not significantly impair self-reported perceived effort or quality of life.

In summary, proactive switching and alternation of antiretroviral regimens with drugs that have different resistance profiles might extend the overall long-term effectiveness of first- and second-line treatment options without adversely affecting patients' adherence or quality of life. Further analyses of resistance are needed to critically test the hypothesis that the alternation approach better limits emergence of resistance and cross-resistance. The potential for this approach to reduce overall drug toxicity by providing rest periods from each combination of drugs is also being studied. Additional larger trials appear warranted and are needed before regimen alternation can be advocated in routine clinical practice. Future studies should compare the resistance patterns selected after failure of two sequential standard-of-care regimens versus failure of the same set of drugs used with an alternating therapy strategy. Other drug regimens suggested by newly reported trials (8, 24, 25) may be more effective than the regimens used here, and other variables, such as the timing of regimen alternation, should also be examined.

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## APPENDIX: THE SWATCH STUDY TEAM

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Appendix Table 1. Drug Resistance in Patients Receiving Regimen A (Continuous Therapy with Efavirenz, Didanosine, and Stavudine)\*

Patient	Duration of Treatment	Plasma HIV RNA Level	CD4 Cell Count	Genotype†	Drug Susceptibility		
					Efavirenz	Stavudine	Didanosine
		<i>wk</i>	<i>copies/mL</i>	$\times 10^9$ <i>cells/L</i>	← -fold increase of the $IC_{50}$ →		
908	0	13 000	0.237	Wild type	1.1	2.1	2.1
	36	1400	0.353	RT: G190A	>534	1.0	0.6
493	0	220 000	0.276	Wild type	1.8	1.8	1.8
	24	53 000	0.283	RT: K103k/n, G190S	>534	0.6	0.9
110	0	76 000	0.333	Wild type	1.0	0.6	0.7
	24	3800	0.517	RT: K103N, Y188L	>534	2.2	7.8
378	0	124 214	0.220	Wild type	0.7	0.8	0.3
	36	9591	0.440	RT: K103N	215.2	0.7	1.4
589	0	630 000	0.107	Wild type	0.8	0.7	0.3
	24	4000	0.158	RT: L74V, V106I, Y188L	>414.5	0.9	0.5
745	0	87 000	0.005	Wild type	59	1.5	4.7
	24	27 000	0.195	RT: K103N	455	2.9	1.2
052	0	16 600	0.320	Wild type	1.1	0.8	0.2
	36	1800	0.426	Wild type	0.9	0.7	0.3
466	0	62 800	0.200	ND	ND	ND	ND
	36	3950	0.258	RT: L100I, K103N	290.7‡	0.9‡	0.8‡

\*  $IC_{50}$  = 50% inhibitory concentration; ND = not determined.

† Amino acid mixtures are indicated with a slash. Genotype was determined for protease and reverse transcriptase. Only mutations associated with drug resistance are shown.

‡ Virtual phenotype.

Appendix Table 2. Drug Resistance in Patients Receiving Regimen B (Continuous Therapy with Nelfinavir, Zidovudine, and Lamivudine)\*

Patient	Duration of Treatment	Plasma HIV RNA Level	CD4 Cell Count	Genotype†	Drug Susceptibility		
					Nelfinavir	Zidovudine	Lamivudine
		<i>wk</i>	<i>copies/mL</i>	$\times 10^9$ <i>cells/L</i>	← -fold increase of the $IC_{50}$ →		
351	0	82 000	0.117	PR: V82I/RT: V118I	1.2	1.3	0.8
	24	110 000	0.135	PR: V82I/RT: V118I	0.3	1.0	0.9
587‡	0	59 793	0.360	Wild type	1.0§	1.1§	0.9§
	48	1666	0.640	PR: M46L, A71T/RT: M184V	6.1§	0.9§	46.0§
207	0	14 000	ND	Wild type	1.0	1.1	0.8
	48	25 600	0.681	Wild type	1.6	1.3	1.8
949	0	60 000	0.077	RT: T69N	0.3	0.6	0.2
	24	5530	0.190	RT: T69N, M184V	1.9	0.3	>33.9
494	0	180 000	0.081	Wild type	1.0	1.3	0.5
	48	1700	0.224	PR: M46L/RT: A62V, M184V	3.6§	0.9§	46.7§
048	0	13 000	0.101	Wild type	0.5	0.4	0.5
	48	5300	0.361	RT: M184V	0.5	0.9	>34.1
397	0	111 400	0.369	RT: M41L, T215S	0.9§	1.3§	1.0§
	36	1250	0.252	No amplification	ND	ND	ND

\*  $IC_{50}$  = 50% inhibitory concentration; ND = not determined.

† Amino acid mixtures are indicated with a slash. Genotype was determined for protease and reverse transcriptase. Only mutations associated with drug resistance are shown.

‡ Although this patient had plasma viremia of 749 copies/mL and therefore met criteria for virologic failure, no genetic material could be amplified until week 48, when plasma viremia reached 1705 copies/mL. This is a non-B subtype of HIV-1.

§ Virtual phenotype.