Pilot Study of a Novel Short-Cycle Antiretroviral Treatment Interruption Strategy: 48-Week Results of the Five-Days-On, Two-Days-Off (FOTO) Study

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Purpose: The challenges associated with daily lifelong antiretroviral therapy (ART) have stimulated interest in alternative treatment schedules, including planned, cyclical interruptions of therapy in patients with virologic suppression and sufficient CD4+ T-cell counts. **Method:** We conducted a 48-week, open-label, single-arm, prospective pilot study of a novel short-cycle treatment interruption strategy. Upon enrollment, 30 HIV+ individuals with a history of durable viral suppression on daily ART changed their weekly treatment schedule to 5 consecutive days on treatment (typically Monday through Friday) followed by 2 days off treatment (five-on, two-off, or FOTO treatment schedule). **Results:** At 24 and 48 weeks, as-treated analysis revealed that virologic suppression was maintained in 26/29 subjects (89.6%), including 100% of subjects taking efavirenz-based regimens. Participants adhered well to the FOTO treatment schedule and expressed a strong preference for the FOTO treatment schedule compared to daily ART. **Conclusion:** If validated, the FOTO treatment strategy with efavirenz-based regimens could avoid the viremia witnessed in longer cycle structured treatment interruptions yet still ameliorate a number of problems associated with the current paradigm of daily ART for HIV infection, including the high cost of therapy and the pill fatigue that, in many patients, leads to erratic adherence and ultimately treatment failure. **Key words:** *antiretroviral therapy, efavirenz, structured treatment interruption*

Initial research indicated that near-complete adherence to highly active combination antiretroviral therapy (ART) is essential for durable suppression of HIV viral replication. Paterson reported that in treatment-experienced patients on unboosted PI-based regimens (primarily nelfinavir), it is necessary to take at least 95% of prescribed pills to have an 80% probability of viral suppression to <400 copies/mL.[1] Despite this widely accepted adherence threshold, less than 95% adherence is well documented among patients asked to self-administer daily ART and behavioral interventions to improve adherence have been shown to have only modest impact.[2] Moreover, daily lifelong drug therapy to manage chronic HIV infection is costly and potentially associated with a number of long-term toxicities including impaired glucose and lipid metabolism and body fat redistribution.[3]

The difficulties inherent in daily ART, coupled with the availability of antiretroviral agents with prolonged half-lives, have stimulated interest in alternative treatment schedules, including planned, cyclical interruptions of ART in patients with virologic suppression and sufficient CD4+ T-cell counts. Two approaches to structured treatment interruptions (STIs) have been investigated: (1) CD4-guided strategies in which both treatment interruption and reinitiation are determined by preset CD4 thresholds; and (2) time-cycled strategies in which ART is stopped for a predetermined period of time. Recently, a large controlled clinical trial of CD4-guided STI in which ART was stopped

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at CD4 counts above 350 cells/mm^3 and restarted at CD4 counts below 250 cells/mm^3 was discontinued early due to an increased rate of death and disease progression in the treatment interruption arm relative to the continuous treatment control arm.[4] In addition, randomized controlled trials of time-cycled STIs employing breaks of 1 week[5] to 4 weeks[6] have been associated with viral rebound and raise concern for the development of drug resistance.

By contrast, interruption strategies that incorporate breaks from ART of less than 7 days may avoid rebound viremia while still addressing the pill fatigue and cumulative long-term toxicities associated with continuous therapy. We conducted a pilot study of a novel short-cycle treatment interruption. Upon enrollment, HIV+ individuals with a history of durable viral suppression on daily ART changed their weekly treatment schedule to 5 consecutive days on treatment (typically Monday through Friday) followed by 2 days off treatment (five-on, two-off, or FOTO treatment schedule). This schedule was based on the assumption that a treatment schedule that mimics the typical 5-day work week and parallels the concept of having weekends "off" from weekday responsibilities would be easier to remember than other short-cycle interruption schedules.

METHOD

The FOTO study was a 48-week, open-label, single-arm, prospective pilot study. Eligibility criteria included established HIV-1 infection; treatment with stable combination ART; CD4+ T-cell count >200 cells/mm^3; and an undetectable HIV RNA on an ultrasensitive assay for at least 3 months prior to study entry. Protease inhibitor (PI)-treated patients with virological failure on a prior PI-based regimen were permitted to participate, but non-nucleoside reverse transcripase inhibitor (NNRTI)-treated patients with a history of viremia on any non-NNRTI–containing regimen were excluded. A convenience sample was chosen from among the clinic practices of physicians affiliated with Community Research Initiative of New England. The three groups were not matched for any characteristics, including age, gender, CD4 count, HIV viral load, or prior antiretroviral exposure.

At enrollment, all subjects changed from a daily ART schedule to 5 consecutive days on treatment (typically Monday through Friday) followed by 2 days off treatment every week. Viral rebound on FOTO (defined as two consecutive viral load results above 500 copies/mL) led to resumption of daily combination ART. The primary endpoint was the proportion of subjects who maintained an undetectable HIV RNA on an ultrasensitive assay on the FOTO schedule at week 48. Secondary endpoints included change in CD4 count and lipid measurements at week 48 and median plasma efavirenz and PI levels at the end of the 2-day treatment interruption.

Plasma samples for drug assays were shipped frozen to the Pharmacotherapy Research Center Core Analytical Laboratory at the University at Buffalo. Efavirenz, saquinavir, and lopinavir were assayed with a previously published method.[7] The lower limit of quantitation for the analytes was 100 ng/mL for efavirenz and saquinavir and 200 ng/mL for lopinavir. Specificity for the analytes was verified using multiple wavelength detection (photodiode array detection). Accuracy was verified via participation in the ACTG proficiency-testing program.[8,9]

Proportions with sustained viral suppression on FOTO at weeks 24 and 48 were calculated with 95% confidence intervals. Repeated measures analysis of variance (ANOVA) was used to analyze change in mean CD4 count and lipid measurements over time.

RESULTS

Thirty subjects were enrolled. Five subjects (17%) were women, and the mean age at enrollment was 43 years (range, 25–58 years). Two (7%) subjects were African Americans, 1 (3%) was Asian/Pacific Islander, 20 (67%) were non-Latino Caucasian, 6 (20%) were Latino, and 1 (3%) was Native American. The mean CD4 count at enrollment was 612 cells/mm^3 (range, 221–1162). Ten subjects were on efavirenz-based regimens, 10 were on nevirapine-based regimens, and 10 were on PI-based regimens (**Table 1**). Seventy percent of participants were not on their first antiretroviral regimen: three in the PI group had prior exposure to PIs; eight in the PI group, seven in the efavirenz group, and four in the nevirapine group had prior exposure to NRTIs; as required by the entry criteria, none in the efavirenz or nevirapine groups had prior exposure to NNRTIs.

Table 1. Antiretroviral regimens

	Regimen anchor				
NRTIs	EFV (*n* = 10)	NVP (*n* = 10)	LPV/SQV/r (*n* = 8)	NFV (*n* = 1)	NFV/SQV/NVP (*n* = 1)
None			5		1
3TC/TDF	5	3	1		
ABC/TDF	2		1		
ABC/ddI			1		
3TC/ddI	1				
ZDV/3TC		3		1	
ZDV/3TC/ABC		3			
ABC/3TC/TDF	1				
3TC/d4T/TDF		1			
ddI/ABC/TDF	1				

Note: NRTIs = nucleoside reverse transcriptase inhibitors; EFV = efavirenz; NVP = nevirapine; LPV = lopinavir; SQV = saquinavir; r = ritonavir boosted; NFV = nelfinavir; 3TC = lamivudine; TDF = tenofovir; ddI = didanosine; ZDV = zidovudine; ABC = abacavir; d4T = stavudine.

Two withdrew from the efavirenz group between weeks 24 and 48: one moved out of state and one stopped ART due to an urticarial rash that was not considered to be related to the study drugs or dosing schedule because it previously—and subsequently—occurred on continuous therapy with both efavirenz and efavirenz-sparing drug combinations. By as-treated analysis, 100% of subjects on efavirenz-based regimens on the FOTO treatment schedule maintained virologic suppression at weeks 24 and 48 (**Table 2**). Among efavirenz recipients who did not meet criteria for virologic failure, one had a single HIV RNA blip to >200 copies/mL (e.g., 217 at week 28) and two had blips <200 copies/mL.

One subject in the nevirapine group voluntarily withdrew from the study after week 24 due to the inconvenience of study visits; his HIV RNA was

Table 2. Virologic suppression on FOTO treatment schedule by as-treated analysis

Treatment subgroup	Week 24 VL <50 copies/mL		Week 48 VL <50 copies/mL	
	Proportion	Percent (95% CI)	Proportion	Percent (95% CI)
Efavirenz[a]	10/10	100 (70–100)	8/8	100 (63–100)
Nevirapine[b]	9/10	90 (71–100)	8/9	89 (68–100)
PI[c]	7/9	78 (51–100)	7/9	78 (51–100)

Note: FOTO = five-on, two-off; VL = viral load; PI = protease inhibitor; LVPr = ritonavir-boosted lopinavir; SQV = saquinavir; NRTIs = nucleoside reverse transcriptase inhibitors; ART = antiretroviral therapy.

[a]Two of 10 withdrew from efavirenz subgroup between weeks 24 and 48 (1 moved; 1 stopped ART due to an adverse effect that was not drug related).

[b]One in the nevirapine group had viral rebound at weeks 12 and 16; one in nevirapine group voluntarily withdrew from the study after week 24.

[c]One withdrew from the PI group prior to week 24. Two in the PI group (both on LPVr/SQV +/– NRTIs) had virologic rebound at week 24, resumed daily ART, and resuppressed through week 48.

suppressed at the time of discontinuation. One subject in the nevirapine group had viral rebound at week 12 that was confirmed at week 16 on the FOTO schedule. He was on a regimen of nevirapine, abacavir, lamivudine, and zidovudine and had no prior antiretroviral exposure. There was no resistance to NRTIs or NNRTIs on a week 16 genotype. He was advised to resume daily ART, subsequently evidenced a downward trend in his HIV RNA, and was then lost to follow-up because he moved out of state. Among nevirapine recipients who did not meet criteria for virologic failure, two had blips to >200 copies/mL (e.g., 210 copies/mL at week 4 in one and 347 copies/mL at week 20 in another) and one had a blip <200 copies/mL.

One subject in the PI group withdrew prior to week 24 due to relapse of substance abuse. Two in the PI group had virologic rebound at week 24: one was on a combination of lopinavir/r, saquinavir, abacavir, and didanosine and had prior exposure to nelfinavir, lamivudine, stavudine, zalcitabine, and zidovudine; one was on a combination of lopinavir/r and saquinavir only and had no prior PI exposure. Both PI subjects with virologic rebound demonstrated no new resistance mutations on genotype testing; both resumed daily ART and resuppressed through week 48. Among PI recipients who did not meet criteria for virologic failure, none had blips >200 copies/mL and one had a single blip <200 copies/mL.

The median plasma concentration of efavirenz after the 2-day treatment interruption was 595 ng/mL. The median plasma concentrations of lopinavir and saquinavir were undetectable after the 2-day treatment interruption (**Table 3**). There was no significant change in CD4 count between baseline (612 cells/mm^3) and week 48 (671 cells/mm^3). There was a significant decline in low-density lipoprotein (LDL) cholesterol from baseline (116 mg/dL) to week 48 (103 mg/dL) ($p < .05$), which was accounted for by LDL changes in the PI subgroup. There were three adverse events that were judged to have at least possible relationship to drug and of at least grade 2 severity: increased depression in one efavirenz recipient that was grade 2 in severity and resolved with antidepressant therapy; leg cramps in one nevirapine recipient; and transient diarrhea in one PI recipient.

After week 24, all subjects noted their preferred treatment schedule by placing a mark on a Likert scale where 0 represented a strong preference for taking medications 7 days per week and 10 represented a strong preference for taking medications for 5 consecutive days per week. Twenty-three of the 26 patients completed this questionnaire. The mean Likert score was 9.7.

Self-reported adherence over the previous 7 days was recorded at every study visit ($n = 378$ visits). At 15 of 378 visits, participants reported taking fewer antiretroviral doses than prescribed on the FOTO schedule over the previous 7 days. At 2 of 378 visits, participants reported taking more antiretroviral doses than prescribed on the FOTO schedule over the previous 7 days. None of the observed rebounds in viral load were associated with the reported adherence of more than 2 days off ART.

DISCUSSION

This pilot study demonstrates the potential to maintain virologic suppression on efavirenz-based regimens with a 5-days-on, 2-days-off, short-cycle treatment interruption schedule. At 24 and 48 weeks, virologic suppression was maintained in all subjects who were on efavirenz-based regimens, thereby challenging the traditional dogma that daily HIV therapy (or >95%) is necessary for ongoing virologic control once suppression has been achieved. Although the median concentration of efavirenz at the end of the 2-day treatment

Table 3. Pharmacokinetic results

Anchor drug	Median concentration (range) in ng/mL after 2 days off drug	Target trough ng/mL (Acosta, 2002[11])
Efavirenz ($n = 7$)	595 (<10–747)	1000–1100
Saquinavir ($n = 7$)	<100 (<100–421)	100–250
Lopinavir ($n = 6$)	<200 (<200–504)	700

interruption (595 ng/mL) was below target trough concentrations, we believe that the prolonged half-life of efavirenz nevertheless provided an adequate inhibitory quotient at the end of the interruption thereby explaining the success of subjects on this agent. Our findings are consistent with a recent study that showed that viral loads of a majority of NNRTI-treated subjects were suppressed (<400 copies/mL) at 54%–100% adherence whereas viral loads of a majority of single-PI-treated subjects were suppressed only at 95%–100% adherence.[10] The NRTIs used with efavirenz in our study (every subject was on tenofovir and/or lamivudine) also have prolonged half-lives and may have contributed to the virologic success of the FOTO treatment schedule in the efavirenz group.

In this study, the FOTO treatment schedule was strongly preferred over daily ART and was well tolerated. In addition, adherence rates were excellent, which we believe reflects the ease of complying with a treatment schedule that mimics the typical work or school week.

This pilot study is limited by its small size and uncontrolled design, and we therefore cannot recommend at this time that the FOTO intervention be used in clinical practice. Moreover, the current benefit of this interruption strategy is uncertain given that treatment-naïve patients can now be treated with a single-pill, once-daily regimen with relatively low potential for long-term toxicity. We are currently conducting a large, randomized controlled trial of the FOTO treatment schedule in patients on efavirenz, emtricitabine, and tenofovir to determine efficacy and to investigate the impact on quality of life and adherence. If validated by a larger randomized controlled trial, the FOTO treatment strategy with efavirenz-based regimens could avoid the viremia witnessed in longer STIs yet still ameliorate problems associated with the current paradigm of daily ART, including the high cost of therapy and the pill fatigue associated with daily treatment that, in many patients, leads to erratic adherence and ultimately to treatment failure.

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