

Perspective Structured Treatment Interruptions—New Findings

A number of recent studies have examined structured treatment interruption (STI) of antiretroviral therapy using CD4+ cell count-guided or time-based strategies in patients with chronic HIV infection and stable suppression of HIV RNA. On balance, data from these studies indicate that STI is associated with worse immunologic, virologic, and clinical outcomes than continuous antiretroviral therapy. However, the potential may still exist for use of short-term STI to manage drug toxicities in patients in this setting or to assess immunologic and virologic outcomes of novel interventions in carefully controlled clinical trials. This article summarizes a presentation on STI made by Constance A. Benson, MD, at the International AIDS Society–USA course in San Francisco in April 2006.

Structured treatment interruption (STI) of antiretroviral therapy has been evaluated in a number of settings. The rationale proposed to support the strategy is based on the following several hypotheses. (1) Investigators have proposed that in acute and chronic HIV infection, a rebound in virus replication after full suppression with antiretroviral therapy may act as a “therapeutic auto-immunization” that may boost host cellular immune responses. (2) In the setting of full suppression of viral replication with antiretroviral therapy in chronic infection, STI has been proposed as a strategy to conserve drug use and cost and to minimize drug toxicities. (3) In the setting of virologic failure in chronic infection, where the virus is resistant to multiple antiretroviral drugs and drug classes, STI has been proposed as a strategy to allow infecting virus to revert to wild-type virus with the theory that this will improve subsequent virologic response to treatment.

Most of the studies completed to date evaluating the use of STI in chronic HIV infection have not demonstrated significant or sustained benefits of the strategy. For example, findings

in the Swiss-Spanish Intermittent Therapy Trial, reported in 2003, did not support the hypothesis for “therapeutic auto-immunization;” improved host cellular responses could not be achieved in most patients with chronic HIV infection, although a small number of patients appeared to have a short-term response (Fagard et al, *Arch Intern Med*, 2003). In the trial, 133 patients on antiretroviral therapy with plasma HIV RNA levels below 50 copies/mL and CD4+ cell counts greater than 300/ μ L underwent 4 cycles of 2 weeks off/8 weeks on antiretroviral therapy. Antiretroviral

therapy was then stopped at week 40 and resumed if HIV RNA levels exceeded 5000 copies/mL at week 52. Only 17% of patients were responders—ie, had HIV RNA levels of less than 5000 copies/mL—at week 52, with the percentage dropping to 8% at week 96. When treatment was restarted, HIV RNA did not return to the baseline level of less than 50 copies/mL in 19% of patients; 1 patient developed resistance and had to switch antiretroviral therapy. Overall, the median CD4+ cell count decreased from 792/ μ L to 615/ μ L during the first 12 weeks off antiretroviral therapy, but stabilized thereafter. No clinical events occurred in the population.

Results in the setting of salvage therapy have also been disappointing. In 4 randomized clinical trials in patients with virologic failure and virus resistant to multiple antiretroviral drugs and drug classes (total n=41–270 across 4 studies; treated with a mean of 3.6–7 antiretroviral drugs) and plasma HIV RNA level ranging from 4.3 to 5 log₁₀ copies/mL at

Table 1. Outcomes in the Staccato Trial

	CD4+ Cell Count-guided Structured Treatment Interruption	Continuous Antiretroviral Therapy	P Value
Time on antiretroviral therapy	37.5%	99%	--
AIDS events	0	0	NS
Deaths	1	1	NS
HIV RNA level <50 copies/mL	90.3%	91.8%	NS
CD4+ cell count >350/μL at end of randomized follow-up	60.5%	96.2%	.002
CD4+ cell count >350/μL after antiretroviral therapy resumed or continued	85.9%	96.9%	.01

NS indicates not significant. Adapted from data presented at the 13th CROI, 2006 (Ananworanich et al, CROI, 2006) and in Ananworanich et al, *Lancet*, 2006.

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baseline, rates of achievement of target HIV RNA level of less than 400 copies/mL in STI groups versus non-STI groups after STIs that ranged from 8 to 16 weeks, were 19% versus 11%, 45% versus 46% (target <50 copies/mL), 32% versus 12%, and 19% versus 33%, respectively (Benson et al, *J Infect Dis*, 2006; Katlama et al, *AIDS*, 2004; Lawrence et al, *N Engl J Med*, 2003; Ruiz et al, *J Infect Dis*, 2003). Only the French national agency for AIDS research (Agence Nationale de Recherche sur le SIDA, ANRS) 097 study demonstrated a statistically significant improvement in virologic response at 32 weeks of follow-up (Katlama et al, *AIDS*, 2004).

Overall, 3 of the 4 studies showed that STI is accompanied by an increase in viral load and a decline in CD4+ cell count, with curves for both after resumption of treatment being virtually superimposable with those in patients in whom treatment was not interrupted. The general conclusion to be made from these data is that STI is not beneficial as a strategy to improve treatment outcome for patients with highly drug-resistant virus and few treatment options.

The use of STI as a strategy to reduce overall drug costs, time on antiretroviral therapy, and to reduce toxicities associated with therapy has been the focus of more recent studies. With these objectives, data from 5 trials of CD4+ cell count-guided or time-based STI in chronic HIV infection,

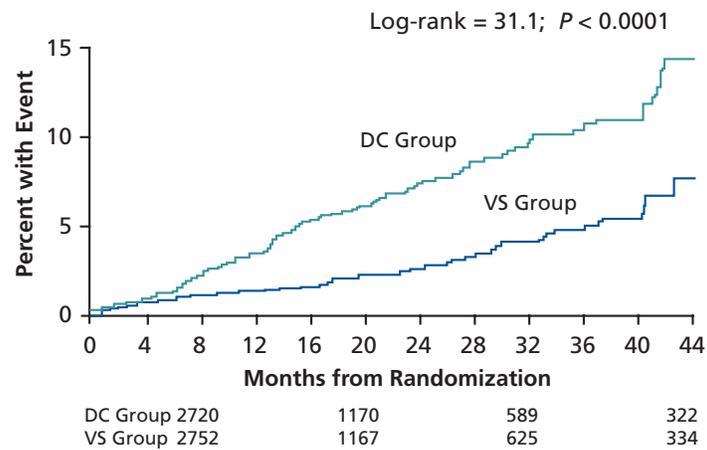


Figure 1. Percentage of drug conservation group (structured treatment interruption) and viral suppression group (continuous antiretroviral therapy) with disease progression or death in the Smart trial. DC indicates drug conservation; VS, viral suppression. Adapted from preliminary data as presented at the 13th CROI, 2006 (El-Sadr et al, CROI, 2006).

presented at the 13th Conference on Retroviruses and Opportunistic Infections (CROI) in 2006 in Denver, Colorado, are discussed below.

Staccato Trial

In the Staccato trial, conducted in Southeast Asia, the Netherlands, and Australia, antiretroviral therapy-naïve patients were treated with antiretroviral therapy until their plasma HIV RNA level was below 50 copies/mL and CD4+ cell count was greater than 350/μL for 6 months; the median time on antiretroviral therapy was 15 months (Ananworanich et al, CROI, 2006; Ananworanich et al, *Lancet*, 2006). Patients were randomized to receive continuous antiretroviral therapy

(n = 146) or STI guided by CD4+ cell count (n = 284), with antiretroviral therapy being stopped for CD4+ counts greater than 350/μL and resumed for counts less than 350/μL. At 96 weeks, continuous antiretroviral therapy was resumed in all patients. Another arm in the trial that assessed STI in a 1 week on/1 week off strategy was discontinued early due to excess virologic failure. The primary endpoints were progression to AIDS or death and proportions of patients with CD4+ cell counts greater than 350/μL at the end of the randomized follow-up period and after resuming continuous antiretroviral therapy. Patients in the STI group spent 37.5% of the study duration on antiretroviral therapy; those receiving continuous antiretroviral therapy spent 99% of the duration on antiretroviral therapy.

There were no differences between groups with regard to the endpoints of AIDS events or deaths and no difference in the proportions of patients with HIV RNA below 50 copies/mL (Table 1). Significantly more patients in the continuous antiretroviral therapy group had CD4+ cell counts greater than 350/μL at the end of randomized follow-up and after continuous therapy was resumed. Among STI patients, CD4+ cell count declined rapidly in the first 8 weeks and more gradually thereafter; 5.8% of STI patients exhibited an acute retroviral syndrome. STI

Table 2. Events Per 100 Patient-years in the Trivacan Trial

	CD4+ Cell Count-guided Structured Treatment Interruption	Continuous Antiretroviral Therapy	Relative Risk
Serious event	15.2	6.7	0.44
Death	1.2	0.6	0.48
Invasive bacterial infection	6.7	0.6	0.08
Tuberculosis	3.6	2.3	0.65
Viral resistance	11%	5%	--

Adapted from preliminary data as presented at the 13th CROI, 2006 (Danel et al, CROI, 2006).

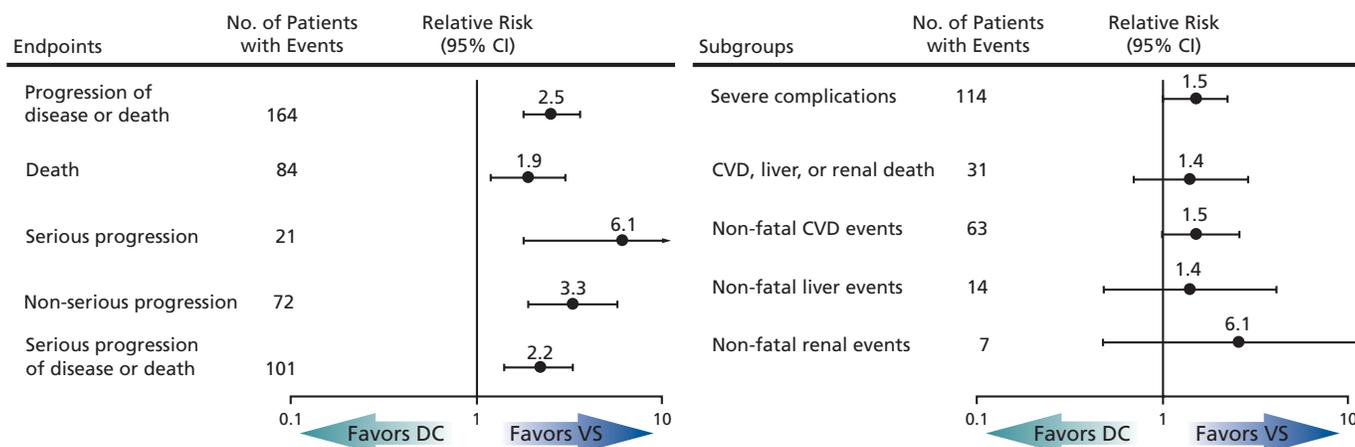


Figure 2. Relative risks for primary (left) and severe complications (right) endpoints for drug conservation (DC) group versus viral suppression (VS) group in the Strategies for Management of Antiretroviral Therapy (Smart) trial. CI indicates confidence interval; CVD, cardiovascular disease. Adapted from preliminary data as presented at the 13th CROI, 2006 (El-Sadr et al, CROI, 2006).

patients had greater frequencies of candidiasis and decreased platelets, whereas patients on continuous antiretroviral therapy had more diarrhea and neuropathy. No differences in low-density lipoprotein cholesterol or triglyceride levels were observed between the groups. Reverse transcriptase inhibitor (RTI) and protease inhibitor (PI) resistance mutations were found in 5.6% and 2.4%, respectively, of STI patients. Overall, there was a 62% savings in the cost of antiretroviral therapy in the STI group.

Trivacan Trial

In the Trivacan trial, antiretroviral therapy-naïve patients with CD4+ cell counts of 150/μL to 350/μL received antiretroviral therapy until their CD4+

cell count was greater than 350/μL and plasma HIV RNA level was below 300 copies/mL for 6 months (Danel et al, CROI, 2006). Patients were randomized to continuous antiretroviral therapy (n = 110), CD4+ cell count-guided STI in which antiretroviral therapy was stopped at 350/μL and resumed at 250/μL (n = 216), or STI consisting of 4 months on/2 months off antiretroviral therapy (n = 325). The primary endpoints were death or serious morbidity and percentage of patients with CD4+ cell count greater than 350/μL after 24 months.

The trial is ongoing for the time-based STI strategy arm, from which data will be available in the near future; however, the CD4+ cell count-based STI arm was stopped early due to an excess of serious morbidity. As

noted in Table 2, the CD4+ cell count-guided group was at increased risk (although the increase did not reach statistical significance for individual categories) for each of the serious events, death, invasive bacterial infection, and tuberculosis, compared with the continuous antiretroviral therapy group and had a higher rate of antiretroviral drug resistance. The STI arm had a smaller CD4+ cell count increase and a lower plateau in CD4+ cell count than the continuous treatment arm. Overall, the serious morbidity rate was 2.6-fold greater (P = .003) in the STI arm, and this group had significantly more days in hospital and numbers of outpatient clinic visits (P < .001).

Smart Trial

In the Strategies for Management of Antiretroviral Therapy (Smart) trial, patients with CD4+ cell counts greater than 350/μL were randomized to antiretroviral therapy to suppress viral load as low as possible (viral suppression) or to the drug conservation strategy of deferring antiretroviral therapy until the CD4+ cell count was below 250/μL and then using episodic antiretroviral therapy to increase the count to greater than 350/μL (El-Sadr et al, CROI, 2006). The trial was planned to enroll 3000 patients in each arm, with an expected 910 primary

Table 3. Baseline Characteristics in the Strategies for Management of Antiretroviral Therapy (Smart) Trial

	Drug Conservation Group (Structured Treatment Interruption)	Viral Suppression Group (Continuous Antiretroviral Therapy)
Median CD4+ cell count	596/μL	599/μL
Median nadir CD4+ cell count	250/μL	252/μL
HIV RNA level ≤ 400 copies/mL	71.0%	70.8%
Prior clinical AIDS	24.7%	23.4%
Antiretroviral therapy-naïve	4.5%	4.8%
Years of prior antiretroviral therapy	6	6

Adapted from preliminary data as presented at the 13th CROI, 2006 (El-Sadr et al, CROI, 2006).

endpoint events at an average of 8 years of follow-up. The primary endpoint was clinical disease progression or death, with secondary endpoints being death alone, serious progression events, and serious complications (including cardiovascular, hepatic, and renal events). The trial was stopped after an interim analysis in January 2006, at which time the occurrence of 164 primary endpoints and an average of 14 months of follow-up showed a significantly increased risk of disease progression or death in the drug conservation group. Baseline characteristics of the study groups are listed in Table 3. There were 117 endpoint events in the drug conservation group, a rate of 3.7 per 100 person-years of observation, and 47 in the viral suppression group, a rate of 1.5 per 100 person-years, yielding a relative risk of 2.5 (95% confidence interval [CI], 1.8–3.6) for disease progression or death in the former ($P < .0001$). As can be seen in Figure 1, the separation between the 2 groups with regard to incidence of the primary endpoint began at about 3 to 4 months.

Relative risks for primary and secondary endpoints are shown in Figure 2; risk for each component of the primary endpoint, including death and

serious progression, was significantly increased in the drug conservation group, and there was a borderline significant increase in risk for severe complications. After 36 months of follow-up, approximately 90% of the VS group remained on antiretroviral therapy; the proportion of patients in the drug conservation group receiving antiretroviral therapy at each month of follow-up steadily increased, with approximately 60% receiving antiretroviral therapy at 36 months. The drug conservation versus viral suppression groups spent 32% versus 7% of follow-up time with CD4+ cell counts below 350/ μ L, 7% versus 2% below 250/ μ L, and 3% versus 1% below 200/ μ L.

Based on preliminary data presented, the risk for disease progression or death was higher in the drug conservation group for all baseline CD4+ cell count strata (although the difference was not statistically significant in the lowest stratum), with these data suggesting that risk associated with the drug conservation strategy was independent of initial CD4+ cell count. Stratification by baseline viral load showed that risk of the primary endpoint was significantly elevated in drug conservation patients versus viral sup-

pression patients with better suppression of viral load at baseline.

Window Trial

In the Window trial, patients with CD4+ cell counts greater than 450/ μ L and plasma HIV RNA levels of 200 copies/mL or less for at least 6 months were randomized to continuous antiretroviral therapy ($n = 203$) or STI ($n = 200$) consisting of 8 weeks on/8 weeks off antiretroviral therapy (Marchou et al, CROI, 2006). Patients with a CD4+ cell count nadir of less than 100/ μ L, those with abacavir or nevirapine in their antiretroviral therapy regimen, and those with hepatitis B virus infection were excluded from the trial. The primary endpoint was CD4+ cell count of less than 300/ μ L at 96 weeks. Overall, 362 patients (90%) completed 96 weeks of study. Results are listed in Table 4. The STI strategy was statistically noninferior to continuous antiretroviral therapy, with 3.6% of the STI group versus 1.5% of the antiretroviral therapy group meeting the primary endpoint. However, significantly smaller proportions of STI patients had CD4+ cell counts greater than 450/ μ L at 96 weeks and HIV RNA levels below 400 copies/mL after 8 weeks back on antiretroviral therapy following the 96-week follow-up period, and the decline in CD4+ cell count was statistically significantly greater in the STI group. Patterns of drug resistance in the 2 groups were similar.

ISS/Part Trial

In the ISS/Part trial, patients with viral suppression for a median of 24 months on their first antiretroviral therapy regimen were randomized to continuous antiretroviral therapy ($n = 137$) or sequential STI ($n = 136$) consisting of interruptions of 1, 1, 2, 2, and 3 months with each interruption followed by 3 months on antiretroviral therapy (Palmisano et al, CROI, 2006). The primary endpoint was proportion of patients with a CD4+ cell count greater than 500/ μ L at 24 months, and secondary endpoints included genotypic evidence of resistance and proportions of patients with an HIV RNA

Table 4. Outcomes in the Window Trial

	Structured Treatment Interruption	Continuous Antiretroviral Therapy	P Value
Time on antiretroviral therapy	52%	100%	--
CD4+ cell count <300/μL at 96 weeks	3.6%	1.5%	STI non-inferior
CD4+ cell count >450/μL at 96 weeks	75%	92%	.0001
HIV RNA level <400 copies/mL after 8 weeks back on antiretroviral therapy	81%	90%	.02
AIDS events	0	0	NS
Other*	9	2	NS
Change in CD4+ cell count	-155/ μ L	-8/ μ L	<.001

*No differences in lipodystrophy or dyslipidemia. NS indicates not significant. Adapted from preliminary data presented at the 13th CROI, 2006 (Marchou et al, CROI, 2006).

Table 5. Outcomes in the ISS/Part Trial

	Structured Treatment Interruption	Continuous Antiretroviral Therapy	P value
CD4+ cell count >500/μL	69.1%	86.5%	.0075
Virologic failure	26%	24%	NS
HIV RNA level <400 copies/mL	90%	91%	
HIV RNA level <50 copies/mL	60%	86.5%	
Change in CD4+ cell count	-26/μL	-8/μL	

NS indicates not significant. Adapted from preliminary data presented at the 13th CROI, 2006 (Palmisano et al, CROI, 2006).

level of less than 50 copies/mL and less than 400 copies/mL at 24 months.

As noted in Table 5, significantly greater proportions of patients in the continuous antiretroviral therapy group had CD4+ cell counts greater than 500/μL and HIV RNA levels less than 50 copies/mL at 24 months. There were 14 serious adverse events in each group. The cumulative risk of antiretroviral therapy resistance in the STI group was 30% at 24 months, significantly higher than that in the continuous antiretroviral therapy group.

Conclusion

Available data do not suggest that harm results from brief analytic treatment interruptions to assess virologic and immunologic responses to therapeutic immunization or other immunologic interventions in patients who retain CD4+ counts above the threshold of 250 to 350 cells/μL during the treatment interruption. Such treatment interruptions should occur only in patients who are being closely monitored in the clinical trial setting. However, the preponderance of data indicate that STI is not appropriate in the setting of chronic HIV infection in patients who are otherwise candidates for antiretroviral therapy—eg, in those with CD4+ cell counts of 350/μL or lower.

Short-term interruptions may be feasible to manage drug toxicities, but it is unclear precisely what duration of

interruption constitutes a safe interruption, although as noted, the risk of progression or death in STI patients in the Smart Trial began to exceed that in the non-STI group at around 4 months, which could be interpreted to suggest that a “safe” interruption would be of shorter duration in a similar population. STI in chronically infected patients with multidrug-resistant HIV appears to offer no clinical or virologic benefit and should not be done. In this setting, however, there are limited data indicating a virologic benefit for interrupting an individual drug in a class for which there has been an accumulation of resistance mutations.

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Suggested Reading

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