

## STRUCTURED TREATMENT INTERRUPTIONS: IS THERE AN ALTERNATIVE TO LIFELONG HAART?

### Insights from the 13th Conference on Retroviruses and Opportunistic Infections

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The 13th Conference on Retroviruses and Opportunistic Infections (CROI) was held in Denver, Colorado, on 5 - 8 February 2006. Several papers were presented on the topic of structured treatment interruptions (STIs) of antiretroviral therapy in adults, and this was probably the most controversial antiretroviral treatment issue discussed at the conference. This article summarises these papers.

Antiretroviral therapy is lifelong and with time carries the risk of cumulative metabolic and cardiovascular toxicities, the accumulation of viral resistance mutations, and treatment fatigue with adherence lapses. The medication is also expensive. For many patients interruptions are inevitable. This had led to an interest in the concept of STIs – providing breaks in therapy in a structured fashion to minimise the long-term complications of highly active antiretroviral therapy (HAART) while not compromising the long-term benefits of therapy or putting patients at risk of immunosuppression-related events during these breaks. The most popular strategy involves a CD4-guided strategy to trigger the recommencement of HAART. STIs are of particular interest for patients who started HAART with high CD4 counts under previous guidelines, the question being whether they can safely interrupt their HAART and allow immunological progression before recommencing.

Major concerns regarding STIs are risk of disease progression during interruptions resulting in new infections and death, promotion of viral resistance, and the acute retroviral syndrome. The latter is a febrile illness similar to seroconversion illness associated with viral rebound after stopping HAART.

Six adult STI studies were reported at CROI from different settings around the world. The study designs, patient baseline characteristics and findings differed. The findings of these studies are summarised in Table I.

#### THE SMART STUDY<sup>1</sup>

The Strategies for the Management of Antiretroviral Therapy (SMART) study was conducted at 318 sites in 33 countries and was a prospective randomised trial comparing a virological

suppression (VS) arm (patients stayed on continuous HAART) to a drug-conservation (DC) arm (in which patients interrupted or deferred HAART with a CD4 count > 350 cells/μl and restarted when CD4 dropped below 250 cells/μl). A total of 5 472 patients had been enrolled in the study by the time it was terminated by the Data Safety Monitoring Board in January 2006 because of an increased risk of disease progression and death in the DC arm. The background of the whole cohort was:

- median age: 46
- median CD4 at entry: 598 cells/μl
- 70% had a viral load (VL) < 400 copies/ml at study entry
- median CD4 nadir was 253 cells/μl (25% of patients had a nadir CD4 less than 154 cells/μl)
- 5% were ART naïve
- median of 6 years on ART
- 24% had previously had an AIDS-defining illness.

The primary endpoint was a combined outcome of death and disease progression. The rate of this was 3.7/100 person-years in the DC arm and 1.5/100 person-years in VS arm giving a relative risk (RR) of 2.5 (95% confidence interval (CI) 1.8 - 3.6). This difference remained significant when the data were stratified according to nadir CD4 (even those with a nadir CD4 > 400 cells/μl showed an increased risk of this primary endpoint in the DC arm). Death was also significantly more common in the DC arm (RR 1.9). The CD4-guided strategy to maintain CD4 > 250 cells/μl and allow STIs was therefore associated with a greater than 2-fold higher short-term risk of disease progression and death, despite the fact that patients in the DC only spent 3% of study follow-up time with a CD4 less than 200 and 32% of the time with a CD4 less than 350.

TABLE I. ADULT STRUCTURED TREATMENT INTERRUPTION STUDIES REFERRED TO AT CROI 2006

	STUDY					
	SMART	ANRS 1269 TRIVICAN	ACTG 5170	STACCATO	ISS PART	WINDOW-ANRS 106
N	5 472	326	167	430	273	403
Setting	33 countries	Cote d'Ivoire	USA	Australia, Thailand, Switzerland	Italy	France
Study design	RCT	RCT	Single arm observational prospective cohort	RCT	RCT	RCT
STI strategy	<b>CD4-guided:</b> Interrupt CD4 > 350 Restart < 250	<b>CD4-guided:</b> Interrupt CD4 > 350 Restart < 250	<b>CD4-guided:</b> Interrupt CD4 > 350 Encouraged to restart with CD4 < 250	<b>CD4-guided:</b> Interrupt CD4 > 350 <u>Restart &lt; 350</u>	CT v. 5 STIs (defined time periods of 1 - 3 months)	CT v. 8-week-on/ 8-week-off HAART
CD4 nadir in STI group (median)	252	272	436	267	418 (mean)	274
Follow-up period	Median 10 months	Median 19 months	96 weeks	Median 22 months	24 months	96 weeks
AIDS or death/100 PY	3.7	17.6	2.9	0.2	NR	2 deaths, 0 AIDS
STI	1.5	6.7	-	0.4	NR	0 deaths, 0 AIDS
Main clinical outcomes	Increased HIV progression and death in STI arm	Increased serious morbidity in STI arm	Safe, 5 died (none AIDS related) and 5 CDC B/C events	Clinically safe	14 serious adverse events in each arm	Clinically and immunologically safe
VL outcome	NR	NR	20% virological failure among the 46 who recommenced HAART	92% (CT) v. 90% (STI) suppressed	Similar rates of VL failure: 24% (CT) v. 26% (STI)	More patients in the STI arm had VL > 400 at 96 weeks (19 v. 10%, p = 0.02)
Resistance	NR	11% in STI arm v. 5% in CT arm (NS)	NR	No difference between 2 arms (2% in each arm)	32% in STI arm demonstrated mutation(s) during STIs	No difference in mutations between 2 arms
SE	More common in STI arm	No significant differences between 2 arms	NR	Diarrhoea, neuropathy and lipodystrophy more common in CT arm	No serious adverse events related to drug toxicity	No difference between 2 arms
Time off HAART	67% in STI arm v. 7% in CT arm	NR	Median 96 weeks	62%	38%	48.5%

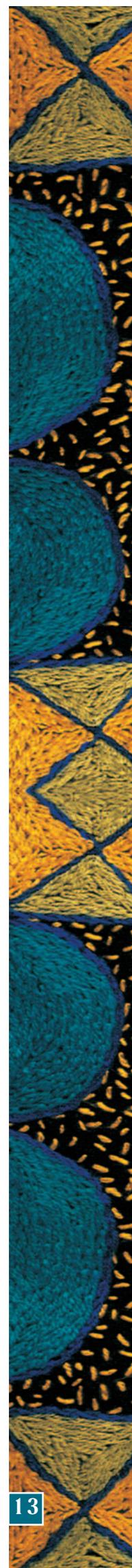
NR = randomised controlled trial; PY = person-years; NR = not reported; CT = continuous treatment; STI = structured treatment interruption; NS = non-significant difference.

What was surprising, given that STIs would be thought to reduce drug side-effects by reducing drug exposure, was that major cardiovascular, hepatic and renal complications were actually significantly more common in the DC arm (RR 1.4).

### ACTG 5170<sup>2</sup>

This study assessed the safety of a single treatment interruption in a cohort of patients who started HAART with

relatively high CD4 counts under old US guidelines. The hypothesis was that these patients could safely interrupt HAART without significant disease progression over 2 years. There was no control group. In addition the study aimed to define the parameters that would identify patients in whom STIs were low risk. Patients in the cohort were on HAART for at least 6 months with a current and nadir CD4 count > 350 cells/μl and VL < 55 000 copies/ml. HAART was stopped then recommenced at the discretion of the patient and provider,



although recommencement was strongly encouraged when CD4 dropped below 250 cells/ $\mu$ l. Primary endpoints were time to Centers for Disease Control (CDC) B or C event or death or CD4 < 250 cells/ $\mu$ l or resumption of HAART. One hundred and sixty-seven patients were enrolled, and the median nadir CD4 count was 436 cells/ $\mu$ l and entry CD4 count 833 cells/ $\mu$ l. The strategy was assessed as being 'generally safe' and patients spent a median of 96 weeks off HAART. Three CDC B and 2 CDC C events occurred, all in patients with CD4 counts > 350 cells/ $\mu$ l. There were 5 deaths, none HIV-related; 3 of the deaths were cardiovascular-related. Of the patients 28% needed to restart HAART during the study period, and only nadir CD4 count was predictive of the need to re-initiate in a multivariate analysis. The predictors of disease progression, death and CD4 decline in this cohort were a lower CD4 nadir and VL > 50 copies/ml at study entry.

### STACCATO<sup>3</sup>

This study was conducted in Thailand, Switzerland and Australia. Of the patients 80% were on ritonavir-boosted saquinavir regimens. In this study the strategy was for patients to stop HAART when the CD4 count was above 350 cells/ $\mu$ l, but to restart when it dropped below 350 cells/ $\mu$ l (higher than the threshold in other studies); 430 patients were randomised to either continuous therapy (CT) or these STIs. Patients had to have a VL < 50 copies/ml on entry. A third arm to the study (one week on and one week off HAART) was prematurely terminated because of a high virological failure rate.

Patients were able to spend a median of 63% of study time off HAART and there was no excess in drug resistance mutations in the STI group. In contrast to SMART there were fewer drug side-effects in the STI group: diarrhoea, neuropathy and self-reported lipodystrophy were all less common in the STI arm. Minor manifestations of HIV infection such as oral and vaginal thrush and thrombocytopenia were more frequent in the STI arm. There were no AIDS-defining illnesses in either arm and there were 2 non-AIDS-related deaths, one in each arm.

At the end of the study continuous HAART was recommenced for 12 - 24 weeks, and 92% (CT) v. 90% (STI) suppressed to a VL < 50 copies/ml. There was little evidence that the STIs predisposed to resistance (resistance mutations were detected in around 2% of patients in both arms).

### TRIVICAN<sup>4</sup>

This study was undertaken in Cote d'Ivoire. Patients on HAART with CD4 counts > 350 cells/ $\mu$ l, VL < 300 copies/ml and CD4 nadir > 150 cells/ $\mu$ l were enrolled. The study compared continuous therapy with two STI strategies, a CD4-guided strategy (treatment interrupted at CD4 > 350 cells/ $\mu$ l and restarted when it dropped below 250 cells/ $\mu$ l) and a 2-month-off/4-month-on therapy strategy. Endpoints were death and serious morbidity (WHO stage 3 or 4 conditions). At the interim analysis the DSMB recommended stopping the CD4-guided STI arm, and the analysis of this arm versus continuous therapy

was presented at CROI. Patients in the study had a median nadir CD4 of 272 cells/ $\mu$ l and median CD4 at entry of 460 cells/ $\mu$ l. A more than 2-fold higher rate of serious morbidity was demonstrated in the STI arm (IRR 2.6, 95% CI 1.3 - 5.6). This was mainly accounted for by invasive bacterial infections (IRR 15.9, 95% CI 2.6 - 64.8). The common bacterial infections were *Salmonella typhi* and *Streptococcus pneumoniae*. There was also a non-significant trend to more tuberculosis and oropharyngeal candida in the STI arm. There were more hospitalisations and outpatient visits in the STI arm. There were no significant differences between the two arms in terms of mortality, drug side-effects or emergence of viral resistance.

### ISS PART<sup>5</sup>

There were two arms in this study: a continuous treatment arm and an STI arm in which there were planned interruptions of 1, 1, 2, 2 and 3 months with a 3-month period of continuous HAART in between each of these interruptions; 70% of patients were on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, and when interrupting they stopped the NNRTI 3 - 6 days before the other drugs. Those on protease inhibitor (PI) regimens were mainly on unboosted PIs. All patients were on their first regimen and all had VLs < 400 copies/ml at study entry. The mean CD4 at study entry in the STI arm was 714 cells/ $\mu$ l and the mean CD4 nadir 418 cells/ $\mu$ l. The primary endpoint was the proportion of patients with CD4 > 500 cells/ $\mu$ l at 24 months. More patients achieved the primary endpoint in the CT arm (87% v. 69%), making the STI strategy inferior to continuous treatment in this regard. There were more protocol discontinuations in the STI arm. Rates of virological failure (defined as VL > 400 copies/ml at 24 months) were the same in both arms (8% in CT arm v. 9% in STI arm). Thirty per cent of patients in the STI arm demonstrated at least one resistance mutation during treatment interruptions and these were associated with a greater risk of virological failure. The emergence of resistance mutations was associated with the presence of archived mutations in proviral DNA at baseline and the use of unboosted PIs. The investigators concluded that potential STI candidates were patients with:

- high pre-HAART CD4
- absence of archived mutations
- absence of residual viral replication (VL < 2.5 copies/ml),
- and not on unboosted PIs.

There were 14 serious adverse events in each arm - none were drug side-effects.

### WINDOW-ANRS 106<sup>6</sup>

Patients with nadir CD4 > 100 cells/ $\mu$ l on HAART with CD4 > 450 cells/ $\mu$ l and VL < 200 copies/ml for at least 6 months were randomly assigned to either continuous therapy or an 8 week-on/8 week-off strategy for 96 weeks. Patients on nevirapine were excluded and if patients were on efavirenz this was stopped 7 days before other drugs in their regimen. At baseline the median CD4 was 741 cells/ $\mu$ l and nadir 280

cells/ $\mu$ l and 8% had AIDS. The primary outcome was immunological failure defined as reaching CD4 < 300 cells/ $\mu$ l; 3.6% v. 1.5% reached this primary endpoint, demonstrating that this STI strategy was not inferior to continuous therapy in this regard. The median loss of CD4 cells was 155 cells/ $\mu$ l in the STI arm over 96 weeks. The interruption strategy was also clinically safe. There were 2 HIV unrelated deaths (1 violent and 1 from alcoholic cirrhosis) in the STI arm and no AIDS-defining illnesses in either arm. There was no difference in drug side-effect rates between the two arms. More patients in the STI arm had VL > 400 copies/ml at 96 weeks (19% v. 10%,  $p = 0.02$ ). There was no significant difference in resistance patterns in patients experiencing virological failure between the two arms. Over the 96 weeks those in the STI arm were spared 49% of drug exposure.

### OTHER ISSUES TO CONSIDER

STIs are also associated with thrombocytopenia (< 5% in all studies) and acute retroviral syndrome (up to maximum 6% in the Staccato study).

Nadir CD4 count is the best predictor of how long patients can spend off HAART. Pre-HAART CD4 nadir was the only independent predictor of time off HAART in ACTG 5170.

After stopping HAART the CD4 declines to the pre-HAART nadir within weeks. The ACTG 5170 study demonstrated a rapid decrease in CD4 count in the first 2 months after stopping HAART (by 198 cells/ $\mu$ l), reflecting a fall back to pre-HAART nadir. Thereafter there was a more gradual decline (1.7 cells/ $\mu$ l/week), reflecting natural progression of immunosuppression. There is also a rapid VL rebound after stopping HAART: VL setpoint was reached 4 weeks after stopping HAART in this study.

Another important issue to consider when interrupting HAART is the potential for the development of viral resistance. This applies particularly to interruptions in an NNRTI regimen, as NNRTIs have much longer half-lives than NRTIs and therefore persist in the plasma after the regimen is stopped, resulting in effective monotherapy and the selection of NNRTI drug resistance mutations. To help avoid this it is advisable to continue the NRTIs for 5 - 10 days after the NNRTI is stopped to 'cover the NNRTI tail'.

On a public health level it must also be considered that STIs, by resulting in episodes of viraemia, may contribute to an increased risk of HIV transmission. Another issue to consider is that in patients with chronic hepatitis B, stopping HAART regimens that contain lamivudine (3TC), emtricitabine (FTC) or tenofovir may result in hepatitis flares and is therefore not advised.

### CONCLUSION

Key messages to emerge from these studies are:

- The largest study on this issue (SMART) demonstrated a clear increase in the risk of morbidity and mortality using

an STI strategy. This particular STI strategy is therefore not advised in clinical practice. Other studies have shown STI to be safe, and this may result from differences in study design and patient population. Further studies to confirm whether STI strategies may be safe in less immunologically advanced patients using more conservative strategies are needed. Until then they are generally not advised in clinical practice.

- Some feel that STIs may still have a role in patients who started HAART early with CD4 counts higher than 350 cells/ $\mu$ l and where a threshold of 350 cells/ $\mu$ l for recommencing HAART during STI is set. Certain studies (Staccato and ACTG 5170) support this. However, in the SMART study even patients with a CD4 nadir > 400 cells/ $\mu$ l had excess morbidity/mortality in the STI arm.
- It is important to remember that most of the HIV-related morbidity associated with STIs in the SMART study occurred when the CD4 was between 250 and 350 cells/ $\mu$ l, and on the basis of SMART STIs that allow CD4 decline into this range therefore seem inadvisable.
- The best predictor of outcome using an STI strategy is nadir CD4. STIs are most risky in patients with low CD4 nadir.
- The setting is also an important consideration. The one study done in Africa showed unique risks, in particular invasive bacterial infections.
- An unexpected outcome of the SMART study was an increase in cardiovascular, hepatic and renal complications in the STI arm. It was speculated that HIV replication and the resulting immune activation during STIs may play a role in inflammation-mediated cardiovascular effects.
- Most studies showed no increased risk of viral resistance using an STI strategy apart from ISS PART. The HAART regimens patients were on and the staggering method of stopping drugs may have influenced this. In the ISS PART study interruptions of an unboosted PI regimen was a particular risk factor for resistance.

It is important to note that the risks associated with progression during STI may well be different from those in naïve patients, and the findings above therefore do not apply to decisions about when to start HAART in naïve patients. The data above are useful for clinicians managing a patient on HAART who requests a self-initiated 'drug holiday'. There are many findings here that allow for an evidence-based discussion regarding the risks associated with this for an individual patient. Clearly the nadir CD4 is the most important factor to consider in such discussions.

#### REFERENCES

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