



CTN 164: A Prospective Randomized Trial of Structured Treatment Interruption (STI) Versus Immediate Switching (IS) in HIV- infected Patients Experiencing Virologic Failure on HAART

Walmsley S¹, LaPierre N², Loutfy M¹, MacLeod J³, Trottier B⁴, Conway B⁵, Trottier S⁵, Thorne A², Zarowny D², Singer J² and the CTN 164 investigators

¹University of Toronto, Toronto, Canada, ²Candian HIV Trials Network, Vancouver, Canada, ³McGill University, Montreal, Canada,

⁴Clinique L'Actuel, Montreal, Canada, ⁵Laval University, Ste Foy, Canada

Dr. Sharon Walmsley
Infectious Diseases
Toronto Hospital
9ES Room 413
200 Elizabeth Street
Toronto, ON M5G 2C4
sharon.walmsley@uhn.on.ca
(Ph) (416) 340-3871
(Fax) (416) 595-5826

Background: This study was designed to determine the impact of switching treatment-experienced patients with VF to a salvage regimen with or without a 12-week STI. The primary endpoint is the % of patients with a viral load (VL) < 50 copies/ml and who were able to maintain this degree of suppression for at least 3 months while still on the initial salvage regimen.

Methods: A randomized, open label multicenter trial, in patients with VF (VL > 1000 copies/ml) on a HAART regimen, requiring a switch in ARV therapy and who had at least 2 new ARV available based on history that could be included in the salvage regimen of 3-5 agents. Patients were stratified as to whether they had received prior therapy with an NNRTI or PI or both. The salvage regimen, determined prior to randomization, was guided by a baseline genotype and virtual phenotype. Patients were followed for 60 weeks after randomization. The trial was terminated prematurely by the SERC after enrollment of 147/196 expected patients due to slow recruitment.

Results: The current analysis includes 134 patients with at least one post-baseline VL and randomized before Jan 1/04 (67 in IS and 67 in the STI arm). Patients were 87% male, had median baseline CD4 count 343/mm³ and VL of 3.9 log. 71 patients had received a prior PI or NNRTI and 63 both. Baseline values were similar for the two groups. Success as defined by the primary endpoint was achieved by 69% patients in the IS and 55% patients in the STI arms (p=0.11; 95% CI= -4% to 31% IS).

Virologic endpoints	IS		STI	
	Total	%	Total	%
VL <50 @ least once	96 (72%)	53 (79%)	43 (64%)	
1 log VL @ least once	118 (88%)	63 (94%)	55 (82%)	

Median difference from baseline in CD4 count and log (VL) were:

	12 weeks		24 weeks		48 weeks		60 weeks	
	CD4	VL	CD4	VL	CD4	VL	CD4	VL
IS	+40	-2.0	+60	-2.0	+50	-1.9	+95	-1.7
STI	-80	+0.8	+7	-1.4	+37	-1.8	+25	-1.7
p value	<0.01	<0.01	<0.01	0.02	0.15	0.98	0.04	0.46

During the 60 wks, there were 2 non-HIV related deaths, (1 IS, 1 STI) 4 AIDS defining events in STI arm (PCP week 7, lymphoma week 57, 2 episodes oesophageal candida in one patient weeks 28, 43) and 7 HIV associated infections (5 episodes of zoster, STI, ZIS and 2 oral thrush in STI).

Conclusion: In this randomized controlled clinical trial, a 12 week STI prior to the initiation of a salvage HAART therapy did not improve outcomes. There was no difference in the % patients who could sustain a VL <50/ml for 3 months, there was a statistically lower CD4 cell count rise but similar VL reduction at 60 weeks.

INTRODUCTION

- The role of an STI prior to salvage ARV remains controversial.
- Cohort studies¹ and the ANRS 097 study² showed improved CD4 and viral load (VL) responses.
- In contrast CPCRA 064³ showed no improvement in CD4/VL responses but an increased rate of disease progression.

- Differences in patient populations, use of OI prophylaxis, duration of the STI and potency of the salvage regimen may explain the differences.

OBJECTIVES

To determine the impact of a 12 week STI prior to salvage therapy in patients with VL failure (HIV RNA > 1000 copies/ml) on HAART.

Primary endpoint:

% of patients with VL < 50 copies/ml and sustained for at least 3 months after initiation of salvage ARV.

Secondary endpoints:

comparison of CD4, viral load responses and clinical end points in patients with/without an STI prior to the use of salvage ARV.

METHODS

- Randomized, open label, multicenter involving 19 Canadian sites.
- Stratified by prior use of PI and/or NNRTI or both.

Inclusion Criteria

- VL failure (> 1000/ml) while on HAART.
- At least 2 new ARV available for inclusion in salvage regimen by history.
- Selection of a salvage regimen of 3-5 agents guided by genotype and virtual phenotype prior to randomization.
- OI prophylaxis: PCP if CD4 < 200/mm³, MAI if CD4 < 75/ml.

RESULTS

Baseline Demographics

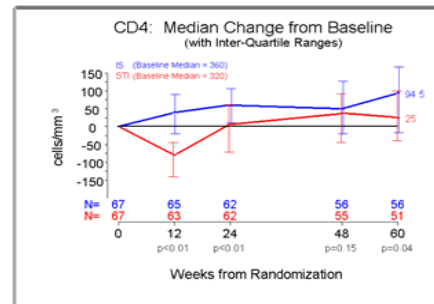
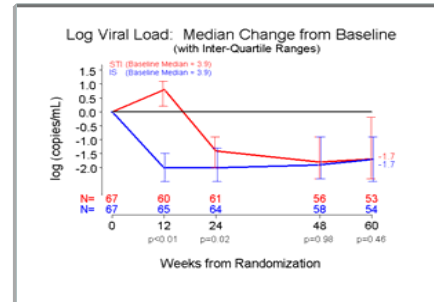
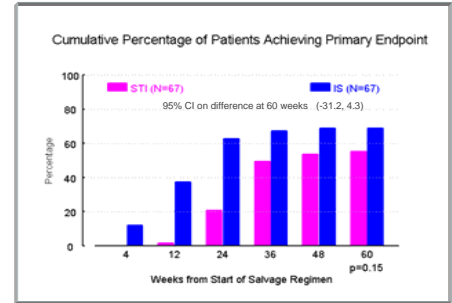
	STI (N=67)	IS (N=67)
Characteristic		
Gender (# of males)	59 (88%)	58 (87%)
Mean age	42	43
Race		
Caucasian	46 (69%)	49 (73%)
Black	13 (19%)	10 (15%)
Other	8 (12%)	8 (12%)
IVDU	5 (7%)	8 (12%)
Baseline (Median)		
CD4	320	360
Log VL	3.9	3.9
Prior AIDS	19 (28%)	20 (30%)

Prior ARV experience

	STI (N=67)	IS (N=67)
NNRTI		
AZT	61 (91%)	61 (91%)
DDI	37 (55%)	29 (43%)
DDC	18 (27%)	10 (15%)
D4t	52 (78%)	53 (79%)
Abc	19 (28%)	8 (12%)
3TC	66 (99%)	63 (94%)
TDF	4 (6%)	1 (1%)
NNRTI		
Efavirenz	22 (33%)	22 (33%)
Nevirapine	23 (34%)	14 (21%)
Delavirdine	2 (3%)	5 (7%)
PI		
Ritonavir	14 (21%)	25 (37%)
low dose	11 (16%)	11 (16%)
Nelfinavir	36 (54%)	36 (54%)
Lopinavir/r	5 (7%)	7 (10%)
Indinavir	26 (39%)	33 (49%)
boosted	5 (7%)	4 (6%)
Saquinavir	26 (39%)	30 (45%)
boosted	5 (7%)	6 (9%)
Ampranavir	3 (4%)	0 (0%)
boosted	0 (0%)	1 (1%)

Sample Size Considerations

- 194 patients would be required to detect a 20% difference in primary endpoint (60-40%) with a power of 80% and alpha of 0.05.
- Study closed prematurely by DSMB after 147 patients randomized due to poor recruitment.
- Present analysis included 134 patients with at least one post base line follow-up and randomized prior to January 2004.



Incidence of Opportunistic Infection, Malignancy or Death

	STI (N=67)	IS (N=67)
Death (non-HIV related)	1	1
Disease progression		
0-3 months	1 (PCP)	0
3-6 months	1*	0
6-12 months	1*	0
12-15 months	1 (Lymphoma)	0

*one patient had 2 episodes of esophageal candidiasis, fluconazole prophylaxis was not maintained and ARV never initiated after the STI, by patient choice

CONCLUSIONS

- In this randomized controlled clinical trial, a 12 week STI prior to the switch to salvage HAART was not associated with a CD4 count or virologic benefit.
- There was no difference in the % of patients who were able to suppress and maintain VL < 50 copies/ml for 3 months in the patients randomized to an STI compared to IS.
- There were an increased number of clinical events in the patients randomized to STI but only 1 OI occurred during the STI.

1. Miller et al. AIDS, 2000, 14:2857-67
2. Kallama et al. AIDS, 2004, 18:217-226
3. Lawrence et al. NEJM, 2003;349: 837-46.

Acknowledgements

CTN 164 site investigators: S. Walmsley, B. Trottier, B. Conway, J. MacLeod, S. Trottier, B. Cameron, S. Dufresne, B. Thompson, S. Rosser, J. Gil, S. Shafran, A. Rachlis, F. Small, K. Williams, J. Cohen, K. Gough, A. Piche, D. Rouleau.

Special thanks also to the co-investigators and research co-ordinators at each of the participating sites, P. Bratstein, J. Kreppner, D. Kraus, and other administrative staff at the Canadian HIV trials network, Richard Harrigan and the staff of the virology lab at the BC Center for Excellence.

This study was supported through an operating grant from the Canadian Institutes of Health Research. Dr. Sharon Walmsley is supported by a Career Scientist award from the Ontario HIV Treatment Network.