Supervised Treatment Interruption (STI) in an Urban HIV Clinical Practice: A Prospective Analysis

Joseph L. Yozviak DO, FACP
Lehigh Valley Health Network, joseph.yozviak@lvhn.org

Peter Kouvatos DO
Albright College

R Eric Doerfler NP, CCH
Bornemann Internal Medicine

William C. Woodward DO
Bornemann Internal Medicine

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William Chris Woodward
Bornemann Internal Medicine
Reading, PA
E-mail: wcwood@pld.net

Supervised Treatment Interruption (STI) in an Urban HIV Clinical Practice: A Prospective Analysis.

J.L. YOZVIAK[1], P. KOUVATSOS[2], R.E. DOERFLER[3], W.C. WOODWARD[3]

[1]Philadelphia College of Osteopathic Medicine, Philadelphia, PA; [2]Albright College, Reading, PA; [3]Bornemann Internal Medicine, Reading, PA

ABSTRACT

Background: In acute HIV-1 infection, STI may induce immunologic control of HIV-1 replication. Several prospective trials of STI in chronic HIV-1 infection have been less encouraging. A previously presented retrospective analysis of our patients showed that in those with a significant CD4 increase (>200 cells) on antiretroviral therapy (ART), 2 or more interruptions may significantly lower viral set point. This prospective study describes STI in a cohort of patients. **Methods:** 10 patients with either a positive response to therapy interruption retrospectively or those expressing interest in the strategy who met inclusion criteria (VL BLQ on ART, good adherence, robust CD4 response) were selected. Interruptions analyzed were prospective and supervised. Timing of STI cycles was based on CD4 and Viral Load (VL) responses not a predetermined schedule. Data collected included demographics, ART, VL, CD4, and illnesses during STI. **Results:** Of 7/10 patients with data at 4 weeks off ART, the mean VL was 1.78 $\log_{10}$ copies/ml below baseline (BL). In 10 patients > 8 weeks off ART, the mean VL was 1.38 $\log_{10}$ below BL. 7/10 maintained VL <5000 for > 8 weeks off ART (mean 27 weeks, 1 > 2 years). 4/7 with data during more than one STI showed an increase in time to reach 5000 copies/ml. None developed resistance-conferring mutations nor HIV-related illnesses during interruption. ART regimen or Hepatitis C seropositivity were not statistically significant factors affecting response to STI (duration <5000 or ΔVL; p>0.05). **Conclusions:** Although no consensus exists concerning the effectiveness of STI in chronic HIV infection, a majority of our subjects were able to stop ART and maintain viral control for a period of time. Closely monitored STI was associated with lowered viral set point during the interruption in most cases. A larger prospective study is warranted but we recommend future trials measure additional parameters and avoid using the same STI schedule for all subjects.

BACKGROUND

Effective antiretroviral treatment of human immunodeficiency virus-1 (HIV-1) infection requires long-term >95% adherence in the face of significant toxicity [1]. Additionally, eradication of HIV-1 infection does not appear to be possible with currently available agents [2]. Furthurmore, the DHHS guidelines for the treatment of HIV-1 infected adults and adolescents have been modified to reserve antiretroviral therapy (ART) until the CD4+ T-cell count (CD4) falls to <350 cells/ml [3]. This has led to debate about the practicality of the present doctrine of providing continuous ART to patients meeting criteria for ART. A large, ongoing, prospective trial may provide answers to this question [4]. Retrospectively, a few studies have attempted to elicit predictors of the ability to remain off ART for longer periods during treatment interruptions (TI) [5,6]. However, the results have been inconsistent. It has been shown that TI may induce immunologic control of viral replication in acute HIV-1 infection, thus reducing the need for ART in this setting [7]. Several trials of structured TI in chronic HIV-1 infection have been less encouraging [8-11]. A previously presented retrospective analysis of our patients showed that in those with a significant CD4 increase (>200 cells/ml) on ART, 2 or more TI may significantly lower the viral set point during the TI [12]. This prospective study describes the response to supervised treatment interruptions (STI) in a select cohort.

METHODS

- A prospective study of a select cohort of patients was conducted from 2/99 – 12/01 at Bornemann Internal Medicine (BIM), an urban HIV clinic.
- Patients were selected on the basis of a prior positive response to TI (>1 $\log_{10}$ decrease in rebound viremia during TI as compared to baseline VL) in our retrospective study or by expressing interest in STI and meeting the following criteria: VL below the level of quantification (BLQ) on ART, good adherence, robust CD4 response. BLQ was defined as less than 400 copies HIV-1 RNA per ml plasma (<50, if available).
- Treatment interruptions were planned and supervised by the medical provider. The timing of STI cycles was based on CD4 and VL responses not a predetermined schedule. All STI involved simultaneous cessation of the entire antiretroviral regimen for greater than seven (7) days.
- Charts were abstracted for the following: baseline study patient demographics, ART regimen, treatment duration, VL, CD4, STI duration, and illnesses during STI.

Table 1: Study Patients

Number of Patients:		10
Mean Age:		36.3 years
Sex:	Male	50.0% (5)
	Female	50.0% (5)
Race:	Hispanic	30.0% (3)
	Black	30.0% (3)
	Asian	10.0% (1)
	White	30.0% (3)
BLVL:	Mean	106991 copies/ml
	Median	73067 copies/ml
Mean Baseline CD4:		450 cells/mm^3

- HAART regimen prior to STI and Hepatitis C Virus seropositivity does not affect outcome (duration <5000 copies/ml plasma or -ΔVL) significantly (p >0.05).
- No patients developed resistance-conferring mutations.

Table 2: Duration of ART and STI

Pt.	Time on ART (weeks)	Time off ART (weeks)	Mean STI Duration	Total F/U (weeks)	% F/U on ART
1	120	30	7.5	150	**80.0%**
2	57	18	9.0	75	**76.0%**
3	96	19	19.0	115	**83.5%**
4	63	11	11.0	74	**85.1%**
5	59	73	36.5	132	**44.7%**
6	169	13	13.0	182	**92.9%**
7	193	32	16.0	225	**85.8%**
8	30	107	107.0	137	**21.9%**
9	19	15	15.0	34	**55.9%**
10	238	47	15.7	285	**83.5%**
Mean	**104.4**	**36.5**	**25.0***	**140.9**	**70.9%**

* Median STI Duration = 11.0 weeks

Table 3: Baseline vs. Latest F/U

Pt.	Baseline VL	Baseline CD4	VL at Latest F/U	CD4 at Latest F/U*	ART Status
1	341000	44	<50	504	On ART
2	94000	349	31600†	560†	On ART†
3	9000	484	2856	555	**STI**
4	120000	706	151	1089	On ART
5	39000	580	878	595	**STI**
6	53242	359	635	600	On ART
7	43391	575	1632†	375†	On ART†
8	92892	435	4701	608	**STI**
9	41700	360	4968	428	**STI**
10	235687	611	242	509	On ART

* Mean CD4 +132 compared to baseline at latest follow-up (p=0.036).
† Started ART at last visit. Last values listed from previous STI.

Table 4: Individual Patient Results

Pt.	# of STI	# of Previous TI	Greatest Duration <5000 copies/ml	Greatest –ΔVL At 4* Weeks (copies/ml)	Greatest –ΔVL At >8 Weeks (copies/ml)	Increase in time to 5000 copies/ml?	Illness during STI?
1	4	1	11 Weeks	-2.339 $\log_{10}$ (3 Wks.)	-2.357 $\log_{10}$ (11 Wks.)	No	None
2	2	0	-	-0.473 $\log_{10}$ (4 Wks.)	-0.210 $\log_{10}$ (9 Wks.)	No (No VL <5000)†	None
3	1	0	12 Weeks	NA**	-0.940 $\log_{10}$ (16 Wks.)	NA (1 STI)	*Strep.* Phayngitis/ Pneumonia
4	1	2	3 Weeks	-1.218 $\log_{10}$ (5 Wks.)	-1.591 $\log_{10}$ (11 Wks.)	NA (No data for TI 1,2)	None
5	2	3	40 Weeks	-1.622 $\log_{10}$ (6 Wks.)	-1.989 $\log_{10}$ (32 Wks.) -1.406 $\log_{10}$ (42 Wks.)	Yes	None
6	1	3	9 Weeks	-1.311 $\log_{10}$ (5 Wks.)	-0.925 $\log_{10}$ (11 Wks.)	Yes	None
7	2	0	22 Weeks	-2.938 $\log_{10}$ (4 Wks.)	-1.425 $\log_{10}$ (22 Wks.)	Yes	None
8	1	3	107 Weeks	-2.521 $\log_{10}$ (5 Wks.)	-2.471 $\log_{10}$ (15 Wks.) -2.199 $\log_{10}$ (79 Wks.) -1.296 $\log_{10}$ (107 Wks.)	Yes	None
9	1	0	15 Weeks	NA**	-0.924 $\log_{10}$ (15 Wks.)	NA (1 STI)	None
10	3	3	-	NA**	-1.012 $\log_{10}$ (8 Wks.)	No (No VL <5000)	None
Mean	**1.8**	**1.5**	**21.9 Weeks**	**-1.78 $\log_{10}$**	**-1.38 $\log_{10}$**	-	-

*Values ranged from 3-6 weeks. **No VLs available during the time period specified. † VL rebound at 4 weeks was 0.503 $\log_{10}$ lower in STI 2 than STI 1.

CONCLUSIONS

- STI allowed this select cohort of chronically-infected, HIV-1+ patients to discontinue ART for extended periods of time (median 11 weeks, mean 25 weeks, range 4-107 weeks). One patient (Pt. 8) remains off ART for more than 2 years.
- Most patients maintained VL >1 $\log_{10}$ below baseline at 4 weeks and at >8 weeks during STI and <5000 copies/ml for a mean of 21.9 weeks. 4 of 7 patients with data from multiple STI showed an increase in time to reach 5000 copies/ml in successive STI. This may be suggestive of an HIV-specific immunologic response. Immunoproliferative data is necessary to corroborate this finding.
- Even in the presence of multiple STI, most patients have improved immunologic status measured by CD4 count at latest follow-up as compared to baseline (p = 0.036). No OIs occurred during STI and no cases of acute retroviral syndrome were noted. Within this cohort, taking ART for only a mean of 70.9% of the total follow-up was sufficient to preserve and, in most cases, improve immunologic status. STI also allowed a respite from the rigors of ART (pill burden, intense compliance, adverse events).
- At latest follow-up, 6 of 10 patients are on ART with one patient BLQ, 2 approaching <50, and 2 patients without data due to starting ART at the last visit. Patient 6 has had persistently detectable, low-level viremia on d4T/ddI/HU, consistent with other patients taking this combination [8]. All 4 patients who are in an STI have VL <5000 copies/ml. No patients have developed resistance-conferring mutations.
- It should be noted that this is a selected cohort of patients, introducing multiple biases. It was our intent to use this study to evaluate our STI strategy, involving the selection of patients with good virologic and immunologic responses to ART and a history of good compliance. Randomization of patients in future trials may not show similar results.
- This cohort had high baseline viral loads and CD4 counts according to current DHHS treatment guidelines. Because treatment was initiated earlier, consistent with guidelines at the commencement of this study, future trials will need to address STI in patients initiating ART with more progressive disease.
- In summary, a majority of our subjects were able to stop ART and maintain viral control for a period of time. Closely monitored STI was associated with lowered viral set point during the interruption in most cases. We recommend that STI timing in future trials be based on virologic and immunologic parameters specific to each patient, not a pre-determined schedule.

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