Structured Treatment interrupion (STI) with Nevirapine (NVP) and Two Nucleoside Reverse Transciptase Inhibitors (NsRTI): Is Re-suppression Achieved Following Treatment Interruption?

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STRUCTURED TREATMENT INTERRUPTION (STI) WITH NEVIRAPINE (NVP) AND TWO NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NsRTI): IS RESUPPRESSION ACHIEVED FOLLOWING TREATMENT INTERRUPTION?

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ABSTRACT

Background: Previous studies have suggested that STI with a protease inhibitor (PI) regimen does not result in resistance-conferring mutations or reduced treatment efficacy upon reinitiation. Prospective trials will likely not be performed with NNRTIs due to their low genetic barrier. This study evaluates the effectiveness of reinitiation of NVP and dual NsRTI after an antiretroviral therapy interruption (ART-i) in patients with viral load (VL) below the level of quantification (BLQ) on the same regimen. **Methods:** Retrospective chart review of all patients (N = 536) seen 9/96 to 4/00 yielded 135 patients on NVP and dual NsRTIs. Charts were abstracted for NVP regimen, treatment duration, VL before/during ART-i, ART-i duration, and VL after reinitiation. ART-i was defined as simultaneous cessation of entire regimen for ≥7 days. BLQ was defined as <400 HIV RNA copies/mL plasma (<50 copies/mL, if available). **Results:** 17/135 had VL BLQ with documented ART-i followed by initiation of the same regimen; 2/17 had a 2nd ART-i and 2/17 had a 3rd ART-i yielding 23 total ART-i for analysis. Mean baseline VL (BLVL) was 108,276 (5.03 $\log_{10}$) copies/mL. Mean initial ART duration was 193 days. Mean ART-i duration was 58 days. Upon reinitiation, VL fell BLQ (<400 copies/mL) in 21 of 23 interruptions (91.3%). Nonadherence was associated with one failure, while viral isolates resistant to NVP (Y181C) were detected in the other. **Conclusions:** After ART-i, reinitiating an NVP regimen resulted in resuppression of VL to BLQ in most adherent patients. These results suggest that an NNRTI does not require switch to a PI prior to planned interruption; however, the possibility of failing to resuppress does exist. A larger retrospective study is indicated. Direct interruption of an NNRTI regimen could lead to design of easier and more efficient STI protocols.

BACKGROUND

Because of the need for long-term adherence to and emerging long-term toxicity of antiretroviral therapy (ART), it has become apparent that long-term continuous ART may not be possible for most HIV-1 chronically infected patients. Alternative treatment strategies are being examined, including Structured Treatment Interruptions (STI). Thus far, the results of numerous small trials have been variable, with some suggesting immunologic control of viral replication off ART and others showing viral rebound to baseline or above.[1-15] Although little has been proven about the safety and theorized induction of virologic control, a few studies have shown that STI does not lead to resistance-conferring mutations; treatment efficacy is not reduced following STI in patients on protease inhibitor (PI)-based regimens.[5,6,13,15] Due to the long half-life of NNRTIs and concerns about the development of resistance, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens have not been included in the design of these trials. With data now available showing comparable potency and better tolerability, ART courses in STI trials may be easier if NNRTIs were utilized. However, there is a lack of data on the efficacy of reinitiating NNRTIs after STI. To answer this question without compromising our patients' ART options, we retrospectively examined the efficacy of nevirapine (NVP)-based regimens following interruption of the same NVP-based regimen in patients with viral load below the level of quantification (BLQ).

METHODS

- A retrospective chart review of all patients (N = 536) seen from 9/96 to 4/00 was conducted at Bornemann Internal Medicine (BIM), an urban HIV clinic
- The term antiretroviral therapy interruption (ART-i) was used instead of STI due to the retrospective nature of this study. Most of the interruptions were due to adverse events (AEs) and other factors, and not due to an attempt at induction of immunologic control of viral replication, or an attempt at reversion of resistant viral populations to wild-type. ART-i was defined as simultaneous cessation of the entire antiretroviral regimen for greater than seven (7) days.
- Charts were abstracted for the following: baseline study patient demographics, NVP-containing regimen, treatment duration, VL before and during ART-i, ART-i duration, and VL after reinitiation of the same NVP-based regimen.
- BLQ was defined as less than 400 HIV-1 RNA copies/mL plasma (<50, if available)

Table 1. Study patients

Number of patients		17
Average age		36.3 years
Sex:	Male	58.8% (10)
	Female	41.1% (7)
Race:	Hispanic	47.1% (8)
	Black	41.1% (7)
	Asian	5.9% (1)
	White	5.9% (1)
BLVL:	Average	108,276 copies/mL
	Median	39,000 copies/mL
Mean CD4+ nadir:		263 cells/mm^3

Table 2. Individual patient results

Patient	BLVL	NsRTI	ART duration (days)	ART-i duration (days)	VL before ART-i	VL during ART-i	VL after ART-i	Noncompliant?
1	23,294	ZDV/3TC	214	72	<400	26,701	<50	-
2	47,177	d4T/3TC	161	21	<400	66,699	<50	-
3	7,490	d4T/3TC	486 229 150	162 35 20	<50 <50 <50	646 <50 -	<50 <50 <50	-
4	2,487	d4T/3TC	141	17	<400	27,879	<50	-
5	39,000	d4T/3TC	213	96	<50	5,200	<50	-
6	8,689	d4T/3TC	151 44	51 82	<400 <400	- 3,000	<400 <50	-
7	64,592	d4T/3TC	150	7	<50	-	<50	-
8	5,500	d4T/3TC	229	116	<50	6,100	<50	-
9	7,219	d4T/3TC	83 125	22 45	<400 <400	- 23,238	<400 <50	-
10	96,177	d4T/3TC	327	116	<400	>30,000	**580**	**Yes**
11	81,000	d4T/3TC	528	87	<50	30,000	<400	-
12	341,000	d4T/3TC	37 26 45	45 32 79	<50 <400 <50	12,278 167 1,500	<400 <50 <50	-
13	20,214	ZDV/3TC	244	39	<400	-	<50	-
14	367,481	ZDV/3TC	49	7	<50	-	<50	-
15	29,000	ddI/3TC	126	7	<50	<50	<50	-
16	349,091	ddI/3TC	364	20	<50	13,000	<50	-
17	351,288	ddI/3TC	314	64	<50	30,440	**1,027***	-
Mean	**108,276**	**-**	**193**	**58**	**-**	**16,830**	**-**	**-**

*Viral isolates contained Y181C mutation.

21/23 patients (91.3%) achieved resuppression of viral load following reintroduction of NVP regimen.

SUMMARY – CONCLUSIONS

- The efficacy of NVP-based regimens was not reduced following reintroduction of ART after ART interruption in most patients
- The failure in patient 10 could be attributed to reported noncompliance (no genotype available). Numerous studies have shown that noncompliance greatly reduces the efficacy of NVP regimens through the selection of resistance-conferring mutations.[16] Patient 17 had an impeccable history of compliance and reported good compliance following STI. Therefore, STI cannot be ruled out as the main contributing factor to the selection of the Y181C mutation in this patient
- Both patients failing to resuppress had a high BLVL (10: 96,177;17: 351,288). However, most patients with BLVL >100,000 copies/mL (75.0%, N = 4) did resuppress after ART-i
- The mean BLVL was significantly higher than the mean VL measured during the ART-i (ΔVL = -0.808 $\log_{10}$, $P = 0.009$). Caution must be exercised when drawing conclusions from this result. The interruption period was not the same for all patients, and a viral load set point may not have been reached in some
- The mean duration of ART was approximately three times the duration of ART-i. Due to the study design, we could not accurately measure the duration of BLQ while on ART. The duration of BLQ would be more appropriate to measure in future prospective trials, as it takes certain patients longer than others to reach BLQ and to have sufficient increase in CD4+ to impact a reduction in rebound VL[1]
- It is important to note that patients in this study stopped ALL medications simultaneously. Recent discussion has suggested the strategy of sequential interruption, stopping NsRTIs 48 hours after stopping NNRTIs. This may provide the necessary additional inhibition of resistant viral outgrowth during the slow decline of NNRTI concentration
- ART interruptions have been a common part of clinical practice since the development of PIs, with interruption rates ranging from 36.2% to 45.9%.[1,17] As the need for long-term ART becomes more evident, we should study and examine the effects of STI. We could then utilize this inevitable event as a benefit to the patient, be it through virologic control or temporary relief from AEs
- **In summary, following ART-i, reinitiating NVP and two NsRTIs resulted in the suppression of viral replication to BLQ in most adherent patients. Utilizing sequential interruption of NNRTI-based regimens should allow for the design of easier STI protocols. Further examination of this and all aspects of STI is warranted**

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