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Cognitive functioning during highly active antiretroviral therapy interruption in human immunodeficiency virus type 1 infection

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Although no longer considered therapeutically beneficial, antiretroviral treatment interruptions (TIs) still occur frequently among patients with human immunodeficiency virus (HIV) infection for a variety of reasons. TIs typically result in viral rebound and worsening immunosuppression, which in turn are risk factors for neurocognitive decline and dementia. We sought to determine the extent of neurocognitive risk with TIs and subsequent reintroduction of highly active antiretroviral therapy (HAART) by using a comprehensive, sensitive neuropsychological assessment and by concurrently determining changes in plasma and cerebrospinal fluid (CSF) viral load and CD4 counts. Prospective, serial, clinical evaluations including neuropsychological (NP) testing and measurement of plasma HIV RNA and CD4 count and mood state were performed on HIV-1–infected individuals ($N=11$) at three time points: (1) prior to a TI, while on HAART; (2) after TIs averaging 6 months; and (3) after reinitiating HAART therapy. During TI, plasma HIV RNA increased and CD4 counts declined significantly, but NP performance did not change. Following reinitiation of HAART, viral loads fell below pre-TI levels, and CD4 counts rose. Improved viral suppression and immune restoration with reinitiation of HAART resulted in significant improvement in neurocognitive performance. No changes on comprehensive questionnaires of mood state were observed in relation to TI. NP performance and mood state remained stable during TIs despite worsened viral loads and CD4 counts. Because ''practice effects'' are generally greatest between the first and second NP testing sessions, improvement at the third, post-TI time point was unlikely

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to be accounted for by practice. TIs of up to 6 months appear to be neurocognitively and psychiatrically safe for most patients. *Journal of NeuroVirology* (2008) **14,** 550–557.

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Introduction

Treatment of human immunodeficiency virus (HIV) infection with highly active antiretroviral therapy (HAART) restores immune function, thereby reducing opportunistic disease and acquired immunodeficiency syndrome (AIDS)-related mortality. Nevertheless, the costs, side effects, and problems with access to antiretroviral medications often lead to treatment interruption (TI), which has become sufficiently common that recommendations on TI implementation have been recently formulated (Taylor *et al*, 2007). Although the landmark STRATEGIES FOR MANAGEMENT OF ANTI-RETROVIRAL THERAPY (SMART) study clearly demonstrated the superiority of continuous antiretroviral therapy to CD4-guided treatment interruption (El-Sadr *et al*, 2006), other recent studies indicate that TIs remain common. For example, in a study of 8300 subjects, 19.3% of subjects initially on stable HAART-interrupted treatment for a median duration of 189 days (Touloumi *et al*, 2006).

Although TIs remain common, no prospective studies have comprehensively assessed their neuropsychological (NP) and psychiatric impact. One small study showed no loss of motor speed during TI (Price and Deeks, 2004). However, the NP battery was limited and thus might have overlooked clinically significant deterioration. There is considerable evidence supporting the notion that ongoing viral replication may worsen neurocognitive function in HIV (Ellis *et al*, 1997, 2002). The purpose of this study was to evaluate whether TI and the ensuing rebound of viral replication and loss of CD4 cells adversely affected cognitive functions and mood. Additionally, we examined the same individuals after reinitiating antiretroviral therapy.

Table 1 Baseline subject demographic and select clinical characteristics.

	Baseline characteristics
Age	35 (32–42)
No. (%) male	9 (82)
No. (%) Caucasian	5 (45)
Education (years)	12 (12–15)
Duration of HIV infection (years)	9 (4–12)
CD4 nadir (cells/μl)	200 (23–371)
% CDC classification of AIDS	45
% neuropsychologically impaired	27
Beck Depression Inventory score	5 (1–15)
POMS (*z*-score)	1.0 (−0.1–1.6)

Note. Values are median (interquartile range) unless otherwise specified.

Results

Baseline demographic and select subject clinical characteristics are shown in Table 1. Subjects were treated with their pre-TI HAART regimens for a median of 10 months (IQR: 2–28; 95% CI: 1–80) at the time of pre-TI NP testing. TIs lasted a median of 6 months (IQR: 3–12; 95% CI: 3–14) and TI NP testing occurred a median of 3 months (IQR: 2–6; 95% CI: 1–10) after cessation of therapy. Post-TI, three subjects restarted their previous antiretroviral regimen, whereas eight subjects initiated a new HAART regimen. Post-TI NP testing occurred a median of 6 months (IQR: 5–12; 95% CI: 4–17) after TI NP testing, at which time subjects had resumed HAART for a median of 3 months (IQR: 2–6; 95% CI: 1–11). The median number of months between pre-TI and post-TI testing was 12 (IQR: 11–25; 95% CI: 6–37). Table 2 contains information regarding HAART regimens pre- and post-TI.

Detailed results of analyses are presented in Table 3. Primary findings are outlined below by assessment interval. Changes in plasma and cerebrospinal fluid (CSF) HIV RNA and GDS scores at the three serial evaluations are depicted in Figure 1.

Pre-TI to TI

Global Deficit Scores (GDSs) did not change significantly from pre-TI to TI testing ($p = .72$). Profile of Mood States (POMS) and Beck Depression Inventory (BDI) total scores also did not change significantly

Table 2 Characteristics of study subjects' antiretroviral (ARV) drug regimens pre- and post-TI.

	Pre-TI	Post-TI
Number of ARVs in regimen (median [range])	3 [3–5]	3 [3–7]
% containing PIs	73	36
% containing NRTIS*	100	100
% containing NNRTIs	27	73
% reporting at least 95% adherence to HAART†	82	91

*NRTIs include NARTIs.
†Adherence information not available for one subject.
PI = protease inhibitors; NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = non-nucleoside reverse transcriptase inhibitors; NARTIs = nucleotide analogue reverse transcriptase inhibitors.

Table 3 Clinical and laboratory characteristics at serial time points.

	Pre-TI	TI	Post-TI
Global Deficit Score	.31 (0.12–0.76)	.31 (0.18–0.71)	.18 (0.00–0.41)[a]
Beck Depression Inventory	5 (1–15)	5 (1–13)	4 (1–19)
Profile of Mood States (z-score)†	1.1 (−0.1–1.6)	0.7 (−0.2–1.7)	1.0 (−0.2–1.6)
Plasma HIV RNA (log copies/ml)	2.60 (2.60–4.02)	4.80 (4.22–5.45)[a]	2.60 (2.60–4.74)[b]
Virologically suppressed*, no. (%)	6 (55%)	0 (0%)	7 (64%)
CD4+ T lymphocytes (cells/μl)	363 (86–717)	247 (16–395)[a]	310 (27–546)

Note. Values are median (IQR), unless otherwise specified.
†Data not available for one subject.
*Plasma HIV RNA < 400 copies/ml.
[a]Significantly different from pre-TI ($p < .01$).
[b]Significantly different from TI ($p < .01$).

from pre-TI to TI testing ($p = .74$ and $p = .63$). Plasma HIV RNA levels increased significantly from pre-TI (median = 2.60 log copies/ml; IQR = 2.60–4.02; 95% CI: 2.60–6.15) to TI (median = 4.80 log copies/ml; IQR = 4.22–5.45; 95% CI: 3.95–6.00) time points ($z = 2.76$, $p = .006$). Plasma viral load increased in all subjects excluding one, and 9 of 11 experienced an increase of ≥1 log. A Spearman's rho analysis indicated that increase in plasma HIV RNA levels was not correlated with length of time since cessation of HAART ($p = .43$), suggesting that all patients had rebounded to their viral load set point at the time of the TI assessment. CD4 counts decreased significantly from pre-TI (median = 363 cells/μl; IQR = 86–717; 95% CI: 40–1214) to TI (median = 247 cells/μl; IQR = 16–395; 95% CI: 0–814; $z = -2.67$, $p = .008$). Median decrease in CD4 count was not significantly correlated with length of time since cessation of HAART ($p = .44$).

TI to Post-TI

GDSs showed a statistical trend towards improvement from TI (.31) to post-TI (.18) assessments ($p = .04$). A Spearman's rho analysis indicated variable

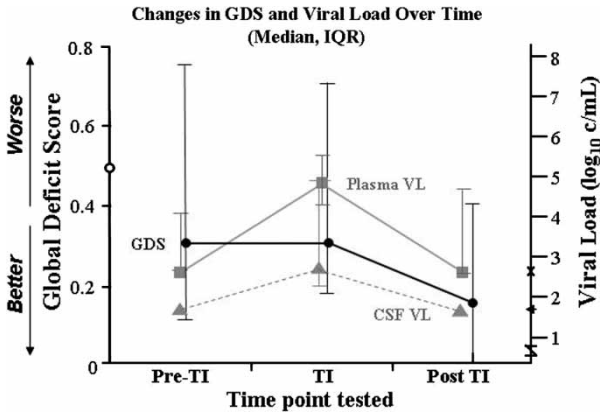

Figure 1 GDS scores evaluated at three serial time points compared to plasma and CSF viral loads (copies/ml). GDS scores > 0.5 are considered cognitively impaired (indicated by 0 on left x-axis) Limits of viral load detection are shown on the right x-axis. x = plasma (2.6 $\log_{10}$ copies/ml)$_j$ ← = CSF (1.7$\log_{10}$ c/mL). No error bars are shown at pre-TI and post-TI time points for CSF because viral load is undetectable.

delays from HAART resumption to post-TI NP testing were not associated with GDS improvement ($p = .47$). POMS and BDI total scores did not change significantly from TI to post-TI testing ($p = .22$ and $p = .16$). Plasma viral load decreased significantly from TI (median = 4.80 log copies/ml; IQR = 4.22–5.45; 95% CI: 3.95–6.00) to post-TI study visits (median = 2.60 log copies/ml; IQR = 2.60–4.74; 95% CI: 2.60–5.89; $z = -2.85$, $p = .004$). Decline in HIV RNA TI to post-TI was not significantly associated with length of time on post-TI HAART regimen ($p = .08$). There was a trend toward increase in CD4 count from TI to post-TI visits ($p = .04$), but duration of HAART was not significantly related to CD4 change ($p = .40$).

Pre-TI to Post-TI

GDSs improved significantly from pre-TI (median = 0.31; IQR = 0.12–0.76; 95% CI: 0.07–2.21) to post-TI assessments (median = 0.18; IQR = 0.00–0.41; 95% CI: 0.00–2.00; $z = -2.81$, $p = .005$). The median improvement in GDS was .13 (IQR = .07–.22; 95% CI: 0.00–0.35). POMS and BDI scores did not change significantly ($p = .37$ and $p = .21$). Plasma HIV RNA levels did not change significantly ($p = .75$), although a somewhat larger proportion of subjects achieved virologic suppression on their new HAART regimens. CD4 counts did not change significantly between the two assessments ($p = .48$). Three subjects (27%) showed a pre- to post-TI increase in CD4 count, whereas the rest did not reach pre-TI CD4 counts. GDS improvement was not related to the length of the interval between evaluations ($p = .88$) or to the magnitude of change in viral load ($p = .36$) or CD4 count ($p = .31$).

Discussion

Contrary to expectations, we found that overall cognitive performance and mood remained stable in 11 individuals undergoing TIs averaging 6 months, despite adverse changes in viral load and CD4 count. Our data are consistent with those of Price and Deeks (2004), and expand on their find-

ings with a comprehensive neuropsychological evaluation and a more methodologically rigorous design that includes follow-up assessment post-TI. These findings support that time-limited TI can be undertaken safely from a neurocognitive and psychiatric standpoint.

Several well-established observations imply that TI might lead to neurocognitive decline. First, elevated plasma and CSF HIV RNA levels, reflecting high levels of ongoing viral replication, are associated with a higher risk of cognitive impairment in HIV infection (Childs *et al*, 1999; Ellis *et al*, 2002; Marcotte *et al*, 2003). Second, reduction of viral load following HAART initiation is associated with improvements in neurocognitive performance and reduced risk of incident impairment (Price *et al*, 1999; Richardson *et al*, 2002; Tozzi *et al*, 1999). Given that TI leads to marked increases in viral load in most patients, TI may deleteriously affect cognitive performance. This prospective study utilized comprehensive neuropsychological (NP) and mood assessments, reducing the likelihood that clinically significant cognitive or psychiatric declines were overlooked.

Because this study evaluated a relatively small sample, it cannot exclude the possibility that TI deleteriously affects a minority of HIV-infected subjects, especially those who have clinical and demographic characteristics different from those studied here. The majority of patients in this study were male, Caucasian, had moderately advanced HIV disease (AIDS-defining opportunistic illnesses, nadir CD4 <200), and were NP normal prior to TI. Individuals with chronic, latent infection and those who were NP impaired prior to TI were less well represented in the sample. In our study, only three subjects (27%) were impaired at baseline. Patients impaired at baseline might be at higher risk for further neurocognitive decline during TI and we were unable to address this question. In addition, because no comparison group was studied (e.g., HIV-infected individuals not undergoing TI), we cannot rule out the possibility that our subjects performed more poorly or better than would have otherwise been anticipated. Studies of larger, more diverse populations in the use of comparison groups will be needed to more definitively address the neurocognitive safety of TI.

Among individuals with advanced HIV disease who are failing HAART, TI is often undertaken in an attempt to reestablish a predominant population of wild-type, antiretroviral drug–susceptible virus. The theoretical goal of TI in this setting is to improve the likelihood of a good virologic response (i.e., suppression) when HAART is reinitiated. Half of our patients were failing their current antiretroviral regimens prior to TI, however, the majority of these (4/5) experienced an increase in viral load during TI, suggesting that although subjects were not achieving complete viral suppression with ART, they were receiving some virologic benefit. Neither subjects failing ART nor those suppressed pre-TI had evidence of neurocognitive or psychiatric decline during TI or post-TI.

Lack of cognitive or affective deterioration during TIs might reflect the relatively short duration of TIs and the slow pace of pathophysiological events that lead to neurocognitive decline. Long delays in reinitiation of HIV replication did not explain this lack of progression. All our subjects showed significant viral rebound after TI, and TIs were of similar duration to, or longer than, those used in most clinical settings (Ruiz *et al*, 2003). Thus, if neurocognitive decline occurred frequently in patients undergoing 'typical' TIs, it should have been evident here.

Resumption of HAART for an average of 3 months in our subjects was associated with suppression of plasma viremia (undetectable HIV RNA) in seven subjects (64%). Because five of these subjects were suppressed prior to TI, viral loads did not change significantly from the pre- to the post-TI visit. However, reinitiation of HAART was followed by a statistically significant, albeit modest, improvement in NP performance to levels exceeding those measured before TI. Because most patients were rated as globally unimpaired at both assessments, the clinical significance of this improvement is uncertain.

Every subject maintained or improved NP performance pre- to post-TI. All participants underwent treatment interruption and nine (82%) initiated a new ARV regimen post-TI. Regimen changes may have resulted in relief from substantial drug-related side effects, allowing for a small overall improvement in functioning. In addition, the percentage of ARV regimens containing protease inhibitors (PIs) decreased dramatically pre- to post-TI, with seven subjects removing PIs from their regimens and replacing them with nucleoside (NRTIs) and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Each class of antiretroviral drugs has a different range of permeabilities with respect to the blood-brain and blood–central nervous system (CNS) barriers. As a drug class, PIs show reduced permeability in comparison to NNRTIs or NRTIs (Letendre *et al*, 2000, 2001; Reddy *et al*, 2003). Replication of HIV in the CNS can occur independently from systemic replication, and CSF HIV RNA levels are elevated among HIV-infected individuals with neurocognitive dysfunction (Ellis *et al*, 1997, 2000, 2002). The replacement of PIs with ARVs conferring greater CNS penetration may have resulted in more effective treatment of HIV in the CNS, allowing for a slight improvement in NP perfor-

mance. However, the small sample size of this study, variations in baseline impairment, and the contribution of other changes within regimens prohibit statistical exploration of this speculation here.

Repeated administration of the tests—i.e., practice effects—might have led to artifactual improvement. However, the pattern of changes in performance over time was incompatible with practice effects as described in previous studies. Improvements in NP performance related to practice are typically most pronounced at the second test exposure (Duff *et al*, 2001; Sattler, 2001), and significant improvement occurred only at the third assessment. In addition, the clinical significance of the NP improvement is uncertain as the median improvement in GDS pre- to post-TI was .13 (IQR = .07–.22; 95% CI: 0.00–0.35), and few subjects were significantly impaired at baseline.

In summary, the results of the current study suggest that although viral load and CD4 count worsen during TIs lasting several months, no pronounced decline in NP functioning or psychiatric status are evident. In fact, improvement in clinical status with re-initiation of HAART may be accompanied by a modest ''boost'' in NP performance.

Methods

Subjects

Subjects were nine men and two women participating in longitudinal studies at the HIV Neurobehavioral Research Center at the University of California, San Diego, between 1999 and 2002. Study participation included multiple visits conducted over an average of 1 year. Inclusion criteria were HIV infection confirmed by measurement of HIV RNA by reverse transcriptase–polymerase chain reaction (RT-PCR) and planned TI with the intention to resume therapy in the future. Exclusion criteria included untreated central nervous system (CNS) or systemic opportunistic disease, active psychosis, or other disorder deemed likely to interfere with study participation. Sample selection is described in Figure 2 and detailed subject characteristics are provided in Table 1. Written informed consent was obtained from all participants according to a protocol approved by the institutional human subjects review panel.

Clinical Evaluations

Subjects were assessed at three time points: (1) pre-TI, during which each subject was on HAART; (2) TI, during which the subjects took no antiretrovirals; and (3) post-TI, during which subjects reinitiated HAART therapy. HAART was defined as an antiretroviral drug regimen containing three or more antiretroviral medications. Detailed information regarding pre- and post-TI HAART regimens are provided in Table 2. TI was defined as a planned cessation of HAART therapy. In consultation with their primary care providers, subjects decided when to interrupt and resume therapy.

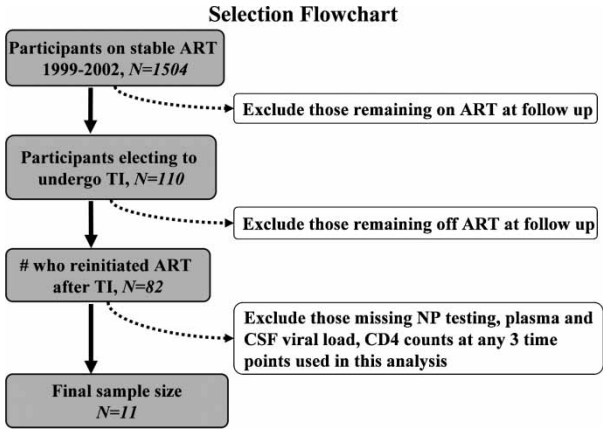

Figure 2 This chart explains how subjects were selected for analyses. The final sample had NP testing, plasma and CSF viral load, CD4 counts at all 3 time points.

At each visit, participants underwent a comprehensive neuromedical evaluation using structured clinical data forms to assess medical and medication use history, antiretroviral medications and self-reported adherence, neurological and general physical examinations, and laboratory studies including CD4 counts, routine hematology, and chemistry measurements. Participants were assessed to exclude central nervous system opportunistic disease, and to assign HIV disease stage according to the Centers for Disease Control guidelines (CDC, 1992). Adherence to antiretroviral medications was assessed in 10 of 11 subjects using the AIDS Clinical Trials Group's brief self-report instrument (Chesney *et al*, 2000).

Laboratory Measures

We measured plasma HIV RNA levels by reverse transcriptase–polymerase chain reaction (RT-PCR) using the Amplicor HIV-1 Monitor Test (Roche Molecular Systems; nominal detection limit 400 copies/ml). HIV RNA values were $\log_{10}$-transformed prior to analysis. The assay's nominal detection limit was used as the lower limit cut-off for HIV RNA values (2.60 log copies/ml). Virologic suppression was defined as a plasma HIV RNA level of <400 copies/ml after at least 2 months of HAART, and virologic failure was defined as a plasma HIV RNA level of >400 copies/ml while on HAART for at least 2 months. CD4+ T-lymphocyte (CD4) counts were quantified by a fluorescence-activated cell sorter.

Neuropsychological Evaluation

All participants completed a comprehensive neuropsychological (NP) testing battery, which was developed to afford a brief (i.e., 2 to 3 h), but

wide-ranging assessment of the NP domains affected by HIV disease. The specific domains tested were information processing speed, executive functions, working memory, verbal fluency, learning, recall, and motor coordination. The test battery consisted of (1) Hopkins Verbal Learning Test—Revised (HVLT-R trials 1 to 3 and delayed free recall) (Benedict *et al*, 1998); 2) Brief Visuospatial Memory Test – Revised (BVMT-R trials 1-3 and delayed free recall) (Benedict, 1997); (3) Controlled Oral Word Association Test (COWAT-FAS total correct) (Benton *et al*, 1994; Gladsjo *et al*, 1999); (4) Semantic verbal fluency—animals (total correct) (Gladsjo *et al*, 1999); (5) Stroop Color-Word Test (interference trial) (Golden, 1978); (6) Trail Making Test, Parts A and B (total time) (United States Army, 1994; Heaton *et al*, 1991); (7) Wisconsin Card Sorting Test—64 Card Version (perseverative responses) (Kongs *et al*, 2000); (8) Halstead Category Test (total errors) (Heaton *et al*, 1991; Reitan and Wolson, 1993); (9) Paced Auditory Serial Addition Test (PASAT-200 total correct) (Diehr *et al*, 1998; Gronwall, 1977; Gronwall and Sampson, 1974); (10) Grooved Pegboard Test (time to completion for dominant and nondominant hands) (Heaton *et al*, 1991; Klove, 1963); and (11) the Digit Symbol, Symbol Search, and Letter-Number Sequencing tests from the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) (The Psychological Corporation, 1997; Heaton *et al*, 2002). All NP tests were administered and scored by trained psychometrists who adhered to the standardized procedures outlined in the various test manuals.

For each of the NP test variables above, raw scores were converted to demographically corrected T-scores using published normative data. T-scores were transformed into deficit scores using the following conversions: $\geq 40T = 0$; $39T–35T = 1$; $34T–30T = 2$; $29T–25T = 3$; $24T–20T = 4$; and $\leq 19T = 5$. To obtain a measure of global NP functioning, the deficit scores from each NP test variable were averaged to derive a Global Deficit Score (GDS) for each participant. Prior research supports the construct validity of the GDS approach as an indicator of global NP functioning in persons with HIV infection (Carey *et al*, 2004; Heaton *et al*, 1995). A score of .50 or above on the GDS indicates global impairment.

To evaluate possible changes in psychiatric status, participants completed the Profile of Mood States (POMS) (McNair *et al*, 1992) at all three time points. The POMS is a reliable and valid comprehensive measure of affective states (e.g., anxiety, depression, confusion, fatigue) on which participants rate 65 mood-related adjectives on a scale ranging from 0 (not at all) to 4 (extremely). Raw scores were converted to *z*-scores using published, demographically corrected normative data (Nyenhuis *et al*, 1999). A *z*-score of >1.5 is traditionally used as a cut-point for considerable affective distress. Participants also completed the Beck Depression Inventory (BDI; Beck *et al*, 1996) at all three assessments. The BDI is a widely used 21-item self-report screening questionnaire on which participants indicate the severity of their experienced depressive symptoms (e.g., sadness) using a 4-point Likert-type scale. Total scores on the BDI range from 0 (no depression) to 63 (severe depression), with scores above nine typically used as an indicator of mild depression.

Statistical Analyses

Because sample sizes were relatively small, and the distribution of the clinical variables in most cases deviated significantly from normal, a series of nonparametric Wilcoxon signed-rank tests were employed in a repeated measures design to assess the direction and magnitude of changes in GDS, POMS, BDI, plasma HIV RNA levels, and CD4 counts between time points. When a significant change in one of these variables occurred, Spearman's rho correlations were performed to determine if the change was related to variability among subjects in length of time between changes in antiretroviral status (on or off). Given the exploratory nature of the study, small sample size, and multiple comparisons, to avoid type 1 error, *p* values $\leq .01$ were considered significant.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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