Published in final edited form as:

AIDS. 2009 January 14; 23(2): 203–212. doi:10.1097/QAD.0b013e32831cc114.

Inferiority of IL-2 alone versus IL-2 plus HAART in maintaining CD4 T cell counts during HAART interruption: a randomized controlled trial

Brian O. Porter,

National Institutes of Health, National Institute of Allergy & Infectious Diseases

Kara B. Anthony,

National Institutes of Health, National Institute of Allergy & Infectious Diseases

Jean Shen,

National Institutes of Health, Critical Care Medicine Department

Barbara Hahn,

National Institutes of Health, Critical Care Medicine Department

Chris E. Keh,

National Institutes of Health, National Institute of Allergy & Infectious Diseases

Frank Maldarelli,

National Institutes of Health, National Cancer Institute

William C. Blackwelder,

National Institutes of Health, National Institute of Allergy & Infectious Diseases, Consultant

H. Clifford Lane,

National Institutes of Health, National Institute of Allergy & Infectious Diseases

Joseph A. Kovacs,

National Institutes of Health, Clinical Center

Richard T. Davey, and

National Institutes of Health, National Institute of Allergy & Infectious Diseases

Irini Sereti

National Institutes of Health, National Institute of Allergy & Infectious Diseases

Abstract

Corresponding Author/Reprint Requests: Dr. Irini Sereti, National Institutes of Health, Building 10-Magnuson Clinical Center, Room 11C103, 10 Center Drive, Bethesda, Maryland, 20982, Phone: (301) 496-5533, Fax: (301) 402-4097, isereti@niaid.nih.gov.

Conflicts of Interest:

The US Government has been granted a patent for the use of intermittent subcutaneous IL-2 as therapy in HIV infection, listing H. C. Lane and J.A. Kovacs as co-inventors.

Prior Publication Disclosure

These findings have not been published previously in their present form. However, preliminary data from this study were presented at the 2008 Conference on Retroviruses and Opportunistic Infections (CROI) and were published in abstract form (Abstract #706) in the 2008 CROI Proceedings (Boston, Massachusetts; February 3–6, 2008).

Objective—To evaluate if interleukin (IL)-2 in patients with chronic HIV infection can maintain CD4 T cell counts during 6 months of highly active antiretroviral therapy (HAART) interruption.

Design—Prospective, randomized, controlled, open-label phase II non-inferiority trial comparing IL-2 with HAART interruption or continuous HAART (ICARUS).

Methods—41 IL-2-experienced (≥3 prior cycles) HIV-1-infected adults with CD4 ≥500 cells/μl were randomized 2:1 to Interrupted (I=27) or Continuous (C=14) HAART for 6 months (M6) following an initial IL-2 cycle. Subsequent IL-2 cycles were triggered by CD4 T cell counts <90% of baseline. Immune, metabolic, and quality of life indices were compared (Mann-Whitney and Fisher's Exact tests), defining non-inferiority as a percent difference (C–I) in Treatment Success (CD4 T cells ≥90% of baseline at M6) with a 95% confidence interval (CI) lower limit > –20%.

Results—Demographic and immune parameters were similar between the groups at baseline. Median CD4 T cell count, HIV viral load, and Treatment Success differed significantly at M6 (I: 866 cells/μl, 39,389 copies/ml, 48.1%; C: 1246 cells/μl, <50 copies/ml, 92.3%; $p = 0.001$). Group I was inferior to C (% difference = –44.2%; 95% CI: –64.2%, –11.2%; $p = 0.013$). Minor statistically significant differences in HgbA1c and energy level occurred at M6 (I>C). Following HAART interruption, single cases of acute retroviral syndrome, secondary syphilis, Non-Hodgkin's Lymphoma, and Kaposi's sarcoma recurrence were observed.

Conclusions—IL-2 alone was inferior to IL-2 plus HAART in maintaining baseline CD4 T cell counts. HAART interruption had a small impact on metabolic parameters and quality of life.

Keywords

Interleukin-2; HIV infections; Highly Active Antiretroviral Therapy; CD4 Lymphocyte Count; Lipodystrophy; Randomized Controlled Trial

Introduction

Highly active antiretroviral therapy (HAART) has dramatically improved the outcome of HIV infection [1–3] but can be associated with high costs, medication fatigue, and adverse effects including hepatotoxicity [4] and a metabolic lipodystrophy syndrome involving insulin resistance, hyperlipidemia, and fat redistribution [5, 6]. HAART interruption strategies have been evaluated to minimize these adverse effects [7], but their safety was questioned by several large, randomized studies [8–12], which revealed increased rates of HIV disease progression and non-HIV-associated clinical events (e.g., the Strategies of Management of Anti-Retroviral Therapy (SMART) trial [11]).

In attempts to abrogate CD4 T cell losses and re-emergence of HIV viremia seen with HAART interruption, immunomodulatory approaches including interleukin (IL)-2 cytokine therapy have been evaluated. When used with anti-retrovirals (ARVs), intermittent courses of intravenous or subcutaneous IL-2 can significantly expand the CD4 T cell pool in HIV-infected patients [13, 14]. This results primarily from increased survival of naïve [15, 16] and central memory [17, 18] CD4 T cells, including a cytokine-expanded naïve CD4+CD25+ FoxP3-expressing subset, which resembles regulatory T cells [19, 20]. Two international, multi-center, phase III clinical trials (ESPRIT, SILCAAT) are currently

underway to determine the clinical relevance of these IL-2 effects with regard to HIV disease progression [21, 22].

In addition to its adjuvant role in ARV therapy [13, 23–25], IL-2 has also been studied with therapeutic immunization [26, 27] and in the absence of ARVs [14, 28–30]. The potential role of IL-2 during HAART interruption was studied in ACTG 5102 [28], which evaluated IL-2 recipients versus non-recipients with chronic HIV infection following HAART interruption. Although higher CD4 T cell counts were observed with IL-2, no differences were noted in virologic rebound or in the time for CD4 T cell counts to fall below 350 cells/ml. The kinetics of CD4 T cell expansion with IL-2 were also studied in a self-paired NIH cohort of HIV-infected patients-first, in the presence of continuous HAART and, second, followed immediately by HAART interruption. This revealed short-term CD4 T cell increases in both settings, although to a lesser extent with HAART interruption [29].

The present study (ICARUS or Interrupted versus Continuous Antiretrovirals involving Randomization from the Umbrella Study) was a randomized, controlled trial in which HIV-infected, IL-2-experienced patients first underwent a baseline IL-2 cycle on HAART and were then randomized to either HAART interruption plus intermittent IL-2 therapy or continuous ARVs for a minimum of 6 months. The ability of IL-2 to maintain CD4 T cells off HAART was evaluated, as well as whether 6 months of HAART interruption could mitigate ARV-associated lipodystrophy syndrome, reduce hepatotoxicity, and improve quality of life.

Methods

Participants

Forty men and 1 woman with HIV-1 infection were recruited between September 2002 and June 2005, primarily from an NIH IL-2-recipient follow-up protocol [14]. Inclusion criteria were a minimum of 3 pre-enrollment IL-2 cycles, a CD4 T cell count ≥ 500 cells/ μ l, and willingness to interrupt or maintain HAART for 6 months, per randomization. Exclusion criteria included chronic hepatitis B, participation in other HAART interruption studies within the previous 6 months, malignancy requiring chemotherapy within the past 2 years, HIV complications necessitating ongoing HAART, and multi-drug resistant HIV requiring salvage ARV therapy. The study was approved by the NIAID Institutional Review Board (IRB), and all participants signed informed consent.

Study Design

The ICARUS study was a prospective, controlled, open-label phase II non-inferiority trial. All participants received a baseline cycle of subcutaneous IL-2 upon enrollment (3–7.5 million international units (MIU) twice daily for 5 days) at the highest tolerated dose from their last IL-2 cycle. Participants were then randomized 2:1 to interrupt or continue HAART, using a permuted block design with masked block size. For HAART Interrupters, non-nucleoside reverse transcriptase inhibitors (NNRTIs) were stopped 2 days after the baseline IL-2 cycle, with all other ARVs discontinued a week later. All participants had monthly clinical and laboratory evaluations. After the 6-month primary study period, HAART

Interrupters could continue this intervention over a 6-month extension phase, while participants randomized to Continuous HAART could crossover to interrupt ARVs (i.e., Late HAART Interrupters) for the next 6 months or end study participation.

Over the entire 12-month study period, intermittent courses of IL-2 were given up to every 8 weeks to participants in either group, if consecutive CD4 T cell counts drawn 1 week apart declined to <90% of baseline, allowing for a maximum of 3 additional IL-2 cycles during the 6-month primary study phase. HAART could be restarted at any point according to patient desirability, clinical indication, or if CD4 count fell to <350 cells/ μ l on 2 occasions within 8 weeks of receiving an IL-2 cycle. HAART Interrupters received 10 days of non-abacavir protease inhibitor-based HAART with each 5-day IL-2 cycle, starting 3 days before and stopping 2 days after its completion, to abate possible IL-2-induced HIV replication [31, 32].

The primary outcome measure was CD4 T cell count at Month 6 (and at least 4 weeks after the last IL-2 cycle), with Treatment Success defined as maintaining randomization assignment and having a CD4 T cell count $\geq$ 90% of baseline. Secondary end-points included HIV viral load at Month 6, Treatment Success at Month 12, and rates of change in CD4 T cells and HIV viremia following HAART interruption.

Study Medications

Recombinant human IL-2 was provided by Novartis (Emeryville, California). ARV usage was recorded and monitored throughout the study.

Immunologic Parameters

CD4 and CD8 T cell counts (total and percent) were measured monthly in a CLIA-approved laboratory. CD4+CD25+ T cells (previously shown to expand with IL-2 [33]) and peripheral blood mononuclear cell (PBMC) 3 H-thymidine proliferation assays using HIV p24, tetanus toxoid, and phytohemagglutinin [34] were also followed.

Virologic Parameters

HIV viral load was measured by ultra-sensitive branched DNA assay (bDNA version 3, Chiron Corporation) with a lower detection limit of <50 copies/ml. HIV genotyping (TRUGENE, Visible Genetics Inc., Suwanee, Georgia) was performed at baseline or a pre-enrollment time point with HIV RNA >1000 copies/ml, the initial time point with similar viral rebound following HAART interruption, and at end-of-study or prior to resuming ARVs (whichever occurred first) to check for new resistance mutations, using TRUGENE Guidelines. Additional pre-enrollment genotypes were completed as needed to determine whether mutations were pre-existent, albeit not detected at baseline. Subjects who remained off HAART after end-of-study were followed up to 4 years to assess their capacity to suppress HIV viremia upon restarting ARVs.

Metabolic Function and Quality of Life Measures

Metabolic indices measured at baseline and Month 6 included external body composition (weight; body mass index; % body fat; multi-site skinfold widths including suprailiac,

subscapular, biceps, triceps, calf, and abdomen; limb circumferences for forearm, mid-arm, calf, and thigh; body widths at the hips, waist, abdomen, and neck) and both subcutaneous and visceral adiposity determined via single-slice axial computed tomography at lumbar vertebral levels 2–3 and 4–5 [35]. Markers of endocrine and hepatic function included total cholesterol, HDL, LDL, fasting triglycerides, apolipoprotein A1 and B, glycosylated hemoglobin (HgbA1c), oral glucose tolerance testing (75 gm bolus), thyrotropin, free and total thyroxine, triiodothyronine, reverse triiodothyronine, uric acid, L-lactate, alkaline phosphatase, AST, ALT, and total bilirubin. The MOS-HIV Health Survey, an established tool in HIV-related quality of life research [36–38], was also administered.

Statistical Considerations

Both intent to treat and per protocol analyses were performed. For the primary study endpoint, the likelihood score method [39] was used to determine a 2-sided 90% confidence interval (CI) to estimate the difference in proportions of subjects with Treatment Success between Interrupted and Continuous HAART groups at Month 6. The target sample size of 65 participants would have provided 79% power to obtain a lower confidence limit > -0.2 for p (Interrupted) – p (Continuous), assuming 90% Treatment Success and 10% attrition (equivalent to 79% power to reject $H_0: p$ (Interrupted) – p (Continuous) $= -0.2$ at a 1-sided 5% significance level). Due to slow recruitment, enrollment was closed at 41 subjects, providing 80% power for 2-sample t-tests of laboratory parameters with an effect size 1 standard deviation at a 2-sided 5% significance level. Mann-Whitney and Wilcoxon signed-rank tests were used for non-parametric median comparisons between and within groups, respectively, while Fisher's exact test was used for proportional comparisons.

Safety Assessments

Safety monitoring was completed via interview and laboratory assessment, following FDA adverse event criteria and NIAID IRB guidelines. Adverse events were graded on a predetermined toxicity scale from 0–4.

Results

Study Participants

Protocol flow of study subjects is summarized in Figure 1. Demographic and baseline characteristics are shown in Table 1.

IL-2 Cycling and HAART Resumption

Following the baseline IL-2 cycle, the need for additional on-study IL-2 cycling triggered by CD4 T cell counts $<90\%$ of baseline differed between the groups, with 8 (29.6%) HAART Interrupters receiving a single IL-2 cycle each during the primary phase (median of 52.5 MIU per subject) and 15 (51.9%) receiving a total of 17 cycles during the secondary phase (median of 45 MIU per subject). In contrast, no one in the Continuous HAART group required IL-2 during the primary phase and only 3 (30%) Late HAART Interrupters received a single IL-2 cycle each during the secondary phase (median of 45 MIU per subject).

No Early HAART Interrupters restarted ARVs during the primary phase, although 6 (22.2%) restarted during the extension phase due to falling CD4 counts or rising HIV viremia, and 1 restarted after end-of-study due to a B cell lymphoma. By comparison, 2 (20%) Late HAART Interrupters restarted ARVs while on-study (Figure 1) due to an acute antiretroviral syndrome and a case of secondary syphilis, with another restarting at end-of-study for recurrent Kaposi's sarcoma. Of the remaining participants, all but 2 Early and 2 Late HAART Interrupters restarted ARVs after end-of-study, due to decreased CD4 counts or increasing viremia.

Primary Outcome: Treatment Success at Month 6

A larger proportion of participants (92.3%) in the Continuous HAART group maintained CD4 T cell counts within 10% of baseline at Month 6 (the primary study endpoint), compared to HAART Interrupters (48.1%), $p=0.013$, Fisher's exact test (Table 2). The 95% CI for the difference in these proportions (-64.2% to -11.2% , Interrupted - Continuous) had a lower limit well below the predetermined non-inferiority standard of -20% . Figure 2A depicts lower median CD4 T cell counts in Interrupted versus Continuous HAART groups throughout the primary study phase and at Month 6 ($p<0.001$). Thus, IL-2 plus HAART interruption was inferior in terms of Treatment Success at Month 6, compared to IL-2 plus continuous HAART.

One subject in the Continuous HAART arm withdrew from the study after 4 months in order to stop ARVs. Inclusion of that subject as a Treatment Non-success gives $p=0.041$ for the difference in Treatment Success rates, and the non-inferiority criterion is still not met. Since Month 6 data are unavailable for that subject, he was excluded from all other analyses.

Secondary Metabolic and Quality of Life Analyses

No significant differences were observed in anthropometric indices between the Interrupted and Continuous HAART groups at baseline or Month 6 (Mann-Whitney test; data not shown). For laboratory measures (Table 3), significantly lower values were seen at Month 6 in the Interrupted versus Continuous HAART group for total cholesterol (161 mg/dl versus 190 mg/dl, $p<0.05$) and apolipoprotein A1 (98.5 mg/dl versus 111 mg/dl, $p<0.05$). In contrast, HgbA1c was significantly higher in HAART Interrupters at Month 6 (5.4% versus 4.95%, $p<0.001$). However, medians in both groups at baseline and Month 6 were within normal range ($<6\%$).

Physical and mental health scores on the MOS-HIV did not differ significantly between the groups at either time point (data not shown). However, the change in score from baseline to Month 6 on the Energy/Fatigue subscale (a vitality measure from 0 to 100) was significantly greater in HAART Interrupters compared to Continuous HAART subjects (Interrupted: median change = 5, 95% CI: 0, 15; Continuous: median change = -5 , 95% CI: -25 , 0; $p<0.001$). Of note, completion rates for the MOS-HIV were lower at Month 6 (Interrupted=74.1%, Continuous=84.6%) than at baseline (Interrupted=96.3%, Continuous=92.3%),

Secondary Treatment Success Analyses

Treatment Success rates at Month 6 versus Month 12 within Early HAART Interrupters (48.1% versus 22.2%; $p=0.016$; McNemar test) indicated declines in CD4 T cells observed in the primary study phase did not abate during the extension phase. Treatment Success rates in Early HAART Interrupters at Month 6 ($n=27$) and Late HAART Interrupters at Month 12 ($n=10$) revealed no difference whether HAART interruption occurred immediately (48.1%) or 6 months (50%) after the baseline IL-2 cycle (Fisher's exact test; $p=1.0$).

Rates of Change in HIV Viral Load and CD4 T Cell Count

Logistic regression analysis was used to calculate median rates of change in HIV viral load and CD4 T cell count over the first 6 months of HAART interruption, using all data points until first HAART re-exposure (i.e., either IL-2 cycling or resumption of HAART). To evaluate the effects of timing of HAART interruption relative to the baseline IL-2 cycle, median rates of change were compared between Early versus Late HAART Interrupters. No significant difference in rate of HIV viral load increase was seen (Early: 6356 copies/mL/month, Late: 1162 copies/mL/month; $p=0.16$; Mann-Whitney test). However, the rate CD4 T cell decline was steeper in Late (-96 cells/ μ L/month) versus Early (-38 cells/ μ L/month) HAART Interrupters ($p<0.001$), indicating 6 months of HAART following a baseline IL-2 cycle did not mitigate and, in fact, may have exacerbated this decline (Figure 2B).

Median rates of change were also compared in intra-group analyses within Early or Late HAART Interrupters between subjects considered Treatment Successes versus Non-successes. Within Early HAART Interrupters, although the rates of HIV viral load increase did not differ significantly (Non-successes: 7631 copies/mL/month, Successes: 3174 copies/mL/month; $p=0.20$), Treatment Non-successes had a steeper CD4 T cell decline compared to Treatment Successes (77 cells/ μ L/month versus 3 cells/ μ L/month; $p<0.001$; Figure 2C). Similar comparisons among Late HAART Interrupters did not reveal any significant differences (data not shown).

T Cell Phenotype and Function

The percentage of CD4+CD25+ T cells did not differ between the groups at baseline (17% for both groups, $p=0.77$) but was significantly lower in HAART Interrupters at Month 6 (18% versus 29%, $p=0.018$). No significant differences in PBMC proliferative responses to HIV p24, tetanus toxoid, or phytohemagglutinin were observed between Interrupted versus Continuous HAART groups or Early versus Late HAART Interrupters during the primary or secondary phases (data not shown). Proportional (Fisher's exact test) and median (Mann-Whitney test) comparisons were done to identify predictors of Treatment Success in either Early or Late Interrupters, including baseline HIV viral load <50 copies/mL, peak on-study HIV viral load, nadir and baseline CD4 T cell counts, %CD4, and %CD4+CD25+ T cells. Only nadir CD4 count in Early HAART Interrupters significantly differed between Treatment Successes (422 cells/ μ L) versus Non-successes (248.5 cells/ μ L; $p=0.023$).

Safety Assessment

Grade 3 adverse events were constitutional symptoms previously reported with IL-2 therapy [40], including fatigue ($n=8$), fever ($n=2$), and abdominal pain ($n=2$). The only Grade 4

event was an episode of transient hyperbilirubinemia due to underlying Gilbert's syndrome. Significant clinical events were detailed in the section on HAART resumption.

HIV genotypic analysis indicated no novel resistance mutations emerged following HAART interruption, although 2 changes were noted. An Early HAART Interrupter with a reverse transcriptase T215Y change prior to enrollment developed a T215NTDA mutation, which reflects pre-existing polymorphisms in ARV-naïve individuals, as reversion from T215Y often occurs after HAART interruption. Another common polymorphism in ARV-naïve individuals (protease I15V mutation; Stanford HIV Drug Resistance Database [41]) was observed in a Late HAART Interrupter. All subjects who restarted HAART had virologic suppression to <50 copies/mL, except for 2 who continued treatment interruption beyond end-of-study: the first had documented medication non-adherence and the second had no prior HIV viral loads of <50 copies/ml, though after restarting HAART, his viral load decreased by more than 1 log from 9742 to 781 copies/ml.

Discussion

This prospective, randomized trial demonstrated IL-2 alone was inferior in maintaining CD4 T cell counts 90% of baseline in IL-2-experienced recipients after 6 months of HAART interruption, compared to IL-2 plus HAART. Despite a baseline IL-2 cycle administered in the setting of moderate to high CD4 T cell counts (range: 538–1390 cells/μl) and largely suppressed HIV viremia, this immune intervention could not sufficiently overcome the CD4 T cell declines associated with HAART interruption, as compared to patients who received IL-2 and remained on HAART.

Several phase II studies have documented IL-2 dose-dependent expansions of CD4 T cells, with increases in naïve and memory subsets due to improved survival and decreased immune activation when administered with HAART [13, 18, 24, 25, 42]. The immune restoration conferred by HAART alone is incomplete, however, despite reductions in CD4 T cell activation, turnover, and lymphopenia [43–46]. Thus, significant interest remains in IL-2 to augment the benefits of HAART by further reducing immune activation [47], as changes in plasma HIV RNA explain only 3–6% of the variability in CD4 T cell loss [48, 49].

Regarding its use with HAART interruption, the results of ANRS 095 [50] and ACTG 5102 [28] suggested IL-2 conferred no benefit to HIV-infected persons, regardless of whether ARVs were initiated during primary infection or later in the disease. Nonetheless, earlier data from the ICARUS cohort comparing pre-enrollment and baseline IL-2 cycling indicated CD4 T cell increases were achievable with IL-2 followed by HAART interruption [29].

The recently published TILT trial demonstrated IL-2 could reduce the probability of restarting ARVs by 50% following 2 years of HAART interruption [51]. The different conclusions in ICARUS and TILT may be explained by the stricter criterion for Treatment Success used in the former. Whereas we sought to maintain CD4 T cells within 10% of baseline levels (947 cells/μl), in TILT, IL-2 cycles were triggered by CD4 T cell counts <350 cells/μl, and HAART was restarted for CD4 T cell counts <200 cells/μl [51]. In fact,

CD4 T cell increases following IL-2 plus HAART were similar in these studies, with half the HAART Interrupters in ICARUS qualifying as Treatment Successes at Month 6. This occurred despite the potential for self-referral bias within the ICARUS cohort of patients who tolerated IL-2 well and had high baseline CD4 T cells counts.

As in past studies [28, 52, 53], higher CD4 T cell nadirs were associated with Treatment Success (i.e., higher CD4 counts) in the ICARUS cohort, although baseline CD4 count [52, 54] and HIV viral suppression [52] were not. Whereas lack of CD4+CD25+ T cell expansion in Early HAART Interrupters suggested the importance of viral suppression in the IL-2-induced expansion of this subset [19, 20, 33], delaying HAART interruption for 6 months after a baseline IL-2 cycle was not more successful in maintaining CD4 T cells, despite greater CD4 increases and prolonged viral suppression prior to interruption. This was reflected in similar Treatment Success rates in Early and Late HAART Interrupters, with a steeper CD4 decline in the latter (−96 cells/μl/month), similar to previous studies [28, 55]. By comparison, CD4 declines in IL-2-naïve patients following HAART interruption range widely in the literature from −10 to −200 cells/μl/month [28, 55–57].

Six months of HAART interruption in our study also provided little benefit to HAART Interrupters, with only small decreases in total cholesterol (similar to ACTG 5102 [58]) and apolipoprotein A1. Although HgbA1c was lower in the Continuous HAART group at Month 6, the clinical relevance of this is unclear, as values in both groups remained within normal range. This may reflect the expected increase in erythrocyte life span after stopping nucleoside reverse transcriptase inhibitors (NRTIs) and reducing subclinical hemolysis [59]. A small (10% median group difference) albeit significant increase in energy level from baseline to Month 6, as measured by the MOS-HIV Health Survey, was also observed in Interrupted versus Continuous HAART subjects, indicating IL-2 cycling (which was more frequent in HAART Interrupters) did not adversely affect this quality of life measurement.

The findings of the ICARUS trial showed that IL-2 alone was inferior in maintaining baseline CD4 T cell counts after 6 months of HAART interruption, compared to IL-2 plus HAART. In the post-SMART era [11], HAART interruptions are of limited scope and conducted under close supervision in clinical trials. However, adjunctive therapies to limit HAART exposure and abrogate the chronic inflammation of HIV infection (presumed to be a major cause of non-HIV-related complications [12, 60]) merit exploration. Studies are underway to evaluate the capacity of IL-2 to delay HAART initiation in early HIV infection (STALWART) [61], and preliminary data from ANRS 119 suggest IL-2 can delay CD4 T cell decline and prolong time to an AIDS-defining event or HAART initiation in ARV-naïve individuals [62]. Although unlikely to be of value as part of a HAART interruption strategy, the clinical impact of IL-2 in HIV disease will become clearer with the availability of data from the ESPRIT and SILCAAT trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank all study participants and the staff of outpatient clinic 8 at NIAID for their help in completing this trial, Christine Salaita for collecting anthropometric measurements, and Francine Thomas for reading the CT scans. B. Porter contributed to data organization, analysis, and interpretation, and wrote the manuscript. K. Anthony, B. Hahn, C. Lane, J. Kovacs, and R. Davey contributed to the development and implementation of the protocol, and review of the manuscript. J. Shen contributed to the implementation of the protocol, data organization and analysis, and review of the manuscript. C. Keh and F. Maldarelli contributed to data organization, analysis, and interpretation, and review of the manuscript. W. Blackwelder contributed to development of the protocol, data organization, analysis, and interpretation, and review of the manuscript. I. Sereti contributed to the development and implementation of the protocol, data organization, analysis, and interpretation, and editing of the manuscript. This work was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Allergy & Infectious Diseases, Clinical and Molecular Retrovirology Section (Bethesda, Maryland). Human recombinant IL-2 was provided by Novartis (Emeryville, California).

Sources of Support

This work was funded through the National Institute of Allergy & Infectious Diseases Clinical and Molecular Retrovirology Section of the National Institutes of Health (Bethesda, Maryland). Human recombinant IL-2 was provided by Novartis (Emeryville, California).

Bibliography

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity mortality among patients with advanced human immunodeficiency virus infection HIV Outpatient Study Investigators. *N Engl J Med*. 1998; 338:853–860. [PubMed: 9516219]
2. Ledergerber B, Egger M, Telenti A. AIDS-Related opportunistic illness and potent antiretroviral therapy. *Jama*. 2000; 283:2653–2654. [PubMed: 10819936]
3. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1 EuroSIDA Study Group. *Lancet*. 1998; 352:1725–1730. [PubMed: 9848347]
4. Ofotokun I, Smithson SE, Lu C, Easley KA, Lennox JL. Liver enzymes elevation and immune reconstitution among treatment-naïve HIV-infected patients instituting antiretroviral therapy. *Am J Med Sci*. 2007; 334:334–341. [PubMed: 18004087]
5. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med*. 2005; 352:48–62. [PubMed: 15635112]
6. Grinspoon SK. Metabolic syndrome and cardiovascular disease in patients with human immunodeficiency virus. *Am J Med*. 2005; 118(Suppl 2):23S–28S. [PubMed: 15903292]
7. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *Aids*. 2004; 18:439–446. [PubMed: 15090796]
8. Ananworanich J, Gayet-Ageron A, Le Braz M, Prasithsirikul W, Chetchotisakd P, Kiertiburanakul S, et al. CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. *Lancet*. 2006; 368:459–465. [PubMed: 16890832]
9. Ananworanich J, Nuesch R, Le Braz M, Chetchotisakd P, Vibhagool A, Wicharuk S, et al. Failures of 1 week on, 1 week off antiretroviral therapies in a randomized trial. *Aids*. 2003; 17:F33–F37. [PubMed: 14523294]
10. Danel C, Moh R, Minga A, Anzian A, Ba-Gomis O, Kanga C, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet*. 2006; 367:1981–1989. [PubMed: 16782488]
11. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006; 355:2283–2296. [PubMed: 17135583]
12. Silverberg MJ, Neuhaus J, Bower M, Gey D, Hatzakis A, Henry K, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *Aids*. 2007; 21:1957–1963. [PubMed: 17721103]

13. Arduino RC, Nannini EC, Rodriguez-Barradas M, Schrader S, Losso M, Ruxrungtham K, et al. CD4 cell response to 3 doses of subcutaneous interleukin 2: meta-analysis of 3 Vanguard studies. *Clin Infect Dis*. 2004; 39:115–122. [PubMed: 15206062]
14. Farel CE, Chaitt DG, Hahn BK, Tavel JA, Kovacs JA, Polis MA, et al. Induction and maintenance therapy with intermittent interleukin-2 in HIV-1 infection. *Blood*. 2004; 103:3282–3286. [PubMed: 14726376]
15. Natarajan V, Lempicki RA, Sereti I, Badralmaa Y, Adelsberger JW, Metcalf JA, et al. Increased peripheral expansion of naive CD4+ T cells in vivo after IL-2 treatment of patients with HIV infection. *Proc Natl Acad Sci U S A*. 2002; 99:10712–10717. [PubMed: 12149467]
16. Kovacs JA, Lempicki RA, Sidorov IA, Adelsberger JW, Sereti I, Sachau W, et al. Induction of prolonged survival of CD4+ T lymphocytes by intermittent IL-2 therapy in HIV-infected patients. *J Clin Invest*. 2005; 115:2139–2148. [PubMed: 16025158]
17. Sereti I, Anthony KB, Martinez-Wilson H, Lempicki R, Adelsberger J, Metcalf JA, et al. IL-2-induced CD4+ T-cell expansion in HIV-infected patients is associated with long-term decreases in T-cell proliferation. *Blood*. 2004; 104:775–780. [PubMed: 15090457]
18. Kovacs JA, Vogel S, Metcalf JA, Baseler M, Stevens R, Adelsberger J, et al. Interleukin-2 induced immune effects in human immunodeficiency virus- infected patients receiving intermittent interleukin-2 immunotherapy. *Eur J Immunol*. 2001; 31:1351–1360. [PubMed: 11465092]
19. Sereti I, Imamichi H, Natarajan V, Imamichi T, Ramchandani MS, Badralmaa Y, et al. In vivo expansion of CD4(+)CD45RO(–)CD25(+) T cells expressing foxP3 in IL-2-treated HIV-infected patients. *J Clin Invest*. 2005
20. Sereti I, Martinez-Wilson H, Metcalf JA, Baseler MW, Hallahan CW, Hahn B, et al. Long-term effects of intermittent interleukin 2 therapy in patients with HIV infection: characterization of a novel subset of CD4(+)CD25(+) T cells. *Blood*. 2002; 100:2159–2167. [PubMed: 12200381]
21. Pett SL, Wand H, Law MG, Arduino R, Lopez JC, Knysz B, et al. Evaluation of Subcutaneous Proleukin (interleukin-2) in a Randomized International Trial (ESPRIT): geographical and gender differences in the baseline characteristics of participants. *HIV Clin Trials*. 2006; 7:70–85. [PubMed: 16798622]
22. Emery S, Abrams DI, Cooper DA, Darbyshire JH, Lane HC, Lundgren JD, Neaton JD. The evaluation of subcutaneous proleukin (interleukin-2) in a randomized international trial: rationale, design, and methods of ESPRIT. *Control Clin Trials*. 2002; 23:198–220. [PubMed: 11943448]
23. Durier C, Capitant C, Lascaux AS, Goujard C, Oksenhendler E, Poizot-Martin I, et al. Long-term effects of intermittent interleukin-2 therapy in chronic HIV-infected patients (ANRS 048–079 Trials). *Aids*. 2007; 21:1887–1897. [PubMed: 17721096]
24. Levy Y, Durier C, Krzysiek R, Rabian C, Capitant C, Lascaux AS, et al. Effects of interleukin-2 therapy combined with highly active antiretroviral therapy on immune restoration in HIV-1 infection: a randomized controlled trial. *Aids*. 2003; 17:343–351. [PubMed: 12556688]
25. Davey RT Jr, Murphy RL, Graziano FM, Boswell SL, Pavia AT, Cancio M, et al. Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: A randomized controlled trial. *Jama*. 2000; 284:183–189. [PubMed: 10889591]
26. Levy Y, Gahery-Segard H, Durier C, Lascaux AS, Goujard C, Meiffredy V, et al. Immunological and virological efficacy of a therapeutic immunization combined with interleukin-2 in chronically HIV-1 infected patients. *Aids*. 2005; 19:279–286. [PubMed: 15718838]
27. Kilby JM, Bucy RP, Mildvan D, Fischl M, Santana-Bagur J, Lennox J, et al. A randomized, partially blinded phase 2 trial of antiretroviral therapy, HIV-specific immunizations, and interleukin-2 cycles to promote efficient control of viral replication (ACTG A5024). *J Infect Dis*. 2006; 194:1672–1676. [PubMed: 17109338]
28. Henry K, Katzenstein D, Cherng DW, Valdez H, Powderly W, Vargas MB, et al. A pilot study evaluating time to CD4 T-cell count <350 cells/mm(3) after treatment interruption following antiretroviral therapy +/- interleukin 2: results of ACTG A5102. *J Acquir Immune Defic Syndr*. 2006; 42:140–148. [PubMed: 16760795]
29. Keh CE, Shen JM, Hahn B, Hallahan CW, Rehm CA, Thaker V, et al. Interruption of antiretroviral therapy blunts but does not abrogate CD4 T-cell responses to interleukin-2 administration in HIV infected patients. *Aids*. 2006; 20:361–369. [PubMed: 16439869]

30. Youle M, Emery S, Fisher M, Nelson M, Fosdick L, Janossy G, et al. A Randomised Trial of Subcutaneous Intermittent Interleukin-2 without Antiretroviral Therapy in HIV-Infected Patients: The UK-Vanguard Study. *PLoS Clin Trials*. 2006; 1:e3. [PubMed: 16871325]
31. Kovacs JA, Baseler M, Dewar RJ, Vogel S, Davey RT Jr, Falloon J, et al. Increases in CD4 T lymphocytes with intermittent courses of interleukin-2 in patients with human immunodeficiency virus infection A preliminary study. *N Engl J Med*. 1995; 332:567–575. [PubMed: 7646637]
32. Davey RT Jr, Chait DG, Piscitelli SC, Wells M, Kovacs JA, Walker RE, et al. Subcutaneous administration of interleukin-2 in human immunodeficiency virus type 1-infected persons. *J Infect Dis*. 1997; 175:781–789. [PubMed: 9086130]
33. Zhang H, Chua KS, Guimond M, Kapoor V, Brown MV, Fleisher TA, et al. Lymphopenia and interleukin-2 therapy alter homeostasis of CD4+CD25+ regulatory T cells. *Nat Med*. 2005; 11:1238–1243. [PubMed: 16227988]
34. Stevens, R.; Lempicki, R.; Natarajan, V.; Higgins, J.; Adelsberger, J.; Metcalfe, J. General Immunologic Evaluation of Patients with Human Immunodeficiency Virus Infection. In: BDetrack, RH.; Folds, J., editors. *Manual of Molecular and Clinical Laboratory Immunology*. 7th ed. Washington, D.C: ASM Press; 2006. p. 847-861.
35. Ellis KJ, Grund B, Visnegarwala F, Thackeray L, Miller CG, Chesson CE, et al. Visceral and subcutaneous adiposity measurements in adults: influence of measurement site. *Obesity (Silver Spring)*. 2007; 15:1441–1447. [PubMed: 17557981]
36. Volberding PA, Lagakos SW, Koch MA, Pettinelli C, Myers MW, Booth DK, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. *N Engl J Med*. 1990; 322:941–949. [PubMed: 1969115]
37. Wu AW, Revicki DA, Jacobson D, Malitz FE. Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). *Qual Life Res*. 1997; 6:481–493. [PubMed: 9330549]
38. Safrin S, Finkelstein DM, Feinberg J, Frame P, Simpson G, Wu A, et al. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim clindamycin-primaquine ACTG 108 Study Group. *Ann Intern Med*. 1996; 124:792–802. [PubMed: 8610948]
39. Gart JJ, Nam JM. Approximate interval estimation of the difference in binomial parameters: correction for skewness and extension to multiple tables. *Biometrics*. 1990; 46:637–643. [PubMed: 2242407]
40. Davey RT Jr, Chait DG, Albert JM, Piscitelli SC, Kovacs JA, Walker RE, et al. A randomized trial of high- versus low-dose subcutaneous interleukin-2 outpatient therapy for early human immunodeficiency virus type 1 infection. *J Infect Dis*. 1999; 179:849–858. [PubMed: 10068580]
41. Stanford University HIV Drug Resistance Database. 2008. <http://hivdb.stanford.edu/>.
42. Mitsuyasu R, Gelman R, Cherng DW, Landay A, Fahey J, Reichman R, et al. The virologic, immunologic, and clinical effects of interleukin 2 with potent antiretroviral therapy in patients with moderately advanced human immunodeficiency virus infection: a randomized controlled clinical trial--AIDS Clinical Trials Group 328. *Arch Intern Med*. 2007; 167:597–605. [PubMed: 17389292]
43. Di Mascio M, Sereti I, Matthews LT, Natarajan V, Adelsberger J, Lempicki R, et al. Naive T-cell dynamics in human immunodeficiency virus type 1 infection: effects of highly active antiretroviral therapy provide insights into the mechanisms of naive T-cell depletion. *J Virol*. 2006; 80:2665–2674. [PubMed: 16501076]
44. Anthony KB, Yoder C, Metcalf JA, DerSimonian R, Orenstein JM, Stevens RA, et al. Incomplete CD4 T Cell Recovery in HIV-1 Infection After 12 Months of Highly Active Antiretroviral Therapy Is Associated With Ongoing Increased CD4 T Cell Activation and Turnover. *J Acquir Immune Defic Syndr*. 2003; 33:125–133. [PubMed: 12794543]
45. Hunt PW, Brenchley J, Sinclair E, McCune JM, Roland M, Page-Shafer K, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with

- undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis.* 2008; 197:126–133. [PubMed: 18171295]
46. Kovacs JA, Lempicki RA, Sidorov IA, Adelsberger JW, Herpin B, Metcalf JA, et al. Identification of dynamically distinct subpopulations of T lymphocytes that are differentially affected by HIV. *J Exp Med.* 2001; 194:1731–1741. [PubMed: 11748275]
 47. Sereti I, Lane HC. Immunopathogenesis of human immunodeficiency virus: implications for immune-based therapies. *Clin Infect Dis.* 2001; 32:1738–1755. [PubMed: 11360217]
 48. Rodriguez B, Sethi AK, Cheruvu VK, Mackay W, Bosch RJ, Kitahata M, et al. Predictive value of plasma HIV RNA level on rate of CD4 T-cell decline in untreated HIV infection. *Jama.* 2006; 296:1498–1506. [PubMed: 17003398]
 49. Mellors JW, Margolick JB, Phair JP, Rinaldo CR, Detels R, Jacobson LP, Munoz A. Prognostic value of HIV-1 RNA, CD4 cell count, and CD4 Cell count slope for progression to AIDS and death in untreated HIV-1 infection. *Jama.* 2007; 297:2349–2350. [PubMed: 17551128]
 50. Goujard C, Marcellin F, Hendel-Chavez H, Burgard M, Meiffredy V, Venet A, et al. Interruption of antiretroviral therapy initiated during primary HIV-1 infection: impact of a therapeutic vaccination strategy combined with interleukin (IL)-2 compared with IL-2 alone in the ANRS 095 Randomized Study. *AIDS Res Hum Retroviruses.* 2007; 23:1105–1113. [PubMed: 17919105]
 51. Angus B, Lampe F, Tambussi G, Duvivier C, Katlama C, Youle M, et al. TILT: a randomized controlled trial of interruption of antiretroviral therapy with or without interleukin-2 in HIV-1 infected individuals. *Aids.* 2008; 22:737–740. [PubMed: 18356603]
 52. Fox Z, Antunes F, Davey R, Gazzard B, Klimas N, Labriola A, et al. Predictors of CD4 count change over 8 months of follow up in HIV-1-infected patients with a CD4 count $\geq$ 300 cells/ μ L who were assigned to 7.5 MIU interleukin-2. *HIV Med.* 2007; 8:112–123. [PubMed: 17352768]
 53. Markowitz N, Bebchuk JD, Abrams DI, Nadir CD4+ T cell count predicts response to subcutaneous recombinant interleukin-2. *Clin Infect Dis.* 2003; 37:e115–120. [PubMed: 14523786]
 54. Read SW, Lempicki RA, Mascio MD, Srinivasula S, Burke R, Sachau W, et al. CD4 T Cell Survival after Intermittent Interleukin-2 Therapy Is Predictive of an Increase in the CD4 T Cell Count of HIV-Infected Patients. *J Infect Dis.* 2008
 55. Davey RT Jr, Bhat N, Yoder C, Chun TW, Metcalf JA, Dewar R, et al. HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression. *Proc Natl Acad Sci U S A.* 1999; 96:15109–15114. [PubMed: 10611346]
 56. Ruiz L, Paredes R, Gomez G, Romeu J, Domingo P, Perez-Alvarez N, et al. Antiretroviral therapy interruption guided by CD4 cell counts and plasma HIV-1 RNA levels in chronically HIV-1-infected patients. *Aids.* 2007; 21:169–178. [PubMed: 17197807]
 57. Tarwater PM, Parish M, Gallant JE. Prolonged treatment interruption after immunologic response to highly active antiretroviral therapy. *Clin Infect Dis.* 2003; 37:1541–1548. [PubMed: 14614678]
 58. Tebas P, Henry WK, Matining R, Weng-Cherng D, Schmitz J, Valdez H, et al. Metabolic and immune activation effects of treatment interruption in chronic HIV-1 infection: implications for cardiovascular risk. *PLoS ONE.* 2008; 3:e2021. [PubMed: 18431498]
 59. Diop ME, Bastard JP, Meunier N, Thevenet S, Maachi M, Capeau J, et al. Inappropriately low glycated hemoglobin values and hemolysis in HIV-infected patients. *AIDS Res Hum Retroviruses.* 2006; 22:1242–1247. [PubMed: 17209766]
 60. Emery S, Neuhaus J, Phillips A, Babiker A, Cohen CJ, Gatell J, et al. Major Clinical Outcomes in Antiretroviral Therapy (ART)-Naive Participants and in Those Not Receiving ART at Baseline in the SMART Study. *Journal of Infectious Diseases.* 2008; 197:000–000.
 61. NIAID HIV and Emerging Infectious Diseases Program: STALWART Study In. 2008. <http://www3.niaid.nih.gov/healthscience/clinicalstudies/HIVandInfectious/HIVstudies/STALWART.htm>
 62. Molina, JLY.; Fournier, I.; Boulet, T.; Bentata, M.; Beck-Wirth, G.; Sereni, D.; Jeanblanc, F.; Simon, F.; Aboulker, J. 15th Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts; 2008. Predictors of slow disease progression in antiretroviral (ART) naive HIV-1

infected patients treated with IL-2: Three-year extended follow-up of the Interstart ANRS 119 trial.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1. Flow of protocol volunteers

Following randomization after a baseline IL-2 cycle, only 1 participant withdrew from the study during the 6-month primary study phase. Other than 3 participants in the Continuous HAART group who did not stop HAART, all subjects continued through the 6-month secondary (extension or crossover) phase.

Figure 2. CD4 T cell counts in the groups throughout the study

A) Median CD4 T cell counts during the primary study phase are shown for Continuous (solid line) and Interrupted (dashed line) HAART groups. Month 6 counts were significantly different (Mann-Whitney test). **B and C)** Median rates of decline in CD4 T cell count determined by logistic regression analysis were extrapolated for the initial 6-month period of HAART interruption for **B)** Early (dashed line; -38 cells/ μ L/month) and Late (solid line; -96 cells/ μ L/month) HAART Interrupters, as well as **C)** Treatment Successes (solid line; -3

cells/ μ l/month) and Non-successes (dashed line; -77 cells/ μ l/month) within Early HAART Interrupters only. Significant intergroup comparisons are shown (Mann-Whitney test).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Participant Baseline characteristics. Medians and ranges in parentheses are shown.

	Interrupted HAART (n=27)	Continuous HAART (n=13)*
Gender (% male)	96	100
Age (years)	46.4 (36–73)	44.6 (35–58)
Ethnicity	96% White; 4% Black	92% White; 8% Black
CD4 T cells/μl	947 (583–1390)	947 (639–1326)
CD8 T cells/μl	922 (553–2604)	909 (240–1601)
Median HIV viral load (copies/ml)	<50 (<50–3346)	<50 (<50–3691)
HIV viral load <50 copies/ml (%)	70	77
Nadir CD4 T cells/μl	314 (86–559)	288 (94–552)
Protease Inhibitor HAART (%)	63	46
Prior IL-2 cycles	9 (3–29)	9 (5–17)
Years since first IL-2 cycle	7.8 (2.6–11)	7 (4.9–9.2)
Years since last IL-2 cycle	2.8 (0.5–9)	2.9 (0.6–6.3)
Pre-randomization IL-2 cycle dose**	60 (30–75)	75 (30–75)

No significant differences were noted (Mann-Whitney test).

* Excludes 1 withdrawn subject.

** Total Baseline IL-2 cycle dose per patient in MIU (million international units).

Table 2

Virologic and immunologic outcomes, including primary study end-point. Median values with ranges in parentheses are shown.

	Interrupted HAART (n=27)	Continuous HAART (n=13)
Month 6 HIV viral load (copies/ml)	39,389 (3252–251,102)	<50 (<50–7783) ⁺
Peak HIV viral load (copies/ml)	53,813 (3252–495,007)	62 (<50–7783) ⁺⁺
Month 6 CD4 T cells/μl	866 (445–1698)	1246 (517–2253) ⁺⁺⁺
Change in CD4 T cells/μl (Month 6 - Baseline)	–87 (–614 – 625)	396 (–122 – 1204) ⁺
Change in % CD4 (Month 6 – Baseline)	–10.2 (–44.2 – 58.2)	49.7 (–19.1 – 114.8) ⁺
Treatment Success (%) [*]	48.1	92.3 ^{**}
% Difference in Treatment Success	–44.2%; 95% Confidence	Interval: –64.2%, –11.2%

^{*} Month 6 CD4 T cell count 90% of baseline.

^{**} p=0.013 by Fisher's exact test (% Treatment Success in Interrupted – Continuous HAART groups),

⁺ p<0.001,

⁺⁺ p<0.0001,

⁺⁺⁺ p=0.001.

Table 3

Metabolic measures assessed at Baseline and Month 6.

	Baseline		Month 6	
	Interrupted	Continuous	Interrupted	Continuous
Total Cholesterol (mg/dL)	209	216	161	190
HDL (mg/dL)	38	41	31	38
LDL (mg/dL)	128	139	104	116.5
Triglycerides (mg/dL)	234	203	137	182
Apolipoprotein A1 (mg/dL)	107	112.5	98.5	111
Apolipoprotein B (mg/dL)	101	111.5	84.5	88
OGTT—Hour 0 (mg/dL)	91	87	94	90
OGTT—Hour 2 (mg/dL)	101	92	103	98
HgbA1c (%)	4.9	4.75	5.4**	4.95
Uric Acid (mg/dL)	5.9	6.7	6.2	5.8
L-Lactate (mmol/L)	1.95	1.45	1.4	1.6
ALK (U/L)	72	65	58	67
ALT (U/L)	32	23	29	22
AST (U/L)	30	23	29	25
Total Bilirubin (mg/dL)	0.8	1	0.7	0.8
TSH (IU/ml)	1.85	2.14	1.87	2.14
Total Thyroxine (ng/dL)	7.15	7.65	7.3	7
Free Thyroxine (ng/dL)	1.1	0.9	1.1	1.1
Triiodothyronine (ng/dL)	138	119	125.5	141
Reverse T3 (ng/dL)	19	21	23	21
Free T3 (pg/dL)	350	330	340	330

Mann-Whitney tests compared median values between Interrupted and Continuous HAART groups separately at Baseline and Month 6. HDL=high density lipoprotein, LDL=low density lipoprotein, OGTT=oral glucose tolerance test, HgbA1c=glycosylated hemoglobin, ALK=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, TSH=thyroid stimulating hormone, T3=triiodothyronine.

* p<0.05 between groups.

** p<0.001 within group compared to Baseline.

Author Manuscript
differences between groups.

Author Manuscript

Author Manuscript

Author Manuscript