Effect of a single bout of acute exercise on plasma human immunodeficiency virus RNA levels

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1Department of Community Health and 2Tupper Research Institute, Department of Medicine, Tufts University School of Medicine, Boston 02111; and 3Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts 02111

Roubenoff, Ronen, Paul R. Skolnik, Abby Shevitz, Laura Snydman, Alicia Wang, Suzanne Melanson, and Sherwood Gorbach Effect of a single bout of acute exercise on plasma human immunodeficiency virus RNA levels. J. Appl. Physiol. 86(4): 1197–1201, 1999.—Acute exercise is known to activate the immune system and thus could lead to increased human immunodeficiency virus (HIV) replication. We sought to determine whether a single acute bout of exercise, similar to what people experience when starting an intense exercise program, has a detrimental effect on plasma HIV RNA levels. Twenty-five patients with HIV infection performed one 15-min bout of acute exercise. Absolute neutrophil counts, serum creatine phosphokinase, and 72-h urinary 3-methylhistidine (a marker of muscle protein breakdown) were measured before and after the exercise, along with plasma HIV RNA levels. There were increases in neutrophil counts (P < 0.06), serum creatine phosphokinase (P < 0.01), and urinary 3-methylhistidine (P < 0.01) in response to exercise, indicating a mild acute-phase response with muscle proteolysis. However, mean HIV RNA, which was elevated at baseline in 22 of the 25 subjects (mean of 4 × 106 ± 0.7 × 106 copies/mL), did not increase during the week after exercise (P = 0.12). Small changes in RNA were seen in the three subjects with initially undetectable HIV RNA, but the significance of these changes is unclear. Acute exercise does not have a deleterious effect on HIV replication in adults with high viral loads. Because regular exercise training has not been shown to activate the acute-phase response, the lack of increased viral loads in response to an acute exercise intervention suggests that exercise training is safe in people with HIV infection.

Immune system; human immunodeficiency virus; human immunodeficiency virus infection; acute exercise

HUMAN IMMUNODEFICIENCY VIRUS (HIV) infection causes a catabolic disease that leads to reduced physical activity, deconditioning, and loss of both aerobic capacity and muscle strength (10, 14). Patients with HIV infection, but without acquired immunodeficiency syndrome (AIDS) or pulmonary disease, have a reduced workload, lower anaerobic threshold, and poorer aerobic capacity than do age-matched controls (15). Exercise training is an attractive adjunct to antiretroviral therapy in rehabilitating the exercise capacity and functional status of patients with HIV infection, and both aerobic and resistance training may be important adjuncts to the medical treatment of HIV infection. To reverse weakness and wasting, it is necessary to employ high-intensity progressive resistance training, with subjects working at >75% of maximum capacity (8, 13, 24). With the advent of highly active antiretroviral therapy, abdominal obesity and regional fat redistribution have been recognized as problems associated with HIV infection (16, 17). However, it is also possible that exercise, especially high-intensity exercise, could activate the immune system and thus increase HIV replication, as occurs after vaccination (27). This has led to concern about the safety of starting a high-intensity exercise program in patients who have been sedentary and/or ill with opportunistic infections.

In healthy adults, a single acute bout of exhaustive exercise clearly activates the immune system, causing leukocytosis, neutrophilia, and lymphopenia, with variable effects on the rate of infection with respiratory viruses (3, 7, 18, 20, 22). Several studies have found an increase in ex vivo neutrophil and monocyte phagocytic capacity after high-intensity aerobic exercise (19, 21, 23). However, other functional indexes of immune cells, such as natural killer (NK) cell function and neutrophil oxidative burst, are unaffected or decline (18). In addition, acute exercise induces production of the inflammatory cytokines interleukin (IL)-1β and tumor necrosis factor (TNF)-α, which exert profound effects on metabolic and endocrine pathways and can increase HIV replication (1, 2, 4, 9, 11, 12, 26). IL-1β has been linked to the induction of muscle protein turnover, which is a requisite for increasing muscle mass in response to exercise (9). IL-1β has also been demonstrated in muscle after acute exercise and correlates well with microscopic evidence of damage after such exercise (5, 6). In contrast to the situation with acute exercise, progressive resistance exercise on an ongoing basis does not appear to activate the immune system (25). However, when a person begins a training program for the first time, he or she is stressing muscles in a way that has much in common with acute exercise. This has raised the question of whether beginning a training program could be deleterious to the health of HIV-infected adults.

Only one study has examined the effect of HIV infection on the immune response to exercise. Ullum et al. (28) examined the difference in the immune response to acute exercise between a group of eight healthy subjects and a group of eight patients with HIV infection, matched in age and gender. All subjects

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exercised on a bicycle ergometer for 1 h at 75% of maximal oxygen uptake. The postexercise increases in neutrophils, NK cells, IL-2-stimulated NK cells, and lymphokine-activated killer cells were blunted in the HIV-seropositive group compared with the control subjects. However, both groups had a comparable transient increase in their CD4 counts during exercise. Thus it appears that HIV infection can suppress features of the immune response to acute exercise. The converse, whether there is an effect of exercise on HIV infection, is not known. Most patients starting exercise therapy as part of their treatment for HIV should perform high-intensity, but not exhaustive, exercise. Therefore, we studied the effect of a single bout of strenuous exercise, comparable to the beginning of a high-intensity training program, on plasma HIV RNA in 25 adults with HIV infection.

METHODS

Study population. Subjects were eligible for this study if they were infected with HIV and were participants in an ongoing, longitudinal study of nutritional status during HIV infection (Nutrition for Life, Tufts University School of Medicine). HIV infection was documented by ELISA in all subjects. Weight loss or AIDS (on the basis of the revised 1993 Centers for Disease Control criteria) were not entry requirements. All subjects had normal renal function (serum creatinine <1.2 mg/dl), hepatic function (aspartate aminotransferase and alanine aminotransferase less than twice the upper limit of normal, total bilirubin and alkaline phosphatase within the normal range) and were able to give informed consent. All subjects were sedentary except for two, who performed mild aerobic exercise two to three times per week. No subject was performing resistance training. Thirty-one volunteers expressed interest in the study and were given informed-consent forms. Two subjects initially participated but did not have adequate venous access and were removed from the study. Four others agreed to enter the study but did not keep a meat-free diet (n = 1) or decided not to participate after their initial agreement (n = 3). The other 25 volunteers completed the study successfully, and data from these subjects are reported here. The study was approved by the Human Investigations Review Committee of Tufts University and the New England Medical Center.

Assessment protocol. Participants were admitted to the Tufts University School of Medicine General Clinical Research Center at the New England Medical Center on a Monday, 3 days before a single bout of acute exercise, which was performed on Thursday morning. They were discharged on Friday morning and were readmitted the following Tuesday for 4 additional days. Subjects were instructed as to a meat-free diet by a registered dietitian and asked to begin this diet on the Friday before their first admission and to continue it during the study. Participants kept dietary records for 3 days before the first admission and during the 4 days between the first and second admission, to allow assessment of their usual dietary intake and compliance with the meat-free diet. During the two admissions, all meals were provided by the General Clinical Research Center staff. Body composition was assessed by dual-energy X-ray absorptiometry by using a Hologic QDR 2000 with version 5.64A software. Grams of lean mass, fat mass, and bone mineral were measured. In addition, 24-h urine collections for creatinine and 3-methylhistidine (3-MH) were obtained during the 3 days preceding the exercise session and again on days 5–7 after the exercise, to estimate muscle protein content and protein breakdown, respectively.

Plasma HIV RNA was measured in a research retrovirology laboratory by using a Roche Amplicor Monitor RT-PCR assay according to the manufacturer’s instructions (Roche Molecular Systems, Somerville, NJ). Blood samples were collected in citric acid-sodium citrate anhydrous-dextrase tubes before the exercise protocol and 2, 6, 24, and 168 h (1 wk) after the exercise session. Plasma was separated within 30 min, frozen at −70°C, and thawed just before assaying. All samples from individual subjects were batched and assayed together. For the three subjects found to have <400 copies/ml, results were checked by repeating the measurements by using the ultrasensitive Amplicor Monitor assay system with a detection limit of −25 copies/ml.

Complete blood counts and differentials, creatine phosphokinase (CPK), and routine chemistries were measured by the New England Medical Center clinical laboratories by using commercial assays. 3-MH was measured in the New England Medical Center Amino Acid Laboratory by using a Beckman 6300 amino acid analyzer (Beckman Instruments, Palo Alto, CA) (29).

Exercise protocol. All subjects completed the exercise protocol, consisting of 15 min of a 60-cm (vertical distance) step aerobic. Participants were instructed to step up with their left leg first, then the right, and step down with their left leg first, followed by the right, at a cadence of 1 step/s. Thus each person lifted his or her weight 225 times and put it down 225 times in 15 min. The left leg completed 225 concentric exercises (generating force while shortening) and the right leg completed 225 eccentric exercises (generating force while lengthening). Even fit participants found this exercise difficult. One subject required a 30-s rest period after 5 min and again after 10 min to complete the protocol.

Statistical analysis. The major outcome of the study was the change in viral load from baseline to after exercise. Data for each subject were plotted, and the percent change from baseline was calculated. Data were examined graphically and statistically for normality. Analyses of viral load were performed after logarithm base-10 transformation by using the original assay results (sensitivity 400 copies/ml). The percent change was compared with the null hypothesis of no change by using repeated-measures ANOVA for HIV RNA levels, CPK, and neutrophil counts. 3-MH results were measured by a paired t-test, comparing the mean 3-MH excretion for the 3 days preceding the exercise to the mean of the 3 days after the exercise. Results were considered statistically significant if the result of a two-tailed P value was <0.05.

RESULTS

Subject characteristics. Table 1 shows the demographic and laboratory characteristics of the study population. There were 21 men and 4 women in the study, of whom 9 were African-Americans, 15 were Caucasians, and 1 was a Native American. Their risk factors for HIV infection were injection drug use in 11, homosexual contact in 13, and unknown in 1. Their mean age was 38 yr. Eighteen of the patients were taking zidovudine, either alone (at the beginning of the study) or in combination with lamivudine, or were taking lamivudine with or without stavudine. Twelve of the patients were taking a protease inhibitor. Two patients were taking no antiretroviral therapy at all. No patients were taking glucocorticoids, anabolic steroids, or growth hormone. Patients were not admitted
within 1 mo of an acute infection or a change in their antiretroviral regimen.

Development of an acute-phase response to exercise. The acute exercise was followed by an increase in circulating neutrophil counts. There was a trend to-ward an increase in neutrophils after exercise ($P_{0.06}$, repeated-measures ANOVA), especially at 2 h after baseline ($P_{0.01}$ post hoc pairwise analysis vs. baseline) (Fig. 1A). There was a significant increase in CPK over baseline ($P_{0.01}$, repeated-measures ANOVA), with a significant rise by 6 h postexercise ($P_{0.05}$, post hoc pairwise analysis), and a fall back to baseline by 1 wk ($P_{0.05}$ vs. 24 h postexercise, post hoc pairwise analysis) (Fig. 1B). Seventy-two-hour urinary excretion of 3-MH, a marker of muscle protein turnover, was significantly higher after the exercise compared with baseline (Fig. 2, $P_{0.01}$), indicating increased muscle protein breakdown in response to the exercise intervention.

Effect of exercise on viral load. Mean HIV RNA concentration in plasma was $4.1 \times 10^5$ copies/ml before the exercise treatment began, and the median was $3.9 \times 10^5$ copies/ml. In contrast to the increase in acute phase markers seen with the exercise intervention, there was no significant increase in circulating viral RNA after exercise (Fig. 3, $P_{0.12}$). In fact, there was a statistically, but not biologically, significant reduction in HIV RNA 2 h after the exercise ($P_{0.01}$, post hoc analysis). The response to exercise did not differ significantly between patients taking protease inhibitors and those not taking these medications (data not shown). No patient had an increase in HIV RNA that exceeded 0.3 log during the study, and no patient required a change in antiretroviral therapy within 2 wk of completing the study.

Table 1. Baseline demographic, clinical, and laboratorv features of the 25 study patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>39.3 (29–55)</td>
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<tr>
<td>Gender, M:F</td>
<td>21:4</td>
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<tr>
<td>Weight, kg</td>
<td>77.3 ± 13.1</td>
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<tr>
<td>Lean body mass, kg</td>
<td>56.3 ± 8.0</td>
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<td>Hemoglobin, g/l</td>
<td>13.8 ± 1.4</td>
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<td>Serum creatinine, mg/dl</td>
<td>0.87 ± 0.18</td>
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<tr>
<td>Aspartate aminotransferase, U/l</td>
<td>34 ± 82</td>
<td></td>
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<tr>
<td>Creatine phosphokinase (baseline), U/l</td>
<td>103 ± 79</td>
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<tr>
<td>Neutrophil count (baseline), no./mm$^3$</td>
<td>2,459 ± 974</td>
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<tr>
<td>CD4 count, no./mm$^3$</td>
<td>335 (10–744)</td>
<td></td>
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<tr>
<td>HIV RNA, copies/ml</td>
<td>4.1 $\times 10^5$ $\pm$ 0.7 $\times 10^5$</td>
<td>3.9 $\times 10^5$ ($&lt;25-2.2 \times 10^6$)</td>
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Values are means ± SD with range in parentheses. M, male; F, female; HIV, human immunodeficiency virus.

DISCUSSION

The purpose of this study was to examine whether a moderately intense bout of exercise, similar in intensity to a first-time training session, would increase circulating HIV RNA in patients infected with this virus. Although the potential benefits of exercise for people with HIV are clear, including improved strength, functional status, lean body mass, and anabolic state, an increase in circulating HIV could be a major negative effect of exercise. There is theoretical reason to be concerned about this, because acute exercise clearly activates the immune system, increasing production of third. The biological significance of these changes is not clear.

![Fig. 1. Acute-phase response to exercise.](http://jap.physiology.org/)

A: circulating absolute neutrophil counts/mm$^3$. B: creatine phosphokinase (CPK) levels (mU/ml). Time points (T) are baseline and 2, 6, 24, and 168 h (1 wk) after 15 min of acute exercise, expressed as a percentage of baseline value for each subject. Mean neutrophil count for each follow-up time is shown below graph. Error bars, SE. Pairwise comparison tests difference for each point compared with its immediate predecessor.
several inflammatory cytokines including IL-1β, IL-6, and TNF-α, which, in turn, have been shown to upregulate HIV replication in vitro (3, 7, 18, 20, 22). An example of immune activation, vaccination, was recently shown to cause a transient increase in circulating HIV (27). We therefore designed this study to examine short-term viral load kinetics in response to one bout of moderately heavy exercise. In our previous studies of the immune response to regular progressive resistance training, we found no immune activation of any sort in healthy volunteers and patients with autoimmune disease (rheumatoid arthritis) after 12 wk of biweekly training (25). Thus the chief concern in relation to increasing HIV replication is at the start of exercise training, because the first time untrained volunteers do regular exercise, they are in essence performing a bout of acute exercise.

The exercise intervention we used did activate the acute-phase response mildly, with increases in neutrophil counts, CPK, and 3-MH, indicating that demargination of circulating neutrophils and mild muscle injury did occur. The exercise intervention required each subject to lift and put down his or her body weight 225 times in 15 min. Observation of the study subjects confirmed that they were working hard during the exercise, with obvious tachycardia, tachypnea, and diaphoresis evident in all of them. Nevertheless, there was no increase in HIV RNA during and after this exercise bout. This exercise was primarily one of muscle endurance, but because subjects had to lower their body weight slowly, there was a considerable eccentric component to the intervention as well. Thus the results of the present study should be applicable to strength training as well as endurance training. However, these results probably should not be generalized to long-duration or very-high-intensity exercise, such as prolonged running, a stimulus that has been studied by others as an example of exercise-induced immune activation (19). Given the sedentary habits and poor physical fitness of our subjects, we were concerned that using such an intensive protocol could lead to injury or untoward immune effects.

We conclude that starting an exercise program at a moderate level of intensity is not associated with an increase in HIV load. It should be noted that the mean HIV load of our participants was relatively high at baseline, and it is possible that large increases in HIV RNA were simply not seen because of a “ceiling effect” in HIV replication. No such ceiling effect was seen in terms of the HIV RNA assay itself. Alternatively, small changes in HIV RNA would be more difficult to see with a high baseline RNA level than in the setting of previously undetectable levels. Because the three subjects with baseline undetectable HIV RNA showed small transient increases in viral load, the effect of acute exercise on HIV RNA in such patients deserves further study. It is possible that patients with low baseline circulating HIV could be more susceptible to an increase after exercise than were those who already have elevated rates of HIV replication. Nevertheless, given the many benefits of exercise for this population, our results suggest that programs of regular exercise,
aimed at increasing strength and muscle mass, reducing fat mass, and improving functional status in patients with HIV infection, should be implemented without excessive concern about the risk of activating HIV replication with moderate exercise.

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REFERENCES


