A Diet High in Saturated Fat and Cholesterol Accelerates Simian Immunodeficiency Virus Disease Progression

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Several lines of evidence suggest that dietary fat and cholesterol may play a role in the pathogenesis of human immunodeficiency virus (HIV) infection and disease progression. We examined the effect that an atherogenic diet (AD) high in saturated fatty acids and cholesterol has on disease progression and systemic inflammation in the simian immunodeficiency virus (SIV)–infected macaque model of acquired immunodeficiency syndrome. Macaques fed an AD had significantly more rapid disease progression, resulting in an increased risk of SIV-related death compared with that in control macaques (hazard ratio, 5.4 [95% confidence interval, 1.7–17.0]; \( P < .001 \)). Peak viral load was higher in the AD group compared with control values, but further statistically significant differences were not detected at viral set point. The baseline plasma interleukin-18 level after 6 months of the AD was predictive of disease progression. Our findings may have important implications for HIV-infected individuals, because they suggest that dietary changes and manipulation of lipid metabolism could offer potential benefits by slowing disease progression.

According to the World Health Organization, HIV is recognized as the leading infectious cause of human morbidity and mortality worldwide. The disease course differs from patient to patient, a fact that may be explained by a combination of viral, host, and environmental factors. Several lines of evidence suggest that dietary fat and cholesterol content may play a role in the pathogenesis of HIV infection and should be considered as an environmental factor that may impact disease progression. It is well recognized that dietary fat and obesity may alter cytokine profiles and promote a proinflammatory environment, which has been linked to a number of clinical conditions, including atherogenesis and type 2 diabetes [1, 2]. Rather than an inert collection of cells, white adipose tissue contains macrophages, dendritic cells, and T cells along with active vascular stromal cells, which produce a variety of proinflammatory cytokines and adipokines that may impact the immune system, including tumor necrosis factor (TNF)–\( \alpha \), monocyte chemoattractant protein (MCP)–1, interleukin (IL)–6, IL-10, and IL-18 [3, 4]. Up-regulation of these and other cytokines in the presence of increased dietary-fat intake may prime the immune system, leading to alterations in the pathogenesis of HIV infection.

In addition to promoting a proinflammatory cytokine environment, dietary lipids and cholesterol may directly alter viral replication. HIV uses cholesterol-rich regions of the plasma membrane (lipid rafts) for viral entry and budding [5–7], and cholesterol depletion significantly reduces HIV-1 particle production in vitro [8]. More recently, the HIV Nef protein has been shown to induce a number of genes involved with cholesterol...
Table 1. Comparison of atherogenic diet (AD) and normal diet (ND) composition.

<table>
<thead>
<tr>
<th>Category, parameter</th>
<th>AD</th>
<th>ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat (ether extract)</td>
<td>18.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Fat (acid extract)</td>
<td>19.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Cholesterol, ppm</td>
<td>10,044</td>
<td>89</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>1.12</td>
<td>1.47</td>
</tr>
<tr>
<td>Linolenic acid</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Arachadonic acid</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Omega-3 fatty acid</td>
<td>0.09</td>
<td>0.11</td>
</tr>
<tr>
<td>Total saturated fatty acid</td>
<td>13.78</td>
<td>1.69</td>
</tr>
<tr>
<td>Total monosaturated fatty acid</td>
<td>1.63</td>
<td>1.65</td>
</tr>
<tr>
<td>Protein</td>
<td>25.3</td>
<td>15.5</td>
</tr>
<tr>
<td>Starch</td>
<td>19.5</td>
<td>41.2</td>
</tr>
<tr>
<td>Calories provided by</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>24.25</td>
<td>17.72</td>
</tr>
<tr>
<td>Fat</td>
<td>39.35</td>
<td>12.87</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>36.4</td>
<td>69.41</td>
</tr>
</tbody>
</table>

NOTE. Nutrients are expressed as percentage of ration on an as-fed basis, unless otherwise indicated. Moisture content was assumed to be 10.0% for the purpose of the calculations. ppm, parts per million.

metabolism and to interact with ATP-binding cassette transporter A1 (ABCA1), an enzyme that functions in reverse cholesterol transport [9–11]. Nef has been found to increase the cholesterol content of newly formed virions and to increase viron infectivity, suggesting that the virus may manipulate cellular and subcellular cholesterol content to enhance viral replication [12, 13].

Infection of macaques and other nonhuman primate species with simian immunodeficiency virus (SIV) was first recognized 20 years ago, and the virus has proven to be an important model for deciphering aspects of the pathogenesis of HIV infection and disease prevention. SIV and HIV share extensive genetic and biological similarities, and the disease course in rhesus macaques parallels that observed in humans [14, 15]. The specific viral targets, progressive loss of CD4 T cells, and acquisition of opportunistic infections recapitulate the pathogenesis of HIV infection in human patients. We wondered whether nonhuman primates may represent a novel model for examining lipid metabolism in the context of AIDS and, thus, could provide additional insight into the pathogenesis of HIV infection. Rhesus macaques have been studied extensively as a model of type 2 diabetes and atherosclerosis [16–19]. These models are characterized by the natural development of obesity, insulin resistance, islet amyloidosis, dyslipidemia, and hypertension in animals with increasing age, alterations that are often exacerbated by a high-fat diet [20]. Macaques placed on diets high in fat and cholesterol develop alterations in serum lipids that parallel those observed in humans, including increases in serum cholesterol, triglycerides, and low-density lipoprotein (LDL) levels with concurrent decreases in high-density lipoprotein (HDL) levels [21, 22]. The study of diet in the context of simian AIDS may give important insight into role played by lipids in the pathogenesis of HIV and SIV infection.

Here, we demonstrate that consumption of a diet high in cholesterol and saturated fatty acids results in an accelerated disease course after experimental SIV infection of rhesus macaques. These changes correlated with alterations in viral load and levels of proinflammatory cytokines measured in plasma. These findings may have important implications in optimizing the dietary intake of HIV-infected individuals.

METHODS

All macaques were housed at the New England Primate Research Center and were maintained in accordance with the guidelines given in the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Resources, National Research Council). The facility is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International, and all work was approved by Harvard Medical School’s Standing Committee on Animals. Test macaques (n = 8) were compared with historical SIVmac239-inoculated control macaques (n = 52) for survival and additional immunological and virological parameters. These control macaques had been included as untreated and unvaccinated animals in a variety of pathogenesis and prevention studies in which the natural course of disease progression was allowed to develop. All macaques were inoculated intrave-
**Diet.** All macaques were maintained ad libitum on commercially available diets in biscuit form (LabDiet); biscuits were provided twice a day. The test subjects were fed a diet high in cholesterol and saturated fat (atherogenic diet [AD]; no. 57JI). This AD is characterized by a high content of total fat (39.35% of energy), saturated fat (13.78% of energy), and cholesterol (1% of diet on an as-fed basis) and is low in omega-3 fatty acids (n-6:n-3 ratio of 7–10:1). Historical control macaques were fed a standard normal diet (ND; no. 5038), which supplies 12.87% of calories through fat and is substantially lower in cholesterol and saturated fatty acids. A comparison of the ND and AD is presented in table 1. Baseline measurements were made, and macaques were placed on the AD for 6 months before inoculation.

**Body composition.** Body weight was measured every 4 weeks using a calibrated scale that measured to the nearest gram, and somatometric measurements were performed as described elsewhere [23]. Measurement of specific body compartments (fat, lean mass, and bone mineral content and bone mineral density) was performed by dual energy X-ray absorptiometry (DEXA) using a Lunar Prodigy Bone Densitometer (Lunar Corporation), and measurements were analyzed using software developed specifically for nonhuman primates [23].

**Statistical analysis.** Means and SDs of outcomes were reported by experimental conditions and weeks after inoculation. Between-week comparisons were conducted using paired t tests (Systat Software). Survival of the experimental macaques was characterized using Kaplan-Meier methods, and the relative risks of risk factors were estimated using Weibull regression models, as described elsewhere [23, 26].

**RESULTS**

**Accelerated progression of simian AIDS in macaques fed an AD.** After SIV inoculation of macaques receiving an AD, animals developed high viral loads and progressive loss of CD4 T cells. Macaques were monitored prospectively via monthly physical examinations, phlebotomy, and body composition measurements and were euthanized on the basis of standard criteria after the development of simian AIDS [23]. Survival was compared with that among 52 SIVmac239-inoculated historical control macaques fed the ND. Survival in the ND historical control group, in which the natural course of disease was allowed to develop, was similar to that described previously [27]. Macaques fed the AD died of a number of opportunistic infections and SIV-specific diseases typical of simian AIDS. Analysis revealed significantly more rapid disease progression in macaques fed the AD, resulting in a marked increased risk of SIV-related death relative to that among age- and sex-matched historical control macaques (hazard ratio [HR], 5.4 [95% confidence interval [CI], 1.7–17.0]; P < .001) (figure 1).

Viral loads, antibody responses, and CD4 T cell numbers were determined by reverse-transcription polymerase chain reaction, and cell immunophenotyping was performed to determine CD4 and CD8 T cell numbers and ratios [23]. Viral neutralizing antibodies were detected as described elsewhere [24]. Euthanasia criteria were developed before the initiation of the study, and euthanasia was done in accordance with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. ELISAs for MCP-1, IL-18, and soluble TNF type 2 receptor (sTNF RII) were performed using commercially available kits provided by R&D Systems, as described elsewhere [25].
Figure 3. Atherogenic diet (AD)–associated AIDS pathology in simian immunodeficiency virus (SIV)–infected macaques. **A,** Atherosclerotic lesion in coronary artery; **B,** Atherosclerotic plaque revealing foam cells and lipid crystals; **C,** Hepatic lipodiposis; **D,** SIV syncytial cell in giant cell pneumonia; **E,** Malignant lymphoma in axillary lymph node; **F,** Intranuclear rhesus lymphocryptovirus in esophageal hairy leukoplakia; **G,** Pneumocystis carinii pneumonia; **H,** SIV encephalitis; **I,** Intranuclear and intracytoplasmic inclusions in cytomegalovirus neuritis.

were evaluated to determine whether alterations in these parameters were associated with increased disease progression (figure 2). There were no statistically significant differences in CD4 T cell numbers before or immediately after inoculation, and all macaques developed neutralizing-antibody responses. A rebound in CD4 T cell number—commonly observed after resolution of acute viremia in macaques—was not observed in animals fed the AD. Peak viral load determined 2 weeks after inoculation was 0.56 log₁₀ higher in the AD group, compared with historical control values (7.75 vs. 7.19 log₁₀ genomic RNA copies/mL of plasma for AD vs. ND; *P* < .001, paired *t* test). However, there was no statistically significant difference at later time points, and the viral set point at 4 weeks was similar to that observed in control macaques (6.29 vs. 6.88 log₁₀ genomic RNA copies/mL of plasma for AD vs. ND; *P* = .141, Mann-Whitney rank sum test).

**Alteration of lipoprotein profiles and the development of atherosclerosis in macaques fed the AD.** Macaques receiving the AD developed atherogenic lipid profiles, including increases in cholesterol levels (130.1 vs. 836.0 mg/dL for AD vs. ND; *P* < .001, paired *t* test), triglyceride levels (66.9 vs. 164.0 mg/dL for AD vs. ND; *P* = .018, paired *t* test), and LDL levels (51.7 vs. 773.6 mg/dL for AD vs. ND; *P* < .001, paired *t* test) relative to baseline ND values. Further changes in lipid profiles were not observed after SIV inoculation (data not shown). Alterations in HDL levels did not reach statistical significance. Macaques developed evidence of atherosclerosis, which was observed at necropsy primarily within the carotid arteries and abdominal aorta (figure 3A and 3B); however, the primary cause of death was AIDS-associated disease. Hepatosteatosis was observed with varying degrees of hepatocellular fatty change, ballooning degeneration, and lobular inflammation.
all macaques (figure 3C). A variety of AIDS-associated pathologies were observed, including *Pneumocystis carinii* pneumonia, disseminated cytomegalovirus infection, disseminated *Mycobacterium avium* complex, progressive multifocal leukoencephalopathy (simian virus 40), SIV encephalitis, and wasting (figure 3D–3I). Morphologically, these conditions are similar to those we have described previously, and, other than accelerating disease progression, the AD did not appear to alter the disease phenotype.

**Correlation of disease course with body composition and somatometric measurements.** There were no statistically significant changes in body weight after 6 months of the AD. However, after SIV inoculation, macaques receiving the AD developed a number of changes in body composition (table 2), including decreases in body weight, waist circumference, total body fat, and percent body fat. There was no statistically significant difference in lean body mass and weight loss, which resulted primarily from loss of fat mass. Regional differences in body composition before and after inoculation with SIV were also investigated on the basis of skinfold thickness and by DEXA. Selective loss of triceps fat and preferential loss of abdominal fat were also observed. These measurements were evaluated as being risk or protective factors for SIV progression. Elevation in initial body weight (HR, 0.42 [95% CI, 0.19–0.94]; *P* = .035) and body mass index (HR, 0.62 [95% CI, 0.40–0.94]; *P* = .013) were associated with a decreased rate of progression. Total body fat in kilograms (*P* = .058), total body fat percentage (*P* = .072), and trunk fat percentage (*P* = .063) all approached but did not achieve statistical significance as additional protective factors. Thus, although high dietary fat shortened survival, elevated body fat at the time of inoculation appeared to confer modest protection against disease progression.

### Table 2. Alterations of somatometrics and body composition measurements in simian immunodeficiency virus–infected macaques receiving an atherogenic diet.

<table>
<thead>
<tr>
<th>Category, parameter</th>
<th>Weeks after inoculation</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td><strong>Anthropometric</strong></td>
<td></td>
<td>0</td>
<td>12</td>
<td>24</td>
<td><em>P</em></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>9.3 (1.9)</td>
<td>9.1 (1.7)</td>
<td>8.3 (1.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>36.9 (4.8)</td>
<td>36.8 (4.3)</td>
<td>34.5 (5.2)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Thigh fat thickness, cm</td>
<td>3.1 (1.1)</td>
<td>3.4 (1.2)</td>
<td>2.8 (0.8)</td>
<td>.237</td>
<td></td>
</tr>
<tr>
<td>Triceps fat thickness, cm</td>
<td>3.2 (1.1)</td>
<td>2.7 (0.9)</td>
<td>2.5 (1.0)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Subscapular fat thickness, cm</td>
<td>8.3 (4.8)</td>
<td>9.4 (4.7)</td>
<td>6.7 (2.8)</td>
<td>.802</td>
<td></td>
</tr>
<tr>
<td>Suprailiac fat thickness, cm</td>
<td>6.5 (3.3)</td>
<td>7.4 (4.8)</td>
<td>5.1 (2.3)</td>
<td>.042</td>
<td></td>
</tr>
<tr>
<td><strong>Body composition (DEXA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body fat, kg</td>
<td>3.34 (1.78)</td>
<td>2.97 (1.54)</td>
<td>2.49 (1.51)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Total lean mass, kg</td>
<td>5.69 (0.50)</td>
<td>5.74 (0.55)</td>
<td>5.52 (0.48)</td>
<td>.790</td>
<td></td>
</tr>
<tr>
<td>Body fat, %</td>
<td>34.8 (13.5)</td>
<td>32.4 (13.5)</td>
<td>29.1 (13.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Peripheral fat:trunk fat ratio</td>
<td>0.40 (0.09)</td>
<td>0.51 (0.34)</td>
<td>0.72 (0.72)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Total bone mineral content, g</td>
<td>343 (41)</td>
<td>331 (40)</td>
<td>317 (38)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Data are mean (SD) values. DEXA, dual energy X-ray absorptiometry.

Alteration of levels of proinflammatory cytokines and chemokines (sTNF RII and MCP-1) by the AD. sTNF RII and MCP-1 levels were measured monthly, and similar patterns were revealed after the initiation of the AD and SIV infection. After the initiation of the AD, there was an increase in both sTNF RII (416.3 vs. 526 pg/mL for ND vs. 8 weeks of AD; *P* = .032, paired *t* test) and MCP-1 (110.7 vs. 132.8 pg/mL for ND vs. 4 weeks of AD; *P* = .044, paired *t* test) levels, which began to return to normal with acclimatization to the dietary change. After inoculation, there was a rapid increase in both sTNF RII (490.8 vs. 910.4 pg/mL for 24 weeks of AD vs. 2 weeks after SIV inoculation; *P* = .032, paired *t* test) and MCP-1 (141.2 vs. 288.8 pg/mL for 24 weeks on AD vs. 2 weeks after SIV inoculation; *P* = .003, paired *t* test) levels, both of which peaked at 2 weeks after inoculation and then began to return to AD baseline levels. With disease progression, there were further increases in both sTNF RII and MCP-1 levels. Comparison of sTNF RII levels to those in SIVmac239-inoculated macaques receiving the ND revealed similar changes, and there were no statistically significant differences on the basis of diet status after SIV inoculation (figure 4).

sTNF RII levels were compared with respect to alterations in regional body composition. During the preinoculation period, in macaques receiving the AD there was a positive correlation between sTNF RII levels and trunk fat percentage (slope, 6.77 [95% CI, 2.64 to 10.9]; *P* = .001). During the progressive phase of disease after SIV inoculation, this relationship reversed, such that high levels of sTNF RII were associated with loss of trunk fat (slope, −17.8 [95% CI, −34.4 to −1.14]; *P* = .036). Comparison of the slopes revealed a statistically significant difference in slope between the preinoculation period in macaques receiving the AD and the pro-
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Figure 4. Soluble TNF type 2 receptor (sTNF RII) and interleukin (IL)–18 levels in rhesus macaques fed either a normal diet (ND) or an atherogenic diet (AD). Postinoculation profiles of sTNF RII levels were similar regardless of diet composition (A and B). In contrast, an exaggerated IL-18 response was observed in AD-fed macaques and was found to correlate with survival (C and D).

Progressive phase of immunodeficiency (16–48 weeks) (−18.2 [95% CI, −44.6 to −4.5]; P = .016). These findings are compatible with a role for abdominal obesity in producing elevated sTNF RII levels in macaques receiving an AD and suggest an alteration of this relationship during SIV disease progression.

Correlation of alterations in IL-18 levels with disease course and viral load. IL-18 levels were measured, and a similar pattern to that observed for sTNF RII and MCP-1 levels was revealed. After initiation of the AD, there was a marked increase in plasma IL-18 levels (73.5 vs. 586.1 pg/mL for ND vs. 4 weeks of AD; P = .003, paired t test), which stabilized at values higher than those observed at baseline (figures 4 and 5A). After 5 months of the AD, a positive correlation developed between sTNF RII and IL-18 levels (r = 0.7171; P = .0058, Pearson correlation), a finding that was not observed for the ND. After SIV inoculation, there was a further increase in IL-18 levels that coincided with peak viral load (222.8 vs. 1163.7 pg/mL for 24 weeks receiving AD vs. 2 weeks after SIV inoculation; P = .024, paired t test). Values then dropped and began to rise again with disease progression. Although macaques receiving the ND did develop an increase in plasma IL-18 levels after SIV inoculation, the AD resulted in an exaggeration of the IL-18 response. Statistically significant differences were observed in baseline IL-18 levels between macaques receiving the AD and those receiving the ND as well as in these same animals after SIV challenge (figure 5A). Comparison of log_{10} viral load to log_{10} plasma IL-18 level over the full course of SIV infection revealed a highly significant positive correlation (r = 0.71 [95% CI, 0.56–0.81]; P = .0001) (figure 5B).

To determine whether IL-18 responses were predictive of disease progression, crude HRs were calculated for plasma IL-18 levels at defined time points after SIV infection by use of a Weibull regression model (table 3). The baseline plasma IL-18 after 6 months of the AD was predictive of accelerated disease progression, revealing a crude HR of 9.38 (95% CI, 1.68–52.3; P = .011) for each 100-ng/mL increase in IL-18 level. Similar findings were observed for peak IL-18 levels at 2 weeks after SIV inoculation (crude HR, 1.23 [95% CI, 1.01–1.49]; P = .038) and mean IL-18 level for week 0–20 after SIV infection (crude HR, 5.59 [95% CI, 1.72–18.1]; P = .004).

DISCUSSION

We have demonstrated that consumption of a diet high in cholesterol and saturated fatty acids may fundamentally alter the disease course after experimental inoculation of SIVmac239, resulting in accelerated disease progression. Macaques died of a variety of opportunistic infections and with lesions compatible with dietary excess of cholesterol and fat, including atherosclerosis and hepatocellular fatty change. The mechanism
behind enhanced SIV disease progression was not identified, but the AD was associated with higher peak viral load and enhanced production of inflammatory cytokines. Interestingly, although the AD was associated with accelerated disease progression, higher body fat percentage and body mass index at the time of inoculation were moderately protective.

Recently, cholesterol metabolism has been linked to the pathogenesis of HIV infection, and one hypothesis for the observed effect of an AD is that higher dietary cholesterol leads to enhanced viral replication. Macrophages, considered to be key host cells for HIV, have reduced ability to degrade cholesterol, such that intracellular levels are dependent on cholesterol uptake and efflux. HIV has been demonstrated to use cholesterol-rich regions of the plasma membrane (lipid rafts) for viral entry and budding [5–7], and cholesterol depletion significantly reduces HIV-1 particle production in in vitro systems [6, 8]. HIV is postulated to exploit cholesterol metabolism pathways by up-regulation of biosynthesis and decreasing cholesterol efflux, subsequently ensuring adequate levels for envelope formation and budding [9, 13]. Recently, the role played by the viral protein Nef in lipid metabolism has been investigated. In vitro studies have indicated that Nef up-regulates key genes involved in cholesterol metabolism and that Nef may interact with ABCA1, an enzyme involved in reverse cholesterol transport [9, 11]. It is suggested that HIV may manipulate cellular and subcellular cholesterol to enhance viral assembly and infectivity [10]. It is possible that a diet high in fat and cholesterol leads to increased intracellular monocyte and macrophage cholesterol content with the potential for optimization of viral replication, leading to higher viral loads and a resulting increase in disease progression. We have demonstrated here a statistically significant elevation in peak viral load in AD-fed macaques 2 weeks after inoculation; however, the difference was modest (0.56 log_{10} viral RNA copies/mL of plasma) and did not persist through the viral set point, suggesting that other mechanisms may be involved in producing an effect on survival.

An alternate and mutually nonexclusive hypothesis is that an AD promotes alterations in levels of key proinflammatory cytokines that may enhance viral replication or virus-induced immunopathology. Up-regulation of these and other cytokines in the presence of increased dietary-fat intake may prime the immune system, leading to alterations in the pathogenesis of HIV infection. The presence of a proinflammatory environment may be critically important to HIV pathogenesis. There is significant crossover in the roles played by proinflammatory cytokines related to adiposity and those cytokines involved in the progression of HIV disease. Adipocytes can directly synthesize TNF-α and other cytokines that may impact viral pathogenesis. TNF-α is one of multiple cytokines thought to play a role in the immune activation of T cells and in activation-induced apoptosis in the setting of HIV infection [15]. Indeed, we observed increased basal production of sTNF RII and MCP-1 in adult macaques placed on an AD. Increased plasma levels of sTNF RII have demonstrated prognostic utility for progression to AIDS in HIV-infected men, with this marker allowing stratification of patients by prognosis for all major categories of HIV RNA levels and CD4 T cell counts [28]. However, we did

<table>
<thead>
<tr>
<th>Time point</th>
<th>Crude HR (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Day of inoculation (week 0)</td>
<td>9.38 (1.68–52.3)</td>
<td>.011</td>
</tr>
<tr>
<td>Week 2 after SIV inoculation</td>
<td>1.23 (1.01–1.49)</td>
<td>.038</td>
</tr>
<tr>
<td>Mean between weeks 0 and 20</td>
<td>5.59 (1.72–18.1)</td>
<td>.004</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval.
not observe a difference in sTNF RII or MCP-1 levels on the basis of diet status after SIV inoculation.

Of particular interest is the role that IL-18 may play in AD enhancement of SIV disease progression. In contrast to sTNF RII, IL-18 profiles in ND- and AD-fed macaques were markedly different after SIV infection. Levels of this proinflammatory cytokine are elevated in obese persons, which is associated with increased risk for cardiovascular disease and atherogenesis [29, 30]. We observed here that AD increased IL-18 levels in plasma and that elevated levels of IL-18 after initiation of the AD but before inoculation were predictive of shorter survival. Furthermore, after infection, plasma IL-18 levels correlated closely with viral load. Elevation of plasma IL-18 levels has previously been observed in HIV-infected patients, in whom it has been correlated with the lipodystrophy syndrome [31, 32], as well as in SIV-infected macaques, in which elevations were observed with pathogenic but not nonpathogenic viral infection [33]. Serum IL-18 levels from healthy human donors positively correlated with viral replicative capacity [34], and in vitro and animal models have suggested that IL-18 may drive viral replication [35, 36].

In addition to its putative effects on viral replication, it has been proposed that, in the context of the low IL-12 levels observed during AIDS, IL-18 may promote a Th2 cytokine profile, which may exacerbate HIV disease progression [35, 36]. It is during the acute stages of HIV infection that the immunological set point is established, which helps to define the pathogenic potential of HIV in a given individual. Critical to the establishment of this set point is the ability of the virus to cause increases in T cell activation [37]. The expression of cell-activation markers on CD8 and CD4 cells during primary infection—and as early as preresorption—correlates with increased HIV RNA levels, decreased CD4 cell counts, and shorter AIDS-free survival [38–40]. T cell activation is thought to occur secondary to induction by specific antigens and to dysregulation of cytokine levels, via viral gene products [39, 41]. Activation of CD4 and CD8 T cells resulting in the apoptosis of uninfected bystander cells is believed to contribute substantially to the observed depletion of uninfected CD4 T cells that occurs with the progression of HIV infection to AIDS. It is possible that diet manipulation altered T cell dynamics in a way that promoted such activation-induced cell death in the context of SIV infection. In fact, the rebound in CD4 T cell number commonly observed after resolution of acute viremia in rhesus macaques was not observed in the animals fed an AD.

Our findings may have important implications for HIV-infected individuals. Given the high prevalence of obesity in Western countries, adipose deposits and dietary-fat intake may prove to be significant and overlooked host factors that are integral to the progression of HIV infection. This is particularly relevant in light of the widely accepted hypothesis that host factors present before the development of HIV-specific immune responses are critical for the establishment of the postacute plasma viral load set point and the subsequent progression of disease [42]. If findings in the macaque model are substantiated in human subjects, then it would seem that dietary changes and manipulation of cholesterol and/or lipid metabolic pathways in HIV-infected patients could offer potential benefits by slowing disease progression and delaying required treatment with antiretrovirals.

References

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33. Kaizu M, Ami Y, Nakasone T, et al. Higher levels of IL-18 circulate during primary infection of monkeys with a pathogenic SHIV than with a nonpathogenic SHIV. Virology 2003; 313:8–12.