times through a 25-gauge needle. We confirmed inoculum size by viable colony counts and used sonication to prepare a homogenous inoculum of lipids for injection of 100, 10, and 1 μg of mycolactone and 100 and 10 μg of the control *M. ulcerans* lipid Red 77. Guinea pigs were prepared for injection by shaving the back and were observed daily for signs of pathology. We used duplicate guinea pigs for each time point. Results shown are from a typical experiment, which was repeated three times.

. Lesions were excised for histopathological examination and fixed for 24 hours in 3.7% formaldehyde. Tissues were embedded in paraffin, cut in 4-μm-thick sections, and stained with hematoxylin and eosin. We stained tissues that had been inoculated with *M. ulcerans* or *M. marinum* with Zeihl-Neelson stain.

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Control of Viremia in Simian Immunodeficiency Virus Infection by CD8$^+$ Lymphocytes

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Clinical evidence suggests that cellular immunity is involved in controlling human immunodeficiency virus–1 (HIV-1) replication. An animal model of acquired immune deficiency syndrome (AIDS), the simian immunodeficiency virus (SIV)–infected rhesus monkey, was used to show that virus replication is not controlled in monkeys depleted of CD8$^+$ lymphocytes during primary SIV infection. Eliminating CD8$^+$ lymphocytes from monkeys during chronic SIV infection resulted in a rapid and marked increase in viremia that was again suppressed coincident with the reappearance of SIV-specific CD8$^+$ T cells. These results confirm the importance of cell-mediated immunity in controlling HIV-1 infection and support the exploration of vaccination approaches for preventing infection that will elicit these immune responses.

Defining the immune mechanisms responsible for controlling HIV-1 replication during primary and chronic infection will be important for understanding the immunopathogenesis of AIDS. The delineation of these mechanisms will also be useful to establish the goals of HIV-1 vaccine approaches. A number of clinical and experimental observations have implicated virus-specific cytotoxic T lymphocytes (CTLs) in this process. CD8$^+$ lymphocytes from infected individuals have been shown to inhibit HIV-1 replication in vitro (*1*). Control of the intense burst of viral replication seen in primary HIV-1 infection coincides with the appearance of virus-specific CTLs (*2*). Finally, potent virus-specific CTL responses have been observed in infected individuals with low viral loads and persistent, nonprogressive infections (*3*). However, these observations provide only circumstantial evidence for the role of virus-specific cellular immune responses in controlling HIV-1 infections.

We directly assessed the role of cellular immunity in controlling HIV-1 infection by means of the SIV of macaques (SIVmac)/rhesus monkey model of AIDS (*4*). In previous attempts to abrogate cell-mediated immune responses in lentiviral infections, only incomplete, transient CD8$^+$ lymphocyte depletion was achieved, and the studies were done with nonpathogenic lentiviruses (*5*). We observed that intravenous administration of the CD8-specific mouse-human chimeric monoclonal antibody cM-T807 resulted in near total depletion of CD8-bearing lymphocytes from the blood and lymph nodes of normal monkeys, whereas the CD4$^+$ T cell subset remained unchanged (*6*). We therefore characterized the replication of SIVmac in monkeys depleted of CD8$^+$ lymphocytes by this antibody.

As in HIV-1 infection of humans, primary infection of rhesus monkeys with SIVmac is characterized by an intense burst of virus replication followed by an abrupt decline in viremia presumably due to the emergence of immune responses that suppress virus replication (*7*) or, potentially, to exhaustion of target cells (*8*). To determine the contribution of CD8$^+$ lymphocyte–mediated immune responses to this control of viremia, we treated rhesus monkeys with cM-T807 or a control monoclonal antibody during primary SIVmac infection (*9*). The cM-T807 treatment resulted in total depletion of CD8$^+$ T cells from the blood of monkeys (Fig. 1, B and C). Near total elimination of CD8$^+$ lymphocytes was also achieved in lymph nodes (Fig. 2, A and B), where immunophenotypic analysis of sequential biopsies confirmed a 90 to 100% decline in CD8$^+$ T cells (*10*). However, the duration of CD8$^+$ lymphocyte depletion varied considerably among monkeys. In three of the six cM-T807–treated monkeys, CD8$^+$ T cell depletion was evident for 17 to 21 days (Fig. 1B). In the other three monkeys, CD8$^+$ lymphocyte depletion was considerably more persistent. CD8$^+$ T cells were depleted in these monkeys for 28 to 60 days (Fig. 1C). The duration of antibody-mediated depletion is partially age-dependent, and the variability we observed was consistent with that seen in normal rhesus monkeys that received similar treatment (*6*, *11*). Nevertheless, we achieved ≥18 days of near total CD8$^+$ lymphocyte depletion in all six monkeys, and the duration of cell depletion from lymph nodes was equal to, or longer than, that observed in the blood. The other lymphocyte subsets showed only the transient decline that is generally seen during the peak of SIVmac viremia irrespective of any antibody treatment (*7*).

To determine the effect of CD8$^+$ lymphocyte depletion on the control of SIVmac infection, we assessed virus replication by measuring plasma viral RNA and SIVmac Gag p27 antigen levels. In all six control mon-

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keys, the peak levels of plasma viral RNA were reached between days 11 and 14 after inoculation. Neither the time of peak viremia nor the peak levels of plasma virus differed substantially between the $CD8^+$ lymphocyte–depleted monkeys and monkeys receiving a control monoclonal antibody (Fig. 1, D to F). SIVmac viral RNA levels decreased rapidly from peak levels in all control antibody–treated monkeys by day 21 and remained at these lower levels through days 28 and 35 (median logarithmic decrease from peak levels: 1.2, 1.4, and 1.6 for days 21, 28, and 35, respectively). A significantly smaller decrease ($P = 0.048$) from peak viral RNA levels was observed at the same time points in the six monkeys that were depleted of $CD8^+$ lymphocytes (median logarithmic decrease: 0.3, 0.7, and 0.7) (*12*). The inability to control primary SIVmac viremia appeared to be affected by the duration of $CD8^+$ T cell depletion. In monkeys in which ≤21 days of $CD8^+$ T cell depletion was achieved, the decrease in plasma viral RNA levels after peak SIVmac replication was less profound at day 21 (median logarithmic decrease: 0.7) than the decrease seen in control antibody–treated monkeys. Twenty-eight or thirty-five days after infection, the plasma viral RNA levels in these monkeys had declined to a level closer to that seen in monkeys treated with the control antibody (median logarithmic decrease: 1.1 and 1.2, respectively) (Fig. 1E). However, in those monkeys in which $CD8^+$ T cell depletion of ≥28 days was achieved, plasma viral RNA levels never decreased substantially (Fig. 1F). At 21, 28, and 35 days after SIVmac infection, the changes in plasma viral RNA from the day 11 to 14 peak values in these three monkeys were consistently less than those seen in control antibody–treated monkeys (median logarithmic decrease: 0.0, 0.4, and −0.3, respectively).

The same pattern of viremia was observed when plasma SIVmac Gag p27 antigen levels were used as a measure of virus replication (Fig. 3, A to C). Peak levels of Gag p27 antigen were also reached between days 11 and 14 after SIVmac infection in all monkeys. In control antibody–treated monkeys, Gag p27 antigen

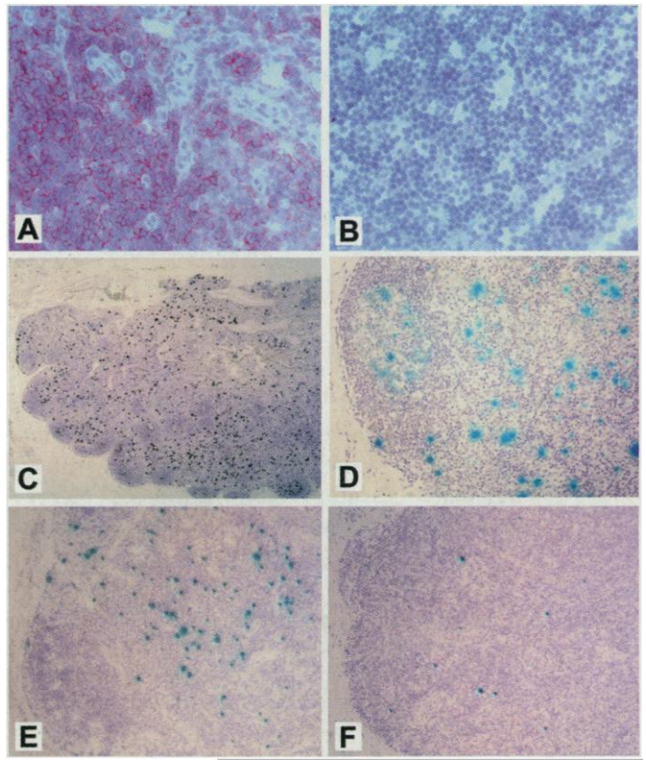

Fig. 2. $CD8^+$ lymphocyte depletion and virus replication in lymph nodes during primary SIVmac infection. (**A** and **B**) Depletion of $CD8^+$ T lymphocytes from lymph nodes by treatment with cM-T807 was demonstrated by immunohistochemical staining of cryostat sections for CD8 (Leu-2a; Becton Dickinson, Heidelberg, Germany, and C8/144B; Dakopatts, Hamburg, Germany) in an alkaline phosphatase antialkaline phosphatase technique. Positively staining cells appear red. (A) Biopsies obtained before treatment. (B) Biopsies obtained 18 days after cM-T807 administration (which corresponded to 14 days after SIVmac infection) (original magnification, ×100). (**C** to **F**) SIVmac replication in lymph node cryostat sections was detected by in situ hybridization as previously described (*18*). (C) High-level replication was evident in a long-term $CD8^+$ lymphocyte–depleted monkey at 14 days after SIVmac inoculation. Low power (original magnification, ×25). (D) High power (original magnification, ×50). (E) A high level of virus replication was still evident in the lymph node of the same $CD8^+$ lymphocyte–depleted monkey 42 days after SIVmac inoculation (original magnification, ×50). (F) Virus replication was well controlled on day 42 in the lymph node of a control antibody–treated monkey (original magnification, ×50).

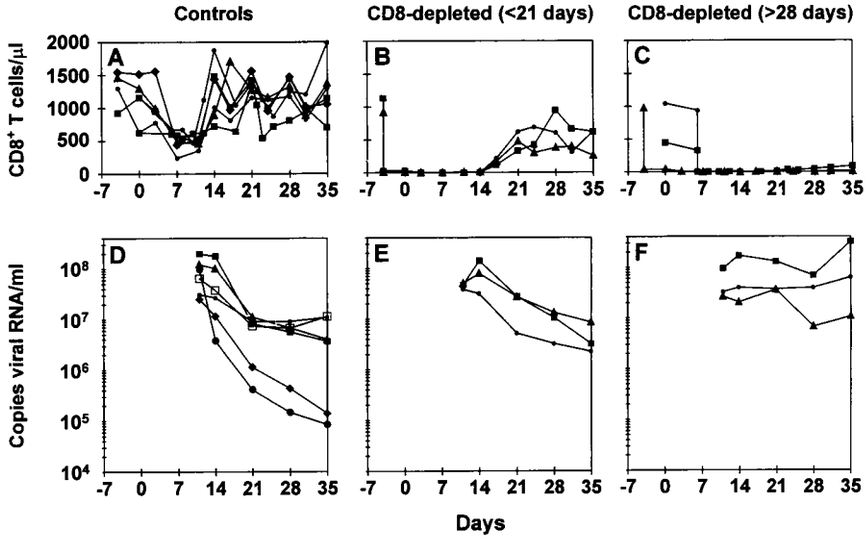

Fig. 1. Effect of $CD8^+$ lymphocyte depletion on control of SIVmac replication during primary infection of rhesus monkeys. Rhesus monkeys were administered the mouse-human chimeric monoclonal antibody to CD8 cM-T807 or a control antibody to deplete $CD8^+$ lymphocytes during primary SIVmac infection as described (*9*). (**A** to **C**) $CD8^+$ T cells were enumerated in blood by four-color flow cytometric analysis with CD4-FITC (OKT4; Ortho Diagnostic Systems, Raritan, NJ), CD8-PE (DK25; Dako, Carpinteria, CA), CD20-ECD (B1; Beckman Coulter, Miami, FL), and CD3-APC (FN18). The CD8-specific monoclonal antibody DK25 could bind to CD8 in the presence of cM-T807, although staining intensity was decreased. When we were unable to detect $CD8^+$ lymphocytes, we confirmed that >95% of the remaining lymphocytes were either $CD20^+$ B cells or $CD4^+$ T cells. (A) $CD8^+$ T lymphocyte counts in control antibody–treated monkeys. (B) In three monkeys, treatment with antibody to CD8 resulted in near complete depletion of $CD8^+$ T cells from peripheral blood for 17 to 21 days. (C) In three monkeys, depletion of $CD8^+$ T cells persisted for 28 to 60 days. (**D** to **F**) SIVmac replication was assessed by plasma viral RNA measurement (SIVmac bDNA RNA Assay; Chiron Diagnostics, Emeryville, CA). (D) Control antibody–treated monkeys. (E) Monkeys depleted of $CD8^+$ lymphocytes for ≤21 days. (F) Monkeys depleted of $CD8^+$ T cells for ≥28 days.

levels had declined substantially by day 21 (Fig. 3A). However, in $CD8^+$ lymphocyte–depleted monkeys, plasma Gag p27 antigen levels remained significantly higher ($P = 0.028$) than in control monkeys during the day 21 to 35 time period (*12*). In cM-T807–treated monkeys that achieved short-term (≤21 days) $CD8^+$ T cell depletion, plasma viral antigen levels declined more slowly and did not reach the same level as control antibody–treated monkeys until day 28 (Fig. 3B). The cM-T807–treated monkeys that achieved long-term (≥28 days) $CD8^+$ T cell depletion maintained high Gag p27 levels in plasma through day 35 (Fig. 3C). The continuous high levels of viral replication in $CD8^+$ lymphocyte–depleted monkeys were also confirmed by in situ hybridization studies that showed that productively infected cells persisted in lymph nodes through day 42 after SIVmac infection (Fig. 2, C to F).

To evaluate virus-specific immune responses mediated by $CD8^+$ T cells in these antibody-treated monkeys, we quantitated the SIVmac-specific CTLs in peripheral blood by flow cytometry. This was done as previously described in those monkeys expressing the rhesus monkey major histocompatibility complex (MHC) class I allele *Mamu A*01* by means of MHC class I/viral peptide tetramers coupled to fluorochromes (*13*). In the *Mamu A*01*$^+$ monkey that received control antibody, SIVmac-specific CTLs were detected at 11 days after virus inoculation, corresponding closely with the clearance of viremia (Fig. 3D). The kinetics of the generation of this CTL response during primary SIVmac infection was identical to that which we have observed in six other monkeys (*14*). In the *Mamu A*01*$^+$ monkey in which ≤21 days of $CD8^+$ lymphocyte depletion was achieved, SIVmac-specific CTLs were first detected at 24 days after virus inoculation, which was 13 days later than in the control antibody–treated monkey. The appearance of this cellular response also paralleled the decline in viremia (Fig. 3E). Finally, in the monkey in which long-term $CD8^+$ lymphocyte depletion was achieved, virus-specific CTLs were never observed in blood, and virus replication was never controlled (Fig. 3F).

The depletion of $CD8^+$ lymphocytes was also associated with a substantial acceleration in the SIVmac-induced course of disease. In normal rhesus monkeys, about 20 to 30% of SIVmac infections result in a rapidly progressive disease course (*15*). As would have been predicted, two of six monkeys that received the control antibody succumbed to a rapidly progressive disease course characterized by a persistent, high-level viremia, weak or absent neutralizing antibody response (*16*), and death due to an AIDS-like syndrome. Survival time was significantly shorter ($P = 0.043$) (*12*) for the six monkeys that received cM-T807 (median survival: 160 days) than for the control antibody–treated monkeys (median survival: >297 days) (Fig. 4). In the $CD8^+$ lymphocyte–depleted group, there appeared to be an association between duration of $CD8^+$ T cell depletion and survival. Two of the three monkeys that achieved short-term $CD8^+$ lymphocyte depletion had a rapidly progressive disease course as described above (median survival: 240 days). Of the three monkeys treated with antibody to CD8 that achieved long-term CD8 cell depletion, all developed a rapidly progressive disease course, succumbing within 120 days of virus inoculation (median survival: 114 days) (Fig. 4).

As these studies indicated that $CD8^+$ lymphocytes affect SIVmac replication during primary infection, we reasoned that this cell population may also control AIDS virus replication during the period of chronic viremia. To test this hypothesis, we administered cM-T807, or the control monoclonal antibody, to rhesus monkeys that had been infected with SIVmac for more than 9 months (*9*). The plasma viral RNA levels varied between monkeys from <1500 to >10^7 RNA copies per milliliter of plasma but were relatively stable over time in each individual monkey. As illustrated in Fig. 5, A to C, top panels, substantial $CD8^+$ lymphocyte depletion was achieved for 9 to 14 days in the three monkeys that received cM-T807. $CD8^+$ lymphocyte depletion in these chronically SIVmac-infected monkeys was considerably less efficient than that observed in cM-T807 treatment of uninfected monkeys or in treatment during primary infection. Although we are unable to explain this inefficiency of lymphocyte depletion seen in chronically infected monkeys, several mechanisms may be involved (*17*).

Despite inefficient $CD8^+$ lymphocyte depletion, in all three monkeys that received cM-T807, plasma viral RNA levels increased rapidly, coincident with the loss of $CD8^+$ lymphocytes (Fig. 5, A to C). The magnitude of this increase in plasma viral RNA levels was in-

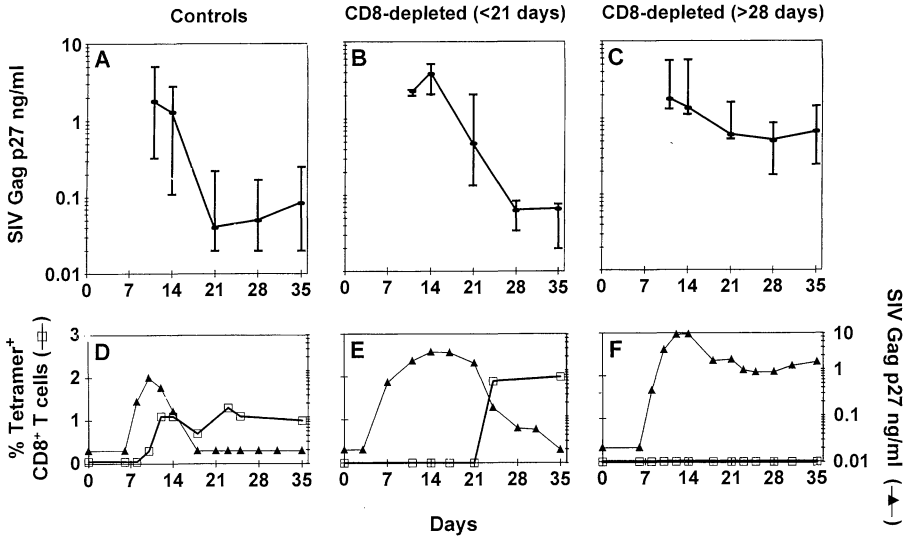

Fig. 3. Plasma SIVmac Gag p27 antigen levels and the appearance of virus-specific CTLs during primary SIVmac infection of $CD8^+$ lymphocyte–depleted rhesus monkeys. (**A** to **C**) Viral antigen was quantitated in plasma with a commercial enzyme-linked immunosorbent assay kit (SIV Core Ag EIA; Beckman Coulter, Miami, FL) (median ± range). (A) Control antibody–treated monkeys. (B) cM-T807–treated monkeys that achieved ≤21 days of $CD8^+$ lymphocyte depletion. (C) cM-T807–treated monkeys that achieved ≥28 days of $CD8^+$ lymphocyte depletion. (**D** to **F**) Emergence of virus-specific CTLs in antibody-treated monkeys after primary SIVmac infection corresponds with clearance of viral antigen. SIVmac-specific CTLs were quantitated in blood with fluorochrome-labeled MHC class I (Mamu-A*01)/SIV peptide (p11C, C-M) tetramers as previously described (*13*). Limits of detection: 0.1%. Data are expressed as percentage of $CD8\alpha\beta^+$ (2ST8-5H7; Beckman Coulter) T lymphocytes that bound tetramer. (D) Control antibody–treated monkey. (E) Monkey transiently depleted of $CD8^+$ lymphocytes for ≤21 days. (F) Monkey in which long-term $CD8^+$ lymphocyte depletion (≥28 days) was achieved.

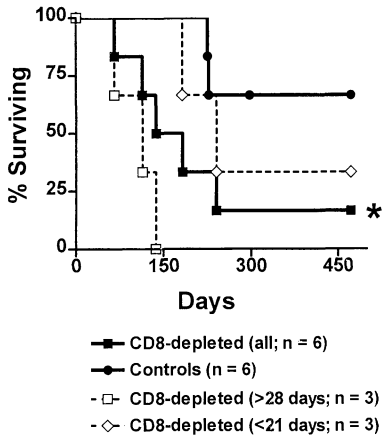

Fig. 4. Survival time of $CD8^+$ lymphocyte–depleted and control antibody–treated monkeys after primary SIVmac infection. *, Significantly different survival time from control antibody–treated monkeys (*12*).

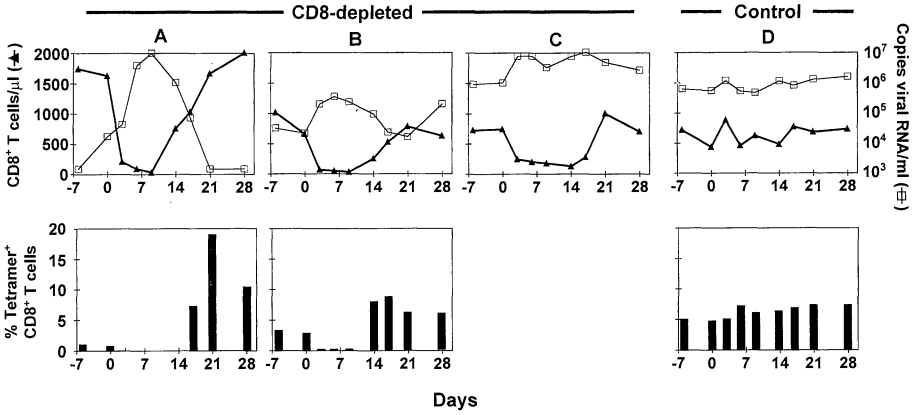

Fig. 5. Effect of $CD8^+$ lymphocyte depletion on control of virus replication in rhesus monkeys during chronic SIVmac infection. (**A** to **D**, top panels) Monkeys infected with SIVmac for >9 months were depleted of $CD8^+$ lymphocytes with cM-T807, or they received a control monoclonal antibody (*9*). $CD8^+$ lymphocyte enumeration and plasma viral RNA levels were measured as described in the legend to Fig 1. (A to C) $CD8^+$ lymphocyte–depleted monkeys. (D) Control monoclonal antibody–treated monkey. (**A**, **B**, and **D**, bottom panels) Mamu A*01/p11C, C-M tetramer-binding CTLs were assessed as described in the Fig. 3 legend in monkeys expressing the MHC class I allele *Mamu A*01*. (A and B) $CD8^+$ lymphocyte–depleted monkeys. (D) Control monoclonal antibody–treated monkey.

versely related to the plasma viral RNA level observed before $CD8^+$ lymphocyte depletion, suggesting that replication in some monkeys was being more efficiently suppressed by $CD8^+$ lymphocytes than in other monkeys. The reappearance of $CD8^+$ T cells in the cM-T807–treated monkeys coincided precisely with a decrease in plasma viral RNA to levels seen before $CD8^+$ lymphocyte depletion. Intravenous administration of protein, which has the potential to activate T cells, appeared to have no effect on viral replication because the monkey that received the control monoclonal antibody showed no change in plasma viral RNA (Fig. 5D, top panel). Although unlikely, increased SIVmac replication due to T cell activation occurring as a consequence of cM-T807–mediated destruction of $CD8^+$ lymphocytes cannot be excluded.

SIVmac Gag p11C, C-M–specific CTLs were enumerated in two monkeys treated with cM-T807 and in one monkey treated with the control antibody (Fig. 5, A, B, and D, bottom panels). Between 1 and 5% of peripheral blood $CD8^+$ T cells bound the Mamu A*01/p11C, C-M tetramer in all monkeys before antibody treatment. After $CD8^+$ lymphocyte depletion, the $CD8^+$ T cells that reappeared contained 3- and 18-fold increases in percentage of tetramer-binding cells (Fig. 5, A and B, bottom panels). A similar phenomenon was observed in neutralizing antibody titers. All three $CD8^+$ lymphocyte–depleted animals also showed a 2- to 15-fold rise in neutralizing antibody titers coincident with the increase in viral replication (*16*). The control antibody–treated monkey had a stable viral load with no change in percentage of tetramer-binding cells (Fig. 5D, bottom panel) or in neutralizing antibody titers (*16*). The increases in SIVmac-specific CTLs and neutralizing antibody titers in cM-T807–treated monkeys were most likely induced by the brief increase of viral antigen. The sudden increase in these immune responses was reminiscent of that seen during primary SIVmac infection.

These studies demonstrate that $CD8^+$ lymphocytes play an important role in controlling virus replication in both primary and chronic SIVmac infection of rhesus monkeys. During primary SIVmac infection, the absence of $CD8^+$ lymphocytes resulted in uncontrolled viremia with a subsequent inability to generate neutralizing antibody responses and a rapid progression of disease. During chronic SIVmac infection, $CD8^+$ lymphocyte depletion resulted in a transient burst of viremia. These results show conclusively the importance of cellular immunity in AIDS virus infections. Furthermore, they suggest that an effective HIV-1 vaccine should elicit strong cellular immune responses that might block a primary infection or modulate viral replication in the newly infected individuals.

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9. Rhesus monkeys in the primary and chronic SIV infection experiments were administered either the mouse-human chimeric monoclonal antibody to CD8 (cM-T807) or a control chimeric monoclonal antibody specific for respiratory syncytial virus (chimeric 1129; MedImmune, Gaithersburg, MD). Antibodies were given intravenously at 3 to 5 mg of antibody per kilogram of body weight, three times over a 4- or 7-day period. For the primary infection experiment, antibody treatments were initiated either 4 days before or 6 days after intravenous inoculation with about 20 animal infectious doses of SIVmac strain 251. Treatments with antibody CD8 resulted in $CD8^+$ lymphocyte depletion during peak SIVmac viremia. In the chronic infection experiment, monkeys were administered monoclonal antibodies >9 months after mucosal infection with SIVmac strain 251. All animals were maintained in accordance with the guidelines of the Committee on Animals for the Harvard Medical School and the *Guide for the Care and Use of Laboratory Animals* (National Research Council, National Academic Press, Washington, DC, 1996).
10. Confirmation of $CD8^+$ lymphocyte depletion from lymph nodes was obtained by four-color flow cytometric immunophenotypic analysis of disaggregated lymph node biopsies with the method described in the legend to Fig. 1. $CD8^+$ T lymphocytes made up 16 to 50% of all T lymphocytes in lymph nodes before antibody treatment and 0 to 1% of all T lymphocytes at the point of maximal $CD8^+$ lymphocyte depletion.
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12. All statistical analyses performed in the primary infection experiment compared results from control antibody–treated monkeys ($n = 6$) with results from cM-T807–treated monkeys ($n = 6$). Differences in the decrease of plasma viral RNA levels from peak levels and differences in plasma SIVmac Gag p27 antigen levels between control group and experimental group on days 21, 28, and 35 were compared by multiple measures analysis of variance. Survival times in the same experimental and control groups were compared by the Wilcoxson rank sum test. In all cases, $P < 0.05$ was considered significant. Although two distinct outcomes after cM-T807 treatment were retrospectively observed (short-term versus long-term $CD8^+$ lymphocyte depletion), statistical analyses between these groups defined by outcome were not performed because these groups were not defined prospectively.
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17. At least three different mechanisms could explain the relative inefficiency of $CD8^+$ lymphocyte depletion we observed in chronically SIVmac-infected monkeys. (i) The immune mechanisms responsible for the cM-T807–induced elimination of $CD8^+$ lymphocytes may be impaired in chronically infected monkeys. (ii) Because the total body $CD8^+$ lymphocyte pool is likely to be substantially increased in chronic SIVmac infection, its elimination in infected monkeys may require the administration of a larger amount of cM-T807 than is needed to eliminate $CD8^+$ lymphocytes in uninfected monkeys. (iii) Chronic SIVmac antigenemia may induce increased $CD8^+$ T cell proliferation, leading to rapid $CD8^+$ lymphocyte repopulation.
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