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Primary Simian Immunodeficiency Virus SIVmnd-2 Infection in Mandrills (*Mandrillus sphinx*)

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Mandrills are the only nonhuman primate (NHP) naturally infected by two types of simian immunodeficiency virus (SIV): SIVmnd-1 and SIVmnd-2. We have already reported that the high SIVmnd-1 replication during primary infection contrasts with only transient changes in $CD4^+$ and $CD8^+$ cell counts. Since early virus-host interactions predict viral control and disease progression in human immunodeficiency virus-infected patients, we investigated the dynamics of SIVmnd-2 primary infection in mandrills to examine the impact on immune effectors in blood and lymph nodes (LNs). To avoid in vitro strain selection, all mandrills in this study received plasma from SIVmnd-2-infected mandrills. SIVmnd-2 plasma viremia peaked at 10^7 to 10^8 RNA copies/ml between days 7 and 10. This peak was followed in all four monkeys by a decline in virus replication, with a set point level of 10^5 to 10^6 RNA copies/ml at day 42 postinfection (p.i.). Viral DNA load in PBMC and LNs also peaked between days 7 and 10 (10^5 to 10^6 DNA copies/10^6 cells) and stabilized at 10^3 to 10^4 DNA copies/10^6 cells during the chronic phase. Anti-SIVmnd-2 antibodies were detected starting from days 28 to 32. A transitory decline of $CD3^+$ $CD4^+$ cells in the LNs occurred in animals with high peak VLs. $CD4^+$ and $CD8^+$ T-cell activation in blood and LNs was noted between days 5 and 17 p.i., surrounding the peak of viral replication. This was most significant in the LNs. Activation markers then returned to preinfection values despite continuous and active viral replication during the chronic infection. The dynamics of SIVmnd-2 infection in mandrills showed a pattern similar to that of SIVmnd-1 infection. This might be a general feature of nonpathogenic SIV natural African NHP models.

More than 30 different simian immunodeficiency virus (SIV) types naturally infect a variety of African nonhuman primates (NHP) of African origin (3, 11). They form at least eight phylogenetic lineages (3, 11, 20) and have evolved through host-dependent evolution (1, 9, 27, 45, 57), cross-species transmissions (12, 37, 62, 65), recombinations (4, 10, 28, 35, 36, 61), and preferential host switching (17). This highly divergent group of viruses may represent a significant threat for cross-species transmission to humans, as shown by the fact that both human immunodeficiency virus type1 (HIV-1) and HIV-2 have originated from cross-species transmission from two different simian sources: chimpanzee for HIV-1 (27) and sooty-mangabey (SM) for HIV-2 (18).

SIVs were repeatedly reported to be nonpathogenic in their natural NHP hosts. Only recently have several studies reported cases of AIDS occurring in captive African NHPs following natural (40, 50) or experimental (2) infections. This apparent lack of pathogenicity may be the result of long-term coevolution of SIVs with their respective NHP hosts (1, 8). This lack of pathogenicity and its mechanisms are currently under investigation in several African NHP models, such as African green monkeys (AGMs) (13, 22, 30) and SMs (16, 59). In order to design better strategies for HIV-1 infection control, results obtained in these models are compared to data existing for SIVmac-infected rhesus macaques (Rh) and HIV-infected humans. In pathogenic SIVsm/SIVmac infections of the susceptible Rh host, the set point plasma viremia during the chronic phase of infection is an excellent predictor of the subsequent disease course (33, 66). Macaques with persistently high plasma viremia succumb more rapidly to disease than those with lower viral loads (VLs), suggesting that viral replication is a major determinant of disease progression. A similar association has been observed in HIV-1-infected humans (42, 43). However, this correlation is less consistent in African NHPs naturally infected with SIVs. In SMs, high levels of viral RNA in plasma and extensive expression of SIVsm in lymphoid tissues are not associated with progression to AIDS (55, 59). AGMs naturally infected with SIVagm display a considerably wider range of VLs than those observed in SMs (13). The DNA VLs in lymph node (LN) mononuclear cells from AGM are also 100-fold lower than the viral DNA loads observed in naturally infected SMs (7). Altogether, these data suggest that VL in the SIVagm-infected AGM is generally lower than that observed in the SIVsm-infected SM (30). Thus, differences in viral replication may occur between different African NHP natural hosts of SIV without significant pathogenic consequences.

Some correlates of reduced pathogenicity of natural SIV infection in African hosts have been described. These include intrinsic target cell resistance or CD8 suppressor factors (24), lack of cytopathology of SIV for $CD4^+$ T cells (48), selective infection of macrophages rather than lymphocytes (47), and immune tolerance and lack of immune activation as a consequence of SIV infection (16, 59). In recent studies, an alter-

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native view emerged suggesting that generalized immune activation is a primary determinant of disease progression following CD4 tropic lentivirus infection of humans and non-natural NHPs hosts (such as Rh) (25). This is based on the observation that nonpathogenic SIV infections of natural host species, such as SMs, are characterized by limited bystander immunopathology despite chronic high-level SIVsm viremia (59). This appears to be mediated by reduced levels of immune activation and T-cell turnover in the SM (16, 59).

SIVmnd-infected mandrills may represent an ideal model for the study of viral and host factors related to SIV pathogenesis in natural African hosts. The mandrill is the only African NHP that has been reported to be naturally infected with two different SIV types, SIVmnd-1 and SIVmnd-2 (61). These two viral types are as divergent as HIV-1 and HIV-2 are in humans (61). Also, like HIV-1 and HIV-2, which have different genomic structures containing either a *vpu* (HIV-1) or a *vpx* (HIV-2), the two types of SIVmnd differ in genome organization. SIVmnd-1 has a Cercopithecini-like genomic structure, with five accessory genes (63), whereas SIVmnd-2 has a Papionini-like structure, carrying an additional *vpx* gene (35, 61). SIVmnd-1 is considered to have possibly emerged following an ancient cross-species transmission from the sympatric sun-tailed monkey (*Cercopithecus lhoesti solatus*) (9). SIVmnd-2, on the other hand, is related to SIVdrl which naturally infect drills (*Mandrillus leucophaeus*). Therefore, SIVmnd-2 is considered to be a result of host-dependent evolution (35, 61). Furthermore, in contrast to SIVmnd-1, SIVmnd-2 is a recombinant virus, sharing the same *env* gene with SIVmnd-1 (61).

One of the most remarkable differences between HIV-1 and HIV-2 infection is the difference in their pathogenic potential. HIV-1 induces higher VLs during the chronic phase of infection and evolves more rapidly to AIDS (21, 43). As a result, HIV-1 shows a significantly higher epidemic potential, making it responsible for the great majority of AIDS cases worldwide (21). Since SIVmnd-1 and SIVmnd-2 have different origins, one may expect that the two types of SIVmnd may have different natural histories in their hosts. However, SIVmnd infection in mandrills is estimated to be significantly more ancient than HIV infection in humans. We have previously shown that SIVmnd-1, although cross-species transmitted, seems to be currently adapted to its mandrill host (46). This is based on the dynamic of primary SIVmnd-1 infection, where only transient changes of $CD4^+$ and $CD8^+$ cells were observed despite high viremia (46). Whether the virological and immunological consequences of SIVmnd-1 and SIVmnd-2 are similar or not remains unknown.

We present data here on the primary infection of mandrills with SIVmnd-2. The VLs of SIVmnd-2 were measured in two compartments. The dynamics of phenotypic markers were analyzed in order to detect whether changes in the activation status of cells in peripheral blood and LNs are associated with SIVmnd-2 infection. Finally, the dynamics of SIVmnd-2 infection were compared to those of SIVmnd-1 and to those reported in other SIV/NHP models.

MATERIALS AND METHODS

Animals. Mandrills used in the study were housed in the semifree enclosure at the Centre International de Recherches Medicales de Franceville, Gabon. Four monkeys (10I, 12D4, 12A2, and 12A2A) were included in the present study. Prior to SIVmnd-2 infection, these mandrills were tested for SIVmnd1/SIVmnd-2 and simian T-lymphotropic virus type 1 and shown to be negative for these two viruses.

To avoid selection of SIVmnd-2 variants in vitro, the same strategy used for SIVmnd-1 infection (46) was followed. All inocula used in the present study were derived from a naturally infected wild-born, free-living host of SIVmnd-2 (PG13), whose infection was asymptomatic. Ten milliliters of total blood was collected, and plasma was separated by centrifugation, divided into aliquots, and frozen at −80°C. The viral RNA load in plasma was then quantified by real-time PCR. One uninfected mandrill was used to prepare a plasma stock of SIVmnd-2 as previously described (46). The peak VL in mandrill 5F was 2.73×10^5 copies/ml. Two milliliters of plasma from 5F was used to infect another mandrill (10I). At day 10 postinfection (p.i.), the peak VL in 10I was 1.3×10^8 copies SIVmnd-2/ml. Twenty-five milliliters of blood of 10I was collected. Mandrills 12D4, 12A2, and 12A2A were inoculated intravenously with plasma corresponding to 1.3×10^8 copies of SIVmnd-2/ml of plasma. Two controls were inoculated with the SIV-negative plasma obtained at day 0 from mandrill 10I.

Animals were anesthetized with ketamine HCl (10 mg/kg, injected intramuscularly). Blood was sampled at days −30, −15, 0, 7, 10, 14, 21, 28, 66, 90, 121, and 240 and 2 years p.i. Transcutaneous biopsies of LNs (axillary and/or inguinal) were performed at days 0, 10, 28, and 240. Mononuclear cells were isolated from blood and LNs as described previously (46). The mock-infected animals were sampled at the same time points as the infected mandrills.

SIVmnd-2 viral quantitation. (i) Plasma SIVmnd-2 RNA quantification. RNA was isolated from plasma of SIVmnd-2-infected mandrills by using the commercially available QiaAmp viral RNA mini-kit (QIAGEN, Courtaboeuf, France). Viral RNA was then resuspended in nuclease-free water and quantified by using reverse transcription-PCR. Viral RNA was measured in all samples by real-time technology with the LightCycler System (Roche Molecular, Indianapolis, IN) using the QIAGEN-Quantitec SYBRgreen RT-PCR kit (QIAGEN). Prior to this study, the sensitivity of the light cycler technology was compared to that of the TaqMan technology by testing samples in duplicate. The discrepancies in results between the two technologies were <0.5 $\log_{10}$. SIVmnd-2 plasma RNA was quantified in comparison to a 10-fold-diluted RNA external standard (MO4-2-RNA, Mobidab; Molekularbiologie GmbH & Co., Germany) construct upon a 233-pb *pol* region of SIVmnd-2. Forward primer M26iF (5′-GCAAAGGAGAT AGTAGCTCAGTGTC-3′) and reverse primer M26iR (5′-GCCATTATCTGT ATGTAAATGTTTCACT-3′) were utilized in a real-time PCR under the following conditions: reverse transcription at 50°C for 20 min, followed by PCR in cycling conditions of 95°C for 15 min, followed by 50 cycles at 95°C for 15 s, 60°C for 15 s, and 72°C for 22 s, with a melting step at 70°C for 10 min, followed by a cooling step at 30° for 30 s. The detection limit of the SIVmnd-2 quantification assays was 5×10^2 RNA copies/0.5 ml of plasma.

(ii) Proviral DNA quantification. Genomic DNA was extracted from mandrill PBMC and LN cells by using a DNA extraction kit (QIAGEN). Proviral *pol* DNA fragments were amplified by nested PCR quantification using PCR technology in the LightCycler System (Roche Molecular, Indianapolis, Ind.) with the QIAGEN-Quantitec SYBRgreen PCR kit (QIAGEN) and the same primers as in plasma VL quantification. We have included a DNA external standard (MO4-2-DNA, Mobidab) constructed upon the same *pol* region as described for the RNA external standard. The same M26iF and M26iR primers were used for proviral DNA quantification. The PCR conditions were as follows: 95°C for 15 min, followed by 50 cycles of denaturation at 95°C for 15 s, annealing at 60°C for 15 s, and extension at 72°C for 22 s, with a melting step at 70°C for 10 min, followed by a cooling step at 7°C for 30 s. The linear range of our assay was 5 to 500,000 copies/10^5 peripheral blood mononuclear cells (PBMC) and LN cells.

To prevent potential real-time PCR contaminations, RNA and DNA extractions were done in separate hoods. Also, preps for different real-time PCR assays were done in different rooms. DNA and RNA quantification were performed in different runs, and the equipment was decontaminated prior to plasma RNA quantification with ELIMINase (Decon Laboratories, Bryn Mawr, PA), which eliminates RNase, DNase, and DNA contamination.

Dynamics of anti-SIVmnd-2 antibodies in mandrills. All of the simian samples were tested by a peptide-based enzyme-linked immunoassay that detects antibodies to the SIVmnd-specific peptides mapping the V3 regions of the *env* glycoproteins. Since the two types of mandrills share the same *env* sequences as a consequence of recombination events (61), this test has a similar sensitivity for both SIVmnd types (60, 61). The test was performed as previously described (60).

Flow cytometry for cell surface markers. Hematological studies and cell separation were performed as previously described (46, 49). PBMC and LN mononuclear cells were analyzed by double- or triple-color fluorescent antibody staining. The following fluorescent antibody combinations were used: CD3 (clone

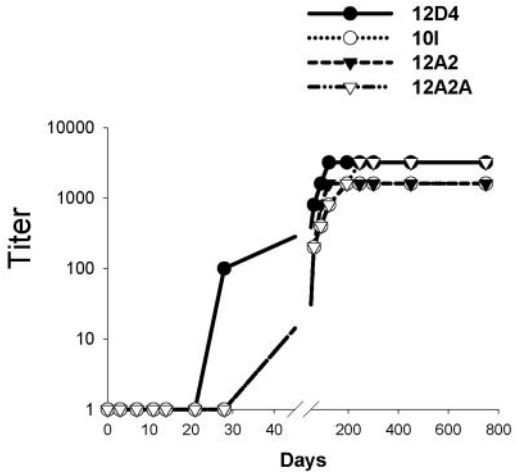

FIG. 1. Humoral immune response of mandrills infected with SIVmnd-2. Anti-V3 antibody titers were measured by enzyme-linked immunoassay plates treated with specific SIVmnd peptide corresponding to the region V3 loop of SIVmnd-1 and -2.

SP34)-fluorescein isothiocyanate (FITC)/CD4 (clone L200)-peridinin chlorophyll A protein (PerCP)/CD28 (clone Leu28)-phycoerythrin (PE), CD3-FITC/CD8 (clone Leu2a)–PerCP/CD28-PE, HLA-DR (clone L243)-FITC/CD4-PerCP/CD3-PE, and HLA-DR (clone L243)-FITC/CD8-PerCP/CD3-PE (Becton Dickinson/BD Biosciences Pharmingen, San Diego, CA). All of these antibodies have been tested for their cross-reactivity with mandrills during our previous studies (46, 49). The percentage and absolute number of specific cell subpopulations were determined as described previously (46, 49).

Statistical methods. The analyses of VL and immune cell subsets include analysis of results using F-test comparison curves (Sigma Plot) with healthy control mandrills. Correlations between different sets of data were determined by using the standard Pearson correlation coefficients.

RESULTS

We have studied the dynamics of SIVmnd-2 primary infection and compared it with that of SIVmnd-1 to investigate any differences in the pattern of viral replication between the two viruses infecting a single host species, as seen with HIV-1 and HIV-2 in humans. Given that in a previous study we observed AIDS after a long period of infection (50), the animals were followed up to 2 years p.i., and the level of variation of viral replication was measured over this period of time.

Clinical and serological data. SIVmnd-2 infection was monitored until day 60 postinfection for the primary infection. All four mandrills became SIVmnd-2 infected and seroconverted by days 21 to 28 p.i. (Fig. 1). None of the animals developed fever after infection with SIVmnd-2. No clinical signs of primary infection, weight loss, opportunistic infection, or increase in size of LNs were observed during the acute phase of infection or later on. Seroconversion patterns were observed on HIV-2 Western blots starting from day 28 p.i. on (data not shown). The dynamics of serological markers of SIVmnd-2 infection is very similar to the dynamics of SIVmac infection in macaques and to SIVmnd-1 infection in mandrills (46).

Plasma VLs during SIVmnd-2 infection are similar to those observed for SIVmnd-1 and for other African hosts of SIVs. A major aim of the present study was to compare the dynamics of SIVmnd-2 viral replication in mandrills to those observed during SIVmnd-1 infection, as well as to other African NHP hosts

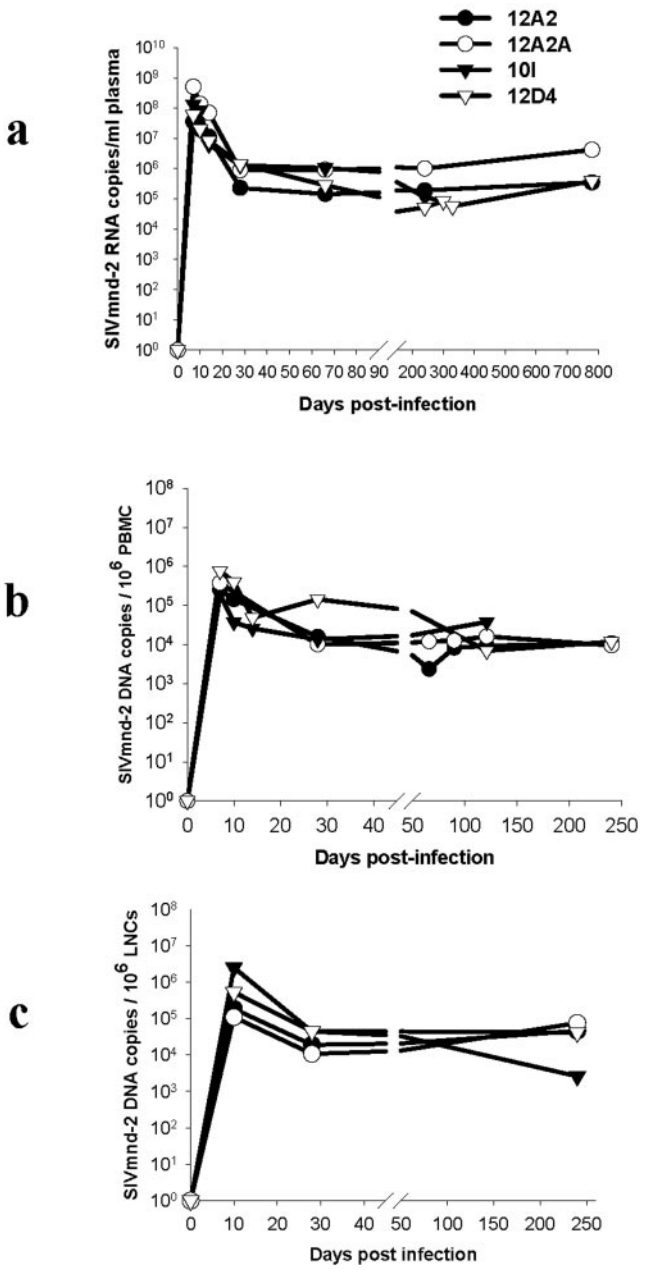

FIG. 2. Analysis of viral replication during primary SIVmnd-2 infection of mandrills. SIVmnd-2 plasma viremia was quantified in four mandrills between days 0 and 480 p.i. Quantitation of SIVmnd-2 RNA in plasma (a), PBMC (b), and LNs (c) was performed by real-time PCR as described in Materials and Methods.

of SIV and to pathogenic SIVmac in macaques. SIVmnd-2 viral replication was evaluated here by measuring the dynamics of both viral RNA VL in plasma, as well as by quantifying the proviral DNA in both PBMC and LNs. All of these quantifications were done by real-time PCR using specific SIVmnd-2 primers mapping a highly conserved region in the *pol* integrase.

An early peak of SIVmnd-2 RNA in plasma was observed between days 7 and 10 p.i., with VLs ranging from 2.04×10^7 to 5.11×10^8 copies/ml (Fig. 2a). These levels, although slightly higher than those observed during primary SIVmnd-1

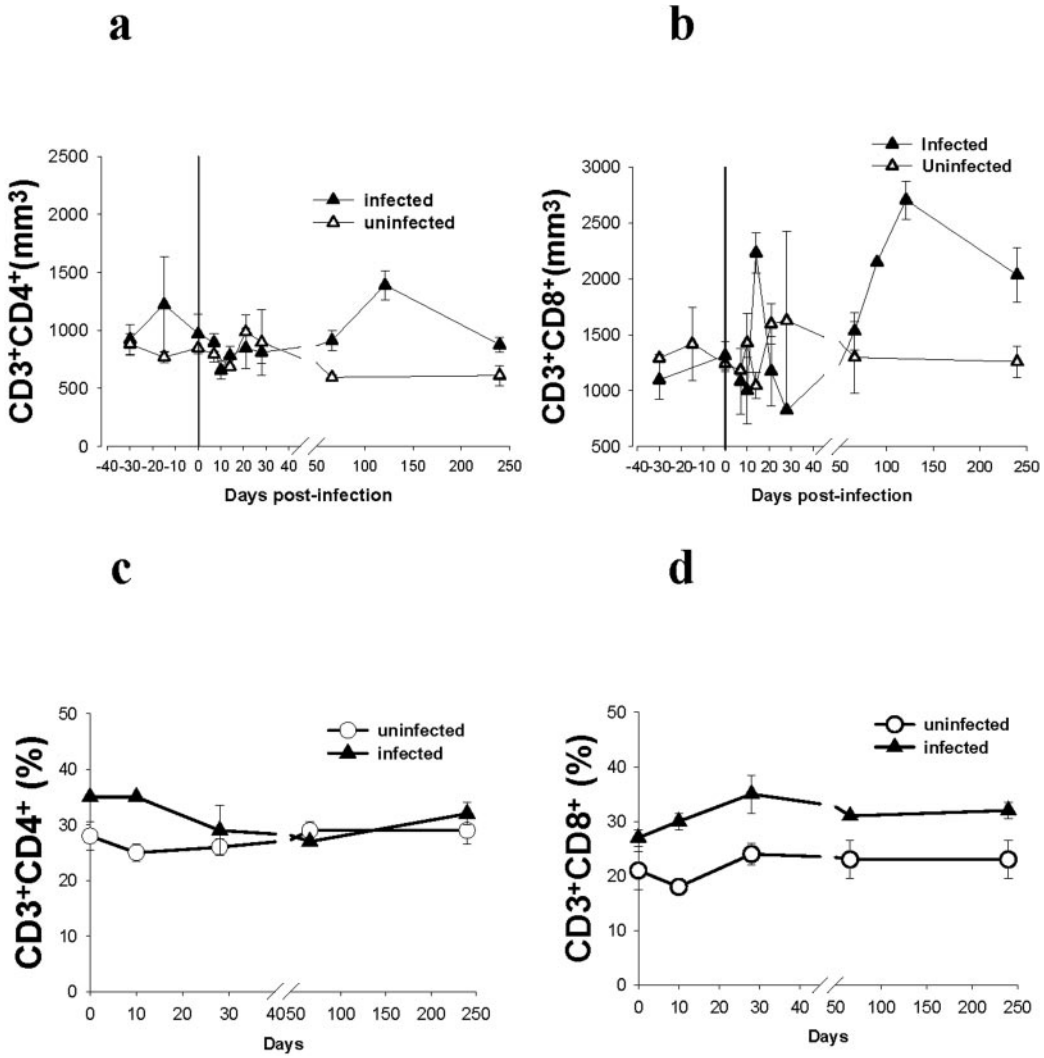

FIG. 3. Kinetics of $CD3^+$ $CD4^+$ and $CD3^+$ $CD8^+$ T lymphocytes (%) in peripheral blood (a and b, respectively) and lymph nodes (c and d, respectively) in SIVmnd-2-infected and uninfected mandrills. The cells of two mock-infected mandrills were analyzed twice before inoculation with negative plasma. For infected SIVmnd-2 mandrills, measures of $CD4^+$ and $CD8^+$ lymphocytes subsets preinfection at days −30 and −15 were not available.

infection (46), were in the same range as those reported for other SIV pathogenic or nonpathogenic infections (22, 33, 34, 46, 48). SIVmnd-2 plasma VL then declined rapidly and between days 21 and 28 p.i. reached set point levels 10- to 100-fold lower than the peak values. No significant variations in plasma VLs were observed during the chronic phase of SIVmnd-2 infection (Fig. 2a). Thus, plasma VLs remained ca. 10^5 to 10^6 copies/ml in all four animals between days 60 to 720 p.i., with only slight variations ($4.88 \times 10^5 \pm 5.08 \times 10^4$ copies/ml to $5.03 \times 10^5 \pm 4.51 \times 10^4$ copies/ml) (Fig. 2a). These values are comparable to those previously observed in SIVmnd-1 experimental infection (46). The dynamics of infection were confirmed by the dynamics of P27 antigenemia (data not shown) and also by in vitro virus isolation. We have isolated the SIVmnd-2 strain at the peak of VL (day 10 p.i.) and after the set point (day 60 p.i.). SIVmnd-2 was more consistently rapidly isolated from plasma collected at day 10 p.i. than at day 60 p.i. (data not shown). Since VLs observed during the chronic phase of SIVmnd-2 infection were in the same range as those observed in naturally SIVmnd-2-infected mandrills (10^5 copies/ml), our study has shown that experimental SIVmnd-2 infections reproduce the features of natural infection.

In order to investigate the sources of plasma VL, we also quantified SIVmnd-2 proviral burden in both PBMC and in LN mononuclear cells. This analysis was done because it was previously reported that lymphoid organs are a major source of virus in HIV-infected patients and SIVmac-infected macaques (5, 23, 26). The results are shown in Fig. 2b and c. The kinetics of SIVmnd-2 proviral DNA loads in PBMC correlated with the profiles of plasma RNA VLs. Proviral DNA peaked between days 7 to 10 p.i. (at 10^5 to 10^6 copies/10^6 PBMC). Then, the DNA proviral loads declined rapidly, albeit less significantly than plasma VLs (1 log), and reached values characteristic for the chronic phase (10^4 to 10^5 copies/10^6 PBMC) by days 21 to 28 p.i. (Fig. 2b). These values were in the same range as those measured in naturally SIVmnd-2-infected mandrills (data not

shown) and higher than those previously reported for SIVagm. sab-infected AGMs (22). Proviral DNA loads in the LN peaked at days 7 at 5×10^6 copies/10^6 LN cells. Set-point values were reached more rapidly in the LN compared to PBMC. Thus, in all four SIVmnd-2-infected mandrills, set point values of DNA VL were reached at day 28 p.i. Set-point DNA loads ranged between 2.8×10^4 to 10^5 copies/10^6 LN cells and were relatively stable during the follow-up. No significant difference between PBMC and LN cells proviral loads were observed in SIVmnd-2-infected mandrills.

Transient changes of $CD4^+$ and $CD8^+$ T lymphocytes in SIV-infected mandrills. To monitor the impact of SIVmnd-2 infection on $CD4^+$ and $CD8^+$ T lymphocytes, changes in peripheral blood and LN lymphocyte subsets were monitored by flow cytometry up to twice weekly for the first 2 weeks p.i., weekly during the first month p.i., and then monthly thereafter. Within the first 2 weeks of SIVmnd-2 infection, $CD4^+$ T cells showed transient change, with a slight decline in both compartments (Fig. 3a and c). This depletion was more important in LNs, where it reached statistically significant magnitude ($P < 0.0001$). Concomitantly, an increase in number and percentage of $CD8^+$ T cells was observed in SIVmnd-2-infected mandrills. This increase in numbers and percentage of $CD8^+$ T cells correlated with the decline of post-peak viremia in all SIVmnd-2-infected mandrills (Fig. 3b). The increase of $CD8^+$ T cells was more pronounced in LNs (Fig. 3d). The analysis of $CD20^+$ cell dynamics in the LNs showed no significant increase, suggesting that the $CD4^+$ T-cell depletion is not relative to the increase of $CD20^+$ cells, as a consequence of germinal center hyperplasia (data not shown).

This dynamics pattern was associated with an increase in activation status of both $CD4^+$ and $CD8^+$ T cells, which occurred within a few days p.i., as demonstrated by the dynamics of DR^+ $CD4^+$ and DR^+ $CD8^+$ (Fig. 4). No significant change was observed in peripheral blood for both subpopulations. Nevertheless, DR^+ $CD8^+$ cells peaked at day 28 postinfection in LNs (11.86% ± 2.95%) and then returned to preinoculation values by day 60 postinfection (5.55% ± 0.71%) (Fig. 4). Activated $CD8^+$ T cells were more abundant than activated $CD4^+$ T cells. In the LNs, this higher activation pattern was more prominent, being also reflected by the significant dynamics of DR^+ $CD8^+$ ($P < 0.0001$), a finding consistent with previous reports in SIV-infected Rh (38).

Dynamics of $CD28^+$ $CD8^+$ and $CD28^+$ $CD4^+$ T cells in the acute-phase SIVmnd-2 infection. The expression of CD28, a differentiation marker, on lymphocyte T cells in blood and LNs was also measured in both SIVmnd-2-infected and SIV-uninfected mandrills (Fig. 5). No significant variations in the percentage of $CD4^+$ $CD28^+$ T cells were observed in blood despite the difference in the level of this subpopulation between the mock-infected mandrills and SIVmnd-2 positive mandrills ($P = 0.946$) around the peak VL (Fig. 5a). No changes of $CD4^+$ $CD28^+$ T cells in LNs were observed in any of the mandrills in both groups. Conversely, the study of $CD8^+$ $CD28^+$ T-cell dynamics revealed transient changes in both compartments around the peak of viremia: the infected mandrills show a significant increase in the percentage of these cells in LNs during the acute phase ($P < 0.0001$) compared to uninfected mandrills. These differences may have a pathogenic significance, as $CD8^+$ T cells play an important control role in

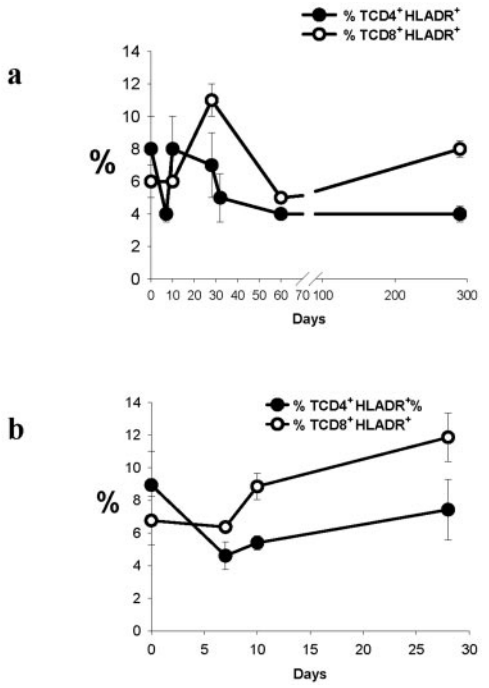

FIG. 4. Kinetic expression of percent HLA-DR upon $CD4^+$ and $CD8^+$ T lymphocytes in peripheral blood (a) and in the lymph nodes (b) in SIVmnd-2-infected mandrills.

SIVmac infection. During the chronic phase, $CD8^+$ $CD28^+$ T cells levels returned to the values displayed by the uninfected mandrills. Then, starting from day 90 p.i. on, they showed constantly increasing levels, which paralleled the $CD3^+$ $CD8^+$ T-cell levels (Fig. 5d). However, the proportion (%) of $CD8^+$ $CD28^+$ T cells did not increase during the chronic phase of SIVmnd-2 infection (data not shown).

DISCUSSION

In this study we investigated the viral and immune dynamics during experimental SIVmnd-2 infection. We have shown that a very active replication of SIVmnd-2 is associated with only limited effects on the immune system and virtually no activation.

Mandrills, the only NHP naturally infected with two different SIVs, offer a unique opportunity for comparative studies of lentiviral infections in a natural NHP host. Our study focused on the earliest events of SIVmnd-2 infection. These very early events of SIV infection are strictly virus dependent (48), and the virus-host interactions during this stage of infection appear critical for disease progression and for rapid evaluation of pathogenic differences (39, 41). We have previously reported on the SIVmnd-1 primary infection in mandrills and have shown that active replication of SIVmnd-1 had virtually no impact on peripheral $CD4^+$ T cells during the primary infection (46). Here we report the same pattern of lentiviral infection during SIVmnd-2 experimental infection. The replication pattern described for SIVmnd-2 is not surprising since there is accumulating data on the kinetics of VL during experimental infection in SIV-infected African monkey. These data reveal

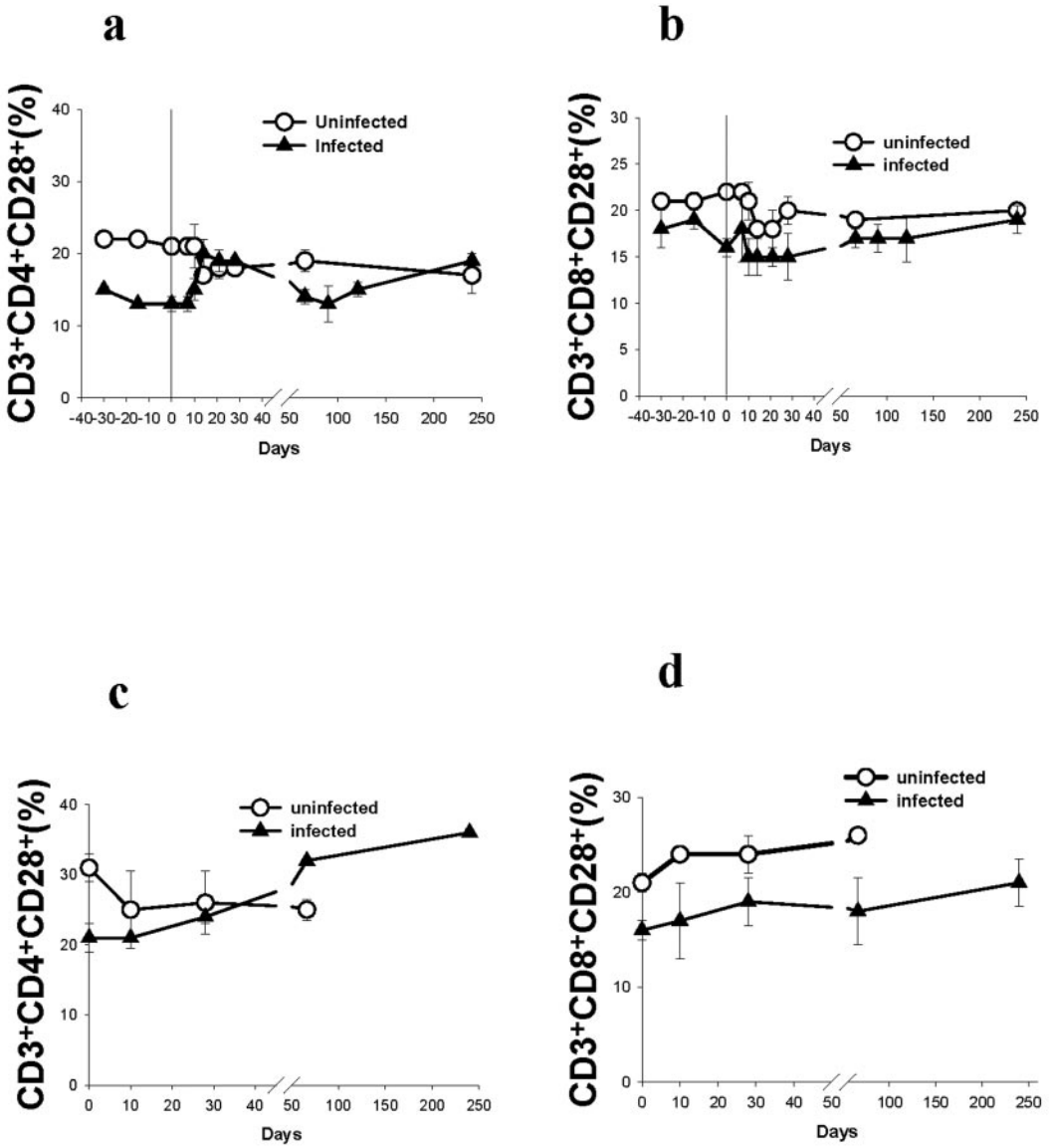

FIG. 5. Longitudinal phenotypic analysis of expression of CD28 (percentages of costimulatory activation) on $CD4^+$ and $CD8^+$ T lymphocytes in peripheral blood (a and b, respectively) and in the lymph nodes (c and d, respectively) of SIVmnd-2-infected and uninfected mandrills. The kinetic expression of CD28 upon $CD4^+$ or $CD8^+$ T cells was obtained by using the ratios $CD4^+CD28/CD3^+CD4^+$ or $CD8^+CD28/CD3^+CD8^+$.

an active viral replication resulting in very high VLs during both the primary infection and the chronic phase (6, 13, 22, 30, 46, 49, 58). Our study shows that primary SIVmnd-2 infection in mandrills is characterized by high viremia (10^7 to 10^8 RNA copies/ml) during the early phase (days 7 to 10 p.i.), which is followed by a viral contraction to reach the set point value of 10^5 to 10^6 RNA copies/ml during the chronic phase. The set point is reached between days 30 to 42 p.i. This pattern of plasma VL dynamics observed in SIVmnd-2-infected mandrills is comparable to that described in other experimental or natural SIV infections in African NHP hosts. SIV levels at the set point are remarkably conserved between different SIV strains and types (6, 13, 22, 30, 46, 49, 58). Also, one should note that these viral kinetics are not significantly different from those observed in long-term progressor macaques (33). In HIV-infected patients a strong association between VL in plasma and the risk of progression to AIDS was described previously (42, 43). It is striking that such VLs are commonly found in mandrills and other African NHPs without detectable pathogenic consequences. The plasma RNA VL pattern was paralleled by the dynamics of the proviral DNA load in PBMC and LNs in mandrills, which also peaked between days 7 and 10 p.i. and stabilized at significant levels during the chronic phase. These levels are not significantly different from those reported in secondary lymphoid organs in the ileum or jejunum of acute and chronically infected Rh, SMs, and AGMs (16, 32, 59). However, proviral DNA levels in SIVmnd-2-infected mandrills are slightly higher than those observed in SIVagm infected-AGMs (13, 22, 32) or HIV-infected humans (51–53).

Despite its chronically active replication, SIVmnd-2 infection has not caused any apparent pathology in mandrills during the primary infection or during the first 2 years of follow-up. This clinical pattern is similar to those reported for long-term nonprogressor (LTNP) SIV-infected macaques and HIV-infected humans. However, the hallmark of LTNP in SIV-infected macaques and HIV-infected humans is marked suppression of viral replication to almost undetectable levels (14, 54). In this respect, SIV-infected African NHPs do not fit this profile. Our studies show that ongoing viral replication in many naturally or experimentally SIVmnd-1- or SIVmnd-2-infected mandrills (46, 49) is considerably higher than in HIV-infected human LTNPs. Thus, our data add to previous reports from other African hosts which show that high levels of SIV VL do not necessarily lead to disease and that specific host factors or particular components of the host response play a critical role in determining whether disease arises after infection.

One of the major differences between SIVsm and SIVagm infections consists of higher viral burdens in SIVsm-infected SMs compared to SIVagm-infected AGMs (7, 55). There are differences in viral genomic organization between the two viruses: SIVagm contains only five accessory genes, whereas SIVsm harbors a *vpx* gene (3). SIVmnd-1 and SIVmnd-2 also have different genomic organizations, with SIVmnd-1 having an SIVagm-like structure, whereas SIVmnd-2 has an SIVsm-like structure (61). The comparison of the replication patterns of SIVmnd-1 and SIVmnd-2 infection did not reveal any significant difference in VL dynamics between the two viruses. This suggests that the different viral burdens observed when comparing different types of SIV in their natural hosts are host related rather than dependent on viral structure.

HIV infection in humans is characterized by a complex set of changes in lymphocyte subpopulations, including progressive diminution of $CD4^+$ T-cell number or percentages, progressive depletion of naive T cells, increased levels of activated $CD8^+$ cells, and loss of $CD8^+$ T cells expressing the costimulatory molecule CD28 (19, 56, 64). Immunophenotypic analyses of SIVmnd-2-infected and uninfected mandrills revealed only relatively minor, statistically insignificant changes in $CD4^+$ T-cell percentages on both compartments. This is similar to SIVmnd-1-infected mandrills (46), which show a rapid and transient activation of $CD4^+$ T cells in peripheral blood but not in LNs, as described in a previous study (29). No significant decline of $CD4^+$ T cells in peripheral blood occurred during the follow-up of the infected monkeys compared to uninfected mandrills or to the chronic phase of SIV infection in different SIV-infected African NHP species (15, 44, 46, 59).

Our study confirmed previous reports showing only transient immune activation during acute SIV infection in African NHPs (58). This contrasts with the chronically high levels of generalized immune activation that accompany pathogenic HIV and SIV infections (31). Our data support the idea that the level of immune activation may contribute to disease progression and that lower immune activation is the rule in African NHPs.

In conclusion, the present study provides evidence that SIVmnd-2 replicates actively and establishes a high VL in its natural host. This pattern of viral replication and host immune response is very similar to that previously shown in SIVmnd-1 infection (46). Since infected mandrills do not progress to disease, our data suggest that host immune responses are a major determinant of SIV pathogenic potential. Understanding the factors responsible for the maintenance of the steady state of infection in African primates should provide help for elaboration of valuable immunostrategies against AIDS. In this respect, the natural infection of mandrills, with two types of SIV, offers ample opportunities for comprehensive pathogenesis studies. Coinfection or superinfection studies using these two viruses may provide important clues regarding the correlates of pathogenicity and immune protection of lentiviral infection in NHPs.

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