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Mother-to-Infant Transmission of Simian Immunodeficiency Virus Is Rare in Sooty Mangabeys and Is Associated with Low Viremia

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Mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) occurs in utero, intrapartum, and through breastfeeding, with a cumulative rate of transmission of 35 to 40%. As a result, ∼400,000 children become infected each year. Little is known about mother-to-infant transmission (MTIT) during natural simian immunodeficiency virus (SIV) infection of sooty mangabeys (SMs) that typically is nonpathogenic despite high viral loads. In this study, we retrospectively investigated the rates of MTIT in a large colony of naturally SIV-infected SMs using serological (anti-SIV antibody by enzyme-linked immunosorbent assay [ELISA] and Western blot analysis) and virological (SIVsmm real-time reverse transcription-PCR) methods. We examined 161 SM infants born to SIV-infected mothers and found that 150 (93.2%) were infected by non-MTIT (n = 120) or remained uninfected (n = 30). The remaining 11 SM infants (6.8%) were defined as acquiring SIV by presumptive MTIT based on (i) the presence of anti-SIV antibodies without seroreversion and (ii) a viral load of >500 copies/ml of serum in the first year of life. SM infants infected with SIV by presumptive MTIT did not show any increased morbidity or mortality, indicating that the infection is nonpathogenic even when acquired early in life. Interestingly, viral loads of SIV-infected SM infants with presumptive MTIT were 2-log lower than those of SIV-infected adult SMs living in the same colony (i.e., ∼1,000 and 100,000 copies/ml, respectively). These results indicate that MTIT is substantially less frequent in naturally SIV-infected SMs than in HIV-1-infected humans and results in nonpathogenic infection associated with low SIV viremia. Evolutionary pressure to reduce MTIT may have contributed to the restriction of SIV pathogenesis in natural hosts.

The rate of mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) in humans is estimated to be 35 to 40% without intervention (www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2009/default.asp). Fortunately, in developed countries, strategies for the prevention of MTCT, including HIV testing of pregnant women, antiretroviral therapy for pregnant women and their infants, caesarian section, and formula feeding, are readily available (6). These interventions have the potential to reduce MTCT of HIV to less than 2%. In contrast, in developing countries with fewer resources, the rates of MTCT of HIV still are unacceptably high.

Sooty mangabeys (Cercocebus atys) are nonhuman primates that are natural hosts for simian immunodeficiency virus (SIV). Natural SIV hosts, including sooty mangabeys (SMs), African green monkeys (AGMs), mandrills, and numerous others in which primate lentiviral infections have been endemic for many thousands of years (32), display distinctive features of SIV infection that distinguish them from nonnatural or recent infections in natural host species is nonpathogenic, with a lack of progression to AIDS.

During the past decade, much effort has been dedicated to understanding the mechanisms by which natural SIV hosts avoid progression to AIDS and maintain healthy CD4+ T-cell counts in the face of high-level virus replication that is not controlled by the host cellular or humoral immunity (reviewed in references 5 and 20). These studies have shown that the acute SIV infection of natural hosts is characterized by the depletion of mucosal CD4+ T cells and robust innate and adaptive immune responses to the virus (similar to those of SIVmac-infected RMs and HIV-infected humans), whereas the chronic infection of natural hosts is distinguished from pathogenic infections of RMs and humans by the resolution of immune activation, the preservation of mucosal immune function, and preferential viral tropism for effector memory CD4+ T cells (4, 8, 9, 12; G. Silvestri, unpublished data).

SIV infection rates in SMs and other natural hosts increase after the onset of sexual maturity (4 to 6 years of age) (11). Infection is thought to occur via the exchange of bodily fluids that occur during sexual activity, as well as fighting, biting, and the licking of wounds. Earlier transmission may occur via aggressive grooming, mock sexual activity (that can begin before 1 year of age), or the premastication of food. Little is known about mother-to-infant transmission (MTIT) in natural hosts for SIV. Observations of AGMs and grivets in the wild suggest that infants of these species have low rates of SIV infection (18, 24). Similarly, MTIT of SIV was not observed in a colony of SIV-infected mandrills in Gabon (C. Apetrei and I. Pandrea,
unpublished data). In SMs, phylogenetic and microsatellite analysis of SIV sequences isolated from fecal samples of wild animals in the Tai Forest in Cote d'Ivoire identified only two likely mother-daughter pairs (with nearly identical virus) in the context of an overall adult prevalence of SIV infection of 59% (26). In stark contrast, MTIT of SIV appears to be a frequent event in experimentally SIV-infected rhesus macaques (1, 2, 10, 15), thus suggesting a direct relationship between pathogenicity and MTIT in SIV-infected nonhuman primates.

In this work, we performed a retrospective analysis of all births to naturally SIV-infected SMs of the Yerkes colony from 1969 to 1999 to determine the rate of MTIT in this natural host species. We found that MTIT of SIV in SMs is relatively rare and is associated with a 2-log reduction in viremia compared to SMs that became SIV infected as adults. The clinical course of SIV infection was not altered by MTIT.

**MATERIALS AND METHODS**

**Animals and serology.** Two hundred forty-nine SMs born to naturally SIV-infected dams from the colony housed at the Yerkes National Primate Research Center of Emory University (YNPRC) were studied. These animals were selected from the 593 SMs born during the period 1969 to 1999 because one or more SIV tests had been performed on them. The breeding of SIV-infected SMs was halted in late 1999 due to budgetary constraints, thus no infants were available for study after this time. The SIV serological status of animals born to SIV-infected SM dams was assessed by HIV-2 ELISA and Western blotting, as described previously (29). All animals were maintained in accordance with National Institutes of Health guidelines.

**SIV<sub>smm</sub> viral load.** For SIV<sub>smm</sub> RNA quantitation, RNA was extracted from plasma or serum and reverse transcribed as described previously (28). Real-time reverse transcription-PCR (RT-PCR) was performed by the amplification of 20 μl of cDNA in a 50-μl reaction mixture containing 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 4 mM MgCl<sub>2</sub>, 0.2 μM forward primer, 0.3 μM reverse primer, 0.1 μM probe, and 5 U of AmpliTaq Gold DNA polymerase (reagents were from Applied Biosystems). Primer and probe sequences were targeted to the 5′-untranslated region of the SIV<sub>smm</sub> genome; the forward primer sequence was 5′-GGCAGGAAATCCCTAGCAG-3′; the reverse primer sequence was 5′-GGCCCTTACTGCTTCATACT-3′; and the probe sequence was 5′-6-carboxytetramethylrhodamine (FAM)-AGTCCTTGTCGCGCACTA-3′ and the probe sequence was 5′-GCCCTTGGGAAGAAAATCCCTAGCAG-3′.

**Cytokine production by intracellular staining.** Intracellular cytokine staining was performed using FlowJo software (Tree Star). Analysis of the acquired data was performed as described previously (8, 31) with whole-blood samples from animals in the YNPRC. Cytokine production was assessed using FlowJo software (Tree Star).

**Cytokine production by intracellular staining.** Intracellular cytokine staining to detect SIV-specific T-cell responses was performed in SM peripheral blood mononuclear cells (PBMCs) as described in reference 8.

**CCR5 genetic analysis.** The analysis of CCR5 gene polymorphisms to detect CCR5<sup>Δ32</sup> and CCR5<sup>Δ34</sup> alleles was conducted as described in reference 25.

**RESULTS**

**Sooty mangabey births at YNPRC.** To ascertain the rate of MTIT in naturally SIV-infected sooty mangabeyes (SMs), we conducted a retrospective analysis of mother-infant pairs housed at the Yerkes National Primate Research Center (YNPRC). During a 30-year time period (1969 to 1999), 593 SM infants were born. Of these, 569 were born to known or likely simian immunodeficiency virus (SIV)-infected mothers. Two hundred forty-nine progeny of SIV-infected SM dams were tested for the presence of anti-SIV antibodies at one or multiple time points, resulting in 2,155 total measurements of SIV serology available for review. In most animals, serial assessments of SIV serological status were conducted during the first year of life (resulting in 511 measurements), allowing for the documentation of the presence or absence of maternal antibody at birth and the subsequent evaluation of infection on a semimonthly basis (Table 1).

**Definition of SIV transmission groups.** The 249 infants with serologic data born to SIV-infected mothers were classified into four groups based on the results of SIV testing: (i) non-transmission; (ii) non-MTIT; (iii) presumptive MTIT; and (iv) indeterminate (Table 2). Serological testing was performed on all animals by ELISA and/or Western blotting. When MTIT was suspected, SIV viral load was assessed by SIV<sub>smm</sub> quantitative real-time RT-PCR. Nontransmission was defined as (i) negative testing at all time points or (ii) persistent seroreversion at any time after birth. The non-MTIT group was comprised of the following SMs: (i) those who were seronegative at birth and then seroconverted after 1 year of life, and (ii) those...
who were seropositive at birth (due to maternal antibodies), seroverted (loss of maternal antibodies), and subsequently seroconverted after 1 year of life. The SMs with presumptive MTIT were defined conservatively as those animals that met the following serologic and virologic criteria: SIV seropositivity from birth with a sample tested between 6 months and 1 year of life (to discount the contribution of passively transferred maternal antibodies that typically waned between 4 and 6 months after birth), and SIV$_{ser}$ viral load of greater than 500 copies/ml of serum within the first year of life. The rationale for using this two-tiered approach was to account for the presence of maternal antibodies in the first 6 months of life and to provide secondary virologic confirmation of infection. Of note, late breastfeeding-related transmission events are virtually impossible to separate from early events of horizontal transmission resulting from mock sexual activity that can occur during the first year of life. As such, it is possible but basically non-provable that a seroconversion occurring early in the second year of life is related to prolonged breastfeeding. On the other hand, it also is possible that some of the presumptive MTIT cases in fact do not reflect MTIT but rather early sexual activity. For these reasons, we believe that this combination of longitudinal serology and quantitative viral load analyses represents the best possible approach based on sample availability, and that our definition incorporates most, if not all, cases of in utero and intrapartum transmission, as well as the majority of cases of breastfeeding-related transmission.

**Rate of MTIT of SIV is low in naturally SIV-infected SMs.** There were 161 SM infants born to naturally SIV-infected dams that could be classified as nontransmission, non-MTIT, or presumptive MTIT. Of these 161 SMs, 150 (93.2%) were cases of nontransmission (30 animals) or non-MTIT (120 animals), and only 11 (6.8%) met the criteria for presumptive MTIT. Figure 1 shows the absolute number of births to naturally SIV-infected mothers at the YNPRC from 1976 to 1999 and illustrates the very infrequent occurrence of SIV transmission from mother to infant relative to overall births, particularly from 1991 to 1995. Data from non-prior to 1976 are not shown graphically, as no animals in the non-MTIT or presumptive MTIT groups were born before this date. This work is the first to comprehensively assess for SIV infection in a large number of infants of naturally SIV-infected SMs, and the rare incidence of MTIT in this natural host species appears to starkly contrast with the 35 to 40% mother-to-child transmission rate found in HIV infection.

**Low levels of virus replication in SIV-infected SMs with presumptive MTIT.** We performed SIV quantitative real-time RT-PCR in SIV-infected SMs with presumptive MTIT at multiple time points during the first year of life. The total number of samples assayed from these 11 infants was 26. As shown in Fig. 2A, the level of viremia in these infants was very low (geometric mean of 934 copies/ml of serum; range, below the limit of detection to 111,000 copies/ml of serum) compared to previously reported data on naturally SIV-infected adult SMs, which consistently show viremia in the range of $10^6$ copies/ml of plasma (Fig. 2A) (31). Of note, three infants had viral loads below the lower limit of detection for the assay at one time point, and one infant was below the lower limit of detection at two time points during the first year of life. In only one instance was the undetectable viral load the first measurement obtained; the exclusion of this measurement from the analysis raised the geometric mean minimally (to 1,031 copies/ml of serum) in SM infants infected with SIV by presumptive MTIT.

We next measured viral loads in the presumptive MTIT group as adults (≥6 years of age, total of 19 samples available from 7/11 SMs) and found a geometric mean viral load of 12,055 copies/ml of serum or plasma (range, 177 to 187,000 copies/ml at ≥1 yr, viral load of ≥500 copies/ml at ≤1 yr)

<table>
<thead>
<tr>
<th>Transmission group</th>
<th>Characteristic(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontransmission</td>
<td>SIV negative at all time points</td>
</tr>
<tr>
<td></td>
<td>SIV seropositive at birth with persistent seroreversion</td>
</tr>
<tr>
<td>Non-mother-to-infant transmission</td>
<td>SIV seronegative at birth with seroconversion after 1 year</td>
</tr>
<tr>
<td></td>
<td>SIV seropositive at birth with seroreversion and then seroconversion after 1 year</td>
</tr>
<tr>
<td>Presumptive mother-to-infant transmission</td>
<td>SIV seropositive from birth with sample tested at ≥6 months and ≤1 yr, viral load of &gt;500 copies/ml at ≤1 yr</td>
</tr>
</tbody>
</table>

**FIG. 1.** SM births in the YNPRC colony from 1976 to 1999. The absolute number of births to naturally SIV-infected dams shown for each time period. Only SMs with ≥1 SIV antibody test are included (n = 249). SMs infected with SIV by presumptive MTIT are depicted by the white bars (n = 11); SMs infected with SIV by non-MTIT are depicted by the gray bars (n = 120); and uninfected SMs (nontransmission) are depicted by the black bars (n = 30). The presumptive MTIT group was SIV seropositive from birth (with a sample tested at ≥6 months and ≤1 year) and had an SIV$_{ser}$ viral load of greater than 500 copies/ml of serum within the first year of life. The non-MTIT infected group was either seropositive at birth with seroreversion (loss of maternal antibody) and subsequent seroconversion after 1 year of life or seronegative at birth with seroconversion after 1 year of life. Nontransmission was defined as negative testing at all time points or persistent seroreversion at any time after birth. There were a further 88 SMs (not shown) who were classified as indeterminate.
FIG. 2. Viral loads of SMs vary by mode of SIV transmission and age. (A) Viral loads in SMs infected with SIV by presumptive MTIT and non-MTIT were measured as SIV RNA copies per ml of serum or plasma. Serial measurements during the first year of life (<1 year of age; n = 26) and as adults (≥6 years of age; n = 19) were performed for the 11 SIV-infected SMs with presumptive MTIT. For comparison, viral loads of 105 adult SMs infected with SIV by non-MTIT are shown. Measurements below the limit of detection for the assay are plotted at 80 SIV RNA copies/ml. Circles represent individual data points, and horizontal lines indicate geometric means. Mixed-effects models were used to determine statistical significance. (B) Direct comparison of the viral loads measured in seven SMs infected with SIV by presumptive MTIT for which samples were available at both <1 year of age and ≥6 years of age. Individual animals are color coded. Measurements below the limit of detection for the assay are plotted at 80 SIV RNA copies/ml. Circles represent individual data points, and horizontal lines indicate geometric means. (C) Representative examples of SIV serology, viremia, and CD4⁺ T-cell counts over time in two SMs infected with SIV by presumptive MTIT and two infected with SIV by non-MTIT.
copies/ml) (Fig. 2A). Statistical analysis using a mixed-effects model revealed that viral loads in SIV-infected SMs with presumptive MTIT tended to be 9.7 times higher at ≥6 years of age than at ≤1 year of age (P < 0.001). Interestingly, the viral loads of adult SMs infected with SIV by presumptive MTIT were approximately 1-log lower than those found in adult SIV-infected SMs with non-MTIT (P < 0.001) (Fig. 2A). We next performed a direct comparison of viral loads in seven SMs infected with SIV by presumptive MTIT, for which measurements were obtained at both ≤1 and ≥6 years of age, and found again that viral loads increased with age by approximately 1 log (Fig. 2B). Individual animals are color coded. Representative examples of SIV serology, viremia, and CD4+ T-cell counts over time in two SMs infected with SIV by presumptive MTIT and two infected with SIV by non-MTIT are shown in Fig. 2C. These results reveal that SIV-infected SMs with presumptive MTIT have low viral loads in infancy, and that, while their levels of virus replication increase later in life, they remain lower than those of SIV-infected SMs with non-MTIT.

**Mortality is not affected by mode of SIV transmission in SMs.** Untreated HIV-1-infected infants have a more rapid and severe course of disease than their adult counterparts (17). To determine if a similarly rapid progression to AIDS was present in the SIV-infected SMs with presumptive MTIT described here, we compared their clinical course of infection to that observed in naturally SIV-infected SMs with non-MTIT. Four of the 11 SIV-infected SMs with presumptive MTIT are still living (14 to 19 years of age as of December 2010). The remaining seven SIV-infected SMs with presumptive MTIT died during the follow-up period, with a median age of death of 10.4 years. SIV-infected SMs in the non-MTIT group who died during follow-up (54 animals) had a median age of death of 13.4 years. We performed Kaplan-Meier survival analysis on these two groups and found no significant difference in the percent survival over time (P = 0.22) (Fig. 3). The fact that MTIT of SIV in SMs has no impact on their survival is indirectly confirmed by the observation that infant mortality in offspring of SIV-infected and uninfected mothers is the same (24 and 21%, respectively; data not shown).

**Immune parameters are similar in SMs infected with SIV by presumptive MTIT and non-MTIT.** In the first comprehensive immunological survey of 110 naturally infected SMs of the YNPRC colony (including a subset of the SIV-infected SMs with presumptive MTIT described here), correlates of preserved CD4+ T-cell counts were described (30). To determine if MTIT of SIV in SMs is associated with specific immunological features, we compared a number of immune parameters in SIV-infected SMs with presumptive MTIT to those of SMs who became infected with SIV as adults (Table 3). Please note that, in this analysis, we used data that were obtained from SIV-infected SMs with presumptive MTIT as adults, since archived PBMC samples from their infancy were not available. Age ranges and medians for the two groups compared in Table 3 were not statistically different at the time of sampling. The SMs infected with SIV by presumptive MTIT described in this study showed an average CD4+ T-cell count of 1,193 cells/mm³ (Table 3), which is similar to the CD4+ T-cell count (1,079 cells/mm³) reported for SMs naturally infected with SIV by non-MTIT (P = 0.336) (30). Additionally, there was no difference between the percentages of CD4+ and CD8+ naïve, memory, and effector T cells (as defined by the markers CD28 and CD95), the activation/proliferation status of CD4+ and CD8+ T cells (as defined by Ki67 positivity), and CD4+ and CD8+ T-cell immune responses to SIV for SIV-infected SMs with presumptive MTIT compared to those of SIV-infected SMs with non-MTIT (Table 3). In a follow-up survey of 78 naturally SIV-infected SMs of the YNPRC colony (including a different subset of the SIV-infected SMs with presumptive MTIT described here), a progressive decline in CD4+ T cells was found, with an average CD4+ T-cell count of 679 cells/mm³ (31). The SIV-infected SMs with presumptive MTIT did not show a steeper decline in CD4+ T cells than SIV-infected SMs with non-MTIT, with average CD4+ T-cell counts of 639 cells/mm³ (Table 3). Numbers presented in Table 3 for the non-MTIT group differ slightly from those reported in the text and previously published, as they represent the sample of naturally infected SMs of the YNPRC colony (including a subset of the SIV-infected SMs with presumptive MTIT described here).

**TABLE 3. Immune parameters in SIV-infected sooty mangabeys**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Presumptive MTIT</th>
<th>Non-MTIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ T-cell count (2004)</td>
<td>1,193</td>
<td>1,071</td>
</tr>
<tr>
<td>CD4+ T-cell count (2009)</td>
<td>639</td>
<td>674</td>
</tr>
<tr>
<td>CD4+ CCR5+ T cells (%)</td>
<td>2.1</td>
<td>2.9</td>
</tr>
<tr>
<td>CD8+ Ki67+ T cells (%)</td>
<td>4.1</td>
<td>3.1</td>
</tr>
<tr>
<td>CD8+ Ki67+ T cells (%)</td>
<td>6</td>
<td>3.2</td>
</tr>
<tr>
<td>CD4+ CD28+ CD95+ (%)</td>
<td>43.6</td>
<td>37.4</td>
</tr>
<tr>
<td>CD4+ CD28+ CD95+ (%)</td>
<td>0.15</td>
<td>0.6</td>
</tr>
<tr>
<td>CD4+ CD28+ CD95+ (%)</td>
<td>56.2</td>
<td>61.8</td>
</tr>
<tr>
<td>CD8+ CD28+ CD95+ (%)</td>
<td>24.8</td>
<td>20.9</td>
</tr>
<tr>
<td>CD8+ CD28+ CD95+ (%)</td>
<td>21.6</td>
<td>21.6</td>
</tr>
<tr>
<td>CD8+ CD28+ CD95+ (%)</td>
<td>52.5</td>
<td>57.0</td>
</tr>
<tr>
<td>Anti-SIV CD4+ T-cell response: IFN-γ (%)</td>
<td>0.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Anti-SIV CD4+ T-cell response: TNF-α (%)</td>
<td>0.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Anti-SIV CD8+ T-cell response: IFN-γ (%)</td>
<td>0.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Anti-SIV CD8+ T-cell response: TNF-α (%)</td>
<td>0.07</td>
<td>0.36</td>
</tr>
</tbody>
</table>

* Means are shown for all parameters; P was not significant for all comparisons by Mann-Whitney U-test or Fisher’s exact test (used for a mean equal to 0). 
* n = 5. Unless stated otherwise, data are from 2004. 
* In cells/mm³. 
* Percentage of CD4+ or CD8+ T cells secreting IFN-γ or TNF-α following stimulation with SIV Gag, Pol, Env, and Nef peptide pools.
urally SIV-infected SMs studied minus those animals subsequently identified as presumptively infected via MTIT. Statistical conclusions were not affected by these minor differences. Therefore, the MTIT of SIV in SMs did not differentially affect key immune parameters compared to the effects of non-MTIT of SIV.

We next investigated the possible role of CCR5 mutations in limiting MTIT of SIV in SMs. As recently described, 8% of the SMs at the YNPRC lack functional CCR5 due to homozygosity for a 2-bp deletion causing a frameshift mutation (CCR5Delta2) or double heterozygosity for CCR5Delta2 and a 24-bp deletion (CCR5Delta24) (25). Of the 11 SM infants with presumptive MTIT, 6 were genotyped and none were homozygous for defective CCR5 alleles (data not shown). The frequency of homozygosity for defective CCR5 alleles in SMs belonging to the non-MTIT and nontransmission groups was 7% and 13%, respectively (data not shown). Of note, the number of genotyped animals in the presumptive MTIT and nontransmission groups was low (such that 0% and 13% frequency represent 0/6 and 1/7 animals, respectively). Thus, it does not appear that major differences in functional CCR5 expression distinguish the transmission groups described in this study.

DISCUSSION

In this study, we performed the first comprehensive longitudinal analysis of SIV acquisition in infants born to naturally SIV-infected SMs and observed that the presumptive rate of MTIT is 6.8%, i.e., much lower than the 35 to 40% MTCT rate found in HIV infection. In addition, we found that the SIV infection of infant SMs is associated with significantly lower levels of viremia than that of adult SMs. From the immunological and clinical point of view, those relatively rare instances of MTIT of SIV are associated with nonpathogenic infection with by-and-large preserved immune function, which is consistent with the phenotype observed in adult SMs.

The restriction of MTIT of SIV in this natural host species may reflect maternal and/or infant factors reducing the risk of acquisition of infection during the in utero, peripartum, and breastfeeding periods. A previous cross-sectional survey conducted in 1990 of a relatively small group of 27 infant SMs between 6 and 12 months of age (none of whom are included in the current work) found a prevalence of SIVnon infection of 14.8%, higher than that in the current study (11). This discrepancy could be explained by the presence of non-MTIT of SIV in relatively older animals (i.e., closer to 1 year of age) via aggressive behavior and/or early mock sexual activity. Indeed, if a less stringent definition of presumptive MTIT is used in the current study, i.e., by including all SMs with a positive serology between 6 months and 1 year of life regardless of earlier seronegativity and without viral load determination, a possible rate of 13.6% MTIT is observed. However, given the generally limited availability of samples as well as the potentially problematic interpretation of serological data for these animals, we feel that the inclusion of positive viral load results in the definition of presumptive MTIT is essential to capture the biology of this type of transmission. In any event, the work described here extends that of Fultz et al. (11) by (i) increasing the number of studied animals from 27 to 249, (ii) longitudinally assessing the serological and virological status of the infants from or very close to birth, and (iii) providing data relative to the key clinical and immunological parameters of SIV infection in these infants. Importantly, our current results are consistent with the observation that MTIT of SIV is rare or absent in wild SMs, grivet, and African green monkeys (18, 24, 26). Similarly, no breastfeeding-related SIV transmission could be documented in six infant mandrills whose mothers were experimentally infected soon after giving birth (23).

We show here that SM infants infected with SIV by presumptive MTIT have 2-log less circulating virus than adults of the same colony who acquired SIV by non-MTIT. In addition, as adults, SMs in the presumptive MTIT group still have 1-log lower viral loads than SMs of similar ages infected with SIV by non-MTIT. These results are particularly intriguing given that untreated human infants with HIV infection acquired by MTCT typically have viral loads that exceed those of HIV-infected adults (7, 21, 27). In fact, asymptomatic HIV-infected infants have been reported to have levels of virus that are similar to those of HIV-infected adults with AIDS-defining illnesses (19). In a study of another natural host species, Beer et al. showed that neonatal AGMs infected either intravenously or intraperitoneally with SIVagm had a delayed onset of viremia, and during chronic infection they tended to have viral loads that were lower than those of adult AGMs infected with the same virus (3). More recently, undetectable plasma viremia but the presence of replication-competent proviral DNA was observed in an infant AGM experimentally inoculated with SIVagm (J. M. Brenchley, unpublished data).

We demonstrate that survival in SIV-infected SMs with presumptive MTIT was not different from that of SIV-infected SMs with non-MTIT. In addition, infant mortality was unchanged by the mother’s SIV status. Previous work has shown that SIV infection does not affect mortality in adult SMs (14), which is consistent with the nonprogressive nature of SIV infection in natural hosts. MTCT of HIV, in contrast, has a significant impact on infant mortality, with more than half of all untreated children dying by the age of 2 (17). Our study also indicates that, as adults, SMs who acquire SIV by MTIT have immunological parameters similar to those of SMs who acquire SIV by non-MTIT.

The mechanisms underlying the restriction of MTIT and virus replication in infant natural hosts for SIV remain poorly understood and are likely to be complex. Conceivably, this lower level of viremia may be the result of more effective antiviral adaptive immune responses. This possibility, however, appears unlikely given the generally low levels of both SIV-specific cellular immune responses and SIV neutralizing antibody titers observed in SIV-infected SMs (8, 16). An alternative possibility, suggested by the previously quoted study of MTIT of SIV in mandrills (23), is that infant SMs have very low levels of activated CD4+ T cells or CD4+ CCR5+ T cells that serve as targets for virus infection. Lower levels of CCR5 expression reflecting a higher fraction of CCR5-negative naïve CD4+ T cells in infant SMs as well as an age-related increase in the fraction of antigen-experienced CD4+ T cells may explain the relative rarity of MTIT in the offspring of SIV-infected SM dams and the low viral loads of the SIV-infected infants following MTIT. While in the current study the fraction of CD4+ CCR5+ T cells was not directly measured in infant SMs, this possibility is consistent with the known observation...
that CCR5 expression on CD4+ T cells is substantially lower in natural SIV hosts than in nonnatural hosts (22). Since SIV<sub>smm</sub> appears to use additional coreceptors in SMs with CCR5 deletions (25), it is also possible that reduced susceptibility to MTIT reflects lower expression of as-yet unidentified coreceptors for SIV in infant SMs.

At this time, we have not identified any specific virological, immunological, genetic, or behavioral feature that can provide a mechanistic explanation for the occurrence of MTIT of SIV in a relatively rare subset of infant SMs. An obvious possibility is that viremia during pregnancy was unusually high in the SIV-infected SM dams who successfully transmitted the virus to their infants. Unfortunately, due to the retrospective nature of the current study, samples were not available to address this hypothesis. The possibility that SIV-infected infants had higher levels of CD4<sup>+</sup> CCR5<sup>+</sup> target cells as a result of genetic factors is not supported by the observation that, as adults, the levels of these target cells were similarly low in SIV-infected SMs with both presumptive MTIT and non-MTIT. However, it is possible that environmental factors induced a transient increase of CD4<sup>+</sup> CCR5<sup>+</sup> T cells in the SIV-infected infants. Since the breeding of the SM colony at the YNPRC was reinitiated in 2010, future prospective studies will allow us to establish whether a threshold of virus replication or target cell availability is needed for MTIT of SIV in SMs.

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