Vaccination of Pregnant Macaques Protects Newborns against Mucosal Simian Immunodeficiency Virus Infection

Koen K. A. Van Rompay, Moses G. Otsyula, Ross P. Tarara, Don R. Canfield, Christopher J. Berardi, Michael B. McChesney, and Marta L. Marthas

Simian immunodeficiency virus (SIV) infection of newborn rhesus macaques is a rapid, sensitive animal model of human pediatric AIDS. Newborn macaques were readily infected by uncloned SIV$_{mac}$ following oral-conjunctival exposure and had persistently high viremia and rapid development of AIDS. In contrast, when 3 pregnant macaques were vaccinated against SIV, 2 of the newborns that had transplacentally acquired antiviral antibodies were protected against mucosal SIV infection at birth. These results suggest that intervention strategies such as active immunization of human immunodeficiency virus (HIV)–infected pregnant women and anti-HIV immunoglobulin administration may decrease the rate of perinatal HIV infection.

The rapid spread of human immunodeficiency virus (HIV) infection among the heterosexual population, including women of child-bearing age, has resulted in an increasing prevalence of HIV infection among newborns and infants. Although transmission can occur early in utero and postnatally through breastfeeding, evidence suggests that a large fraction of infants become infected around birth [1–6] by contact with maternal blood and body fluids, possibly by a mucosal route of infection [7, 8].

A recent clinical trial showed that zidovudine administration to HIV-infected pregnant women and their newborns can reduce the rate of viral transmission by two-thirds [9]. Because zidovudine is not 100% effective and the prevalence of zidovudine-resistant HIV variants will continue to increase, additional intervention strategies should be investigated, including those that are immune-based [10]. The rationale for active and passive maternal immunization to prevent infectious diseases in the neonate has been reviewed elsewhere [11–13]. Active immunization of mothers could be especially useful in developing countries, because vaccination is less costly than a prolonged chemoprophylactic treatment regimen with antiretroviral drugs.

Studies of possible correlations between levels and specificity of maternal HIV-specific antibody and vertical transmission have shown conflicting results [14]. Thus, although clinical trials have been initiated recently, it is currently unclear whether increased levels of maternal anti-HIV antibodies, achieved either by passive administration of anti-HIV immunoglobulins or by active vaccination, can interrupt vertical transmission. In addition, it is unknown whether maternally derived anti-HIV antibodies can have beneficial therapeutic properties (e.g., reducing viral replication and delaying disease progression) for infants who become infected.

Because the pathogenesis of vertical HIV transmission and pediatric AIDS is multifactorial (determined by many variables, such as maternal virus load, immunologic status, and virulence and dose of the virus to which the newborn is exposed), the specific role of maternal antibodies has been difficult to identify. An appropriate animal model can allow distinction of these important variables.

Simian immunodeficiency virus (SIV) infection of rhesus macaques (Macaca mulatta) is an excellent animal model of HIV infection in humans [15]. In contrast to other laboratory animal species, nonhuman primates have a reproductive physiology (including placentation and fetal-neonatal development) very similar to that of humans and are thus most appropriate for studying the effects of maternal immunization and transplacental antibody transfer [16]. We have demonstrated previously that infection of newborn macaques by intravenous inoculation with uncloned SIV$_{mac}$ resembles HIV infection of many human infants in causing high levels of viral replication, poor antiviral immune responses, and rapidly progressive disease [17]. Therefore, we next investigated whether the mucosal (oral-conjunctival) route of infection could alter the disease course in rhesus neonates and whether maternally derived anti-SIV antibodies obtained through vaccination of pregnant female macaques could prevent this infection or alter the rate of disease progression.

Materials and Methods

Animals. All rhesus macaques (M. mulatta) were from the type D retrovirus– and SIV-free colony at the California Regional Primate Research Center, University of California, Davis.
Primate Research Center. When necessary, animals were immobilized with ketamine HCl (Parke-Davis, Morris Plains, NJ), 10 mg/kg injected intramuscularly.

**Immunization of pregnant macaques against SIV.** Two pregnant rhesus macaques were used as unvaccinated controls. Three other pregnant females were first given a perivaginal inoculation with the nonpathogenic molecular clone SIV\textsubscript{mac1AI} [17–19] between gestational days 41 and 50 and were subsequently boosted intramuscularly with a β-propiolactone—inactivated whole virus preparation plus adjuvant between gestational days 109 and 127. Perivaginal inoculation was done with 1 mL (~10^{-5.5} TCID\_50) of an SIV\textsubscript{mac1AI} stock grown in rhesus peripheral blood mononuclear cells (PBMC) and previously shown to be infective and to elicit anti-SIV antibodies following perivaginal inoculation [20]. For the booster immunization, uncloned SIV\textsubscript{mac} grown in HuT 78 cells was sucrose-gradient–purified and inactivated with β-propiolactone as described previously [21]. Then 0.2 mL of Montaniade ISA 51 adjuvant (Seppic, Fairfield, NJ) was mixed with 0.2 mL (100 μg) of this whole, inactivated SIV and injected intramuscularly. Pregnancies were monitored via ultrasound.

**Inoculation and sampling of newborn macaques.** Shortly after delivery, the newborn rhesus macaques were removed from their mothers and hand-reared in a primate nursery. Between 12 and 72 h after birth, all newborns were inoculated with SIV twice, with a 24-h interval between inoculations. For each inoculation, 1 mL of an uncloned SIV\textsubscript{mac251} stock was administered intratraumatically by applying 1 droplet of virus inoculum (~50–100 μL) onto the cornea of each eye and dispensing the remainder of the virus slowly into the mouth. The animals were monitored to ensure swallowing of the oral inoculum. The virus stock used in this study consisted of uncloned SIV\textsubscript{mac251} propagated on rhesus PBMC with a titer of 10\textsuperscript{5} TCID\_50/mL [22]; this virus dose gives consistent infection after genital mucosal inoculation [22]. A single dose (1 mL) of this stock was sufficient to cause persistent infection in 4 of 4 juvenile-adolescent macaques following oral inoculation (unpublished data).

To monitor the immune response to nonviral, nonreplicating antigens, all newborn rhesus macaques were immunized with 0.5 mL of tetanus toxoid in alum (Wyeth Laboratories, Marietta, PA) intramuscularly and 0.1 mg of cholera toxin B subunit (List Biological Laboratories, Campbell, CA) subcutaneously, just before the first virus inoculation. A booster immunization with the nonpathogenic molecular clone SIV\textsubscript{mac1AI} (positive control) or aliquots of PBMC lysates, (the same as the virus inoculum) instead of molecular clones also reduces the neutralization titer significantly (unpublished data).

Thus, although neutralization titers by this PCR method are low, they may have more biologic relevance than those obtained by other methods. Also, unlike neutralization assays that measure reduction in virus output (e.g., by syncytia or p27), this PCR assay measures reduction of virus that enters cells.

**Quantitative virus isolation (cell-associated and cell-free).** Cell-associated and cell-free virus levels in peripheral blood were determined regularly by a limiting dilution culture assay (four replicates per dilution) of PBMC and plasma, respectively, with CEMx174 cells in 24-well plates and subsequent p27 core antigen measurement, according to methods previously described [23, 28]. In addition, for animals with low or undetectable virus load, 1 × 10\textsuperscript{6} to 10 × 10\textsuperscript{6} PBMC were cocultivated for 8 weeks with CEMx174 cells in tissue culture flasks, as described previously [23, 28].

**PCR amplification.** Nested PCR was done in a GeneAmp 9600 thermocycler. Two rounds of 30 cycles of amplification were performed on aliquots of plasmid DNA containing the complete genome of SIV\textsubscript{mac1AI} (positive control) or aliquots of PBMC lysates, using SIV\textsubscript{mac}-specific gag primers and conditions described else-
the 3 female macaques were then given a booster immunization with whole, inactivated SIV mac plus adjuvant intramuscularly between gestational days 109 and 127 (figure 1; the normal SIV-specific antibody levels following perivaginal SIV maclAl1 first given a perivaginal inoculation with SIV maclAl1 between gestational days 41 and 50. SIV maclAII is a nonpathogenic molecular clone that causes a transient viremia, development of immune responses that could be generated in women following natural transplacental antibody transfer.

**Results**

**Immunization of pregnant macaques with SIV results in transplacental antibody transfer.**

Two pregnant rhesus macaques were used as unvaccinated controls. Three other pregnant females were immunized against SIV. To mimic immune responses that could be generated in women following natural HIV infection by the vaginal route, the 3 female macaques were first given a perivaginal inoculation with SIV maclAII between gestational days 41 and 50. SIV maclAII is a nonpathogenic molecular clone that causes a transient viremia, development of immune responses, and no disease in macaques of all age groups (fetus to adult) [17–19]. As previously observed [20], SIV-specific antibody levels following perivaginal SIV maclAII inoculation were low (figure 1). To boost immune responses, the 3 female macaques were then given a booster immunization with whole, inactivated SIV mac plus adjuvant intramuscularly between gestational days 109 and 127 (figure 1; the normal gestation of rhesus macaques is 155–165 days). No adverse effects on the health of the mother or fetus were seen following these immunizations.

All 3 vaccinated mothers made antibodies to SIV, but titers were relatively low. At the time of delivery, total serum anti-SIV IgG titers in the mothers ranged from 1/500 to 1/2500 (figure 1). The ratios of infant to maternal plasma titers of anti-SIV antibodies at the time of delivery were 1.0 in all 3 mother-infant pairs, indicating efficient transplacental transfer of IgG (figure 1). As expected, immunoblotting demonstrated that transplacentally derived antibodies in the newborns had antigenic specificities similar to those in their mothers (figure 2). Sera from 2 mother-infant pairs had strong reactivity to SIV gp120 envelope in addition to other viral structural proteins. For 1 mother-infant pair, however, anti-gp120 antibodies were undetectable by immunoblotting (figure 2).

**Maternal antibodies can protect newborns against mucosal SIV infection.**

Four animals were born at term by vaginal delivery, while the other (animal 28481) was delivered by cesarean section on gestational day 160. No virus could be isolated from blood samples collected at birth (prior to mucosal inoculation with uncloned SIV mac) from the 3 infants born to SIV maclAII-inoculated females in this study, indicating no evidence of transplacental transmission of SIV maclAII.

Shortly after delivery, the newborn rhesus macaques were removed from their mothers and hand-reared in a primate nursery. Between 12 and 72 h after birth, all newborns were inoculated twice (24 h apart) with 1 mL (~103 TCID50) of uncloned SIV mac (grown in rhesus PBMC) via the oral-conjunctival route. To monitor the immune response to nonviral, nonreplicating antigens, all newborn rhesus macaques were immunized with tetanus toxoid intramuscularly and cholera toxin B subunit subcutaneously, just before the first virus inoculation; a booster immunization of these two antigens was given at 1 month of age.

The 2 control SIV-infected neonates that had no neutralizing or SIV-specific antibodies at birth (animals 28011 and 28012, table 1), developed a pronounced cell-free (plasma) and cell-associated (PBMC) viremia within 2 weeks that persisted until death (figure 3A, B). Both animals made a transient anti-SIV IgM response (figure 3C). SIV-specific IgG or IgA antibody responses were detected in both animals, but for animal 28012, these anti-SIV antibodies declined rapidly prior to the development of fatal immunodeficiency (figures 2, 3D–E). Absolute CD4 lymphocyte counts varied significantly over time, and due to elevated lymphocyte counts during the development of AIDS (total lymphocyte counts, 9200–24,600/μL), no reduction in absolute numbers of CD4 lymphocytes was observed (data not shown). In contrast, the CD4:CD8 lymphocyte ratio for animal 28011 was consistently below normal values [24] after 2 weeks (figure 3F). Animal 28012’s weight gain was significantly below that of uninfected infants (table 1); both SIV-infected control infants developed severe clinical signs of simian AIDS and were euthanized at 11 and 19 weeks (animals 28012 and 28011, respectively). Their clinical abnormalities

**Statistical analysis.**

Statistical analysis was used to compare growth rates of the rhesus infants in this study. Growth rates (weight gained in grams per day) were calculated by regression analysis on daily body weight measured during the first 10 weeks of age, using Excel software (version 5.0; Microsoft, Redmond, WA). The slopes (growth rates) of regression lines for daily weights of SIV-inoculated neonates and of control neonates were compared by z test for parallelism as described previously [23, 24, 29].

**Necropsy and preparation of tissue samples.**

Euthanasia of animals with simian AIDS was indicated by three or more of the following clinical observations: weight loss of >10% in 2 weeks or >30% in 2 months; chronic diarrhea unresponsive to treatment; infections unresponsive to treatment; inability to maintain body heat or fluids without supplementation; persistent, marked hematologic abnormalities, including lymphopenia, anemia, thrombocytopenia, or neutropenia; and persistent, marked splenomegaly or hepatomegaly [17].

A complete necropsy was done on every animal that died during the course of the study. Tissues collected at necropsy were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 6 μm, stained with hematoxylin-eosin, and examined by light microscopy.
plus gross and microscopic pathologic changes (table 1) were consistent with terminal stages of SIV infection in infant rhesus macaques [17].

In contrast to the 2 control animals born to unvaccinated mothers, 2 of the 3 neonates that had received maternal anti-SIV immunoglobulin through transplacental transfer, including the 1 with the lowest antibody titer, were protected against infection. Both of these animals (28373 and 28468) had detectable neutralizing antibodies (table 1) and anti-envelope antibodies (figure 2). No infectious virus could be isolated from SIV immunized dams (left) and their offspring (right). Bars = antibody titers (highest of 5-fold dilutions that gave positive OD above cutoff value) measured by SIV-specific IgG ELISA [24]. Identical bar patterns represent each mother-infant pair. Pregnant females were immunized between gestational day (GD) 41 and 50 and boosted between GD 109 and 127 (arrows). Newborns were challenged twice within the first 72 h after birth (arrow).

Figure 1. SIV-specific antibody titers in immunized dams (left) and their offspring (right). Bars = antibody titers (highest of 5-fold dilutions that gave positive OD above cutoff value) measured by SIV-specific IgG ELISA [24]. Identical bar patterns represent each mother-infant pair. Pregnant females were immunized between gestational day (GD) 41 and 50 and boosted between GD 109 and 127 (arrows). Newborns were challenged twice within the first 72 h after birth (arrow).

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Figure 2. Protein immunoblot analysis for detection of anti-SIV IgG was done as described [25]. Molecular weights of major structural proteins of SIV are at left: gp120 (envelope surface glycoprotein), p65 (RT protein), p55 (gag polyprotein), gp32 (envelope transmembrane glycoprotein), and p27 (core protein). Lanes a and b: positive and negative control sera, respectively. Lanes j, o, and t: samples of vaccinated mothers are in lanes that precede serial samples of their respective infants. Lanes c–f, g–i, k–n, p–s, and u–v: serial samples obtained at various weeks of age (3–29) from 5 rhesus neonates. Time 0 = first oral-conjunctival inoculation. Time of death (euthanasia) with simian AIDS.
multiple samples of plasma or PBMC from these 2 animals, and no proviral DNA was detected in PBMC lysates by a nested PCR technique [27] (data not shown). No SIV-specific IgM or IgA responses were detected by ELISA (table 1), and maternal anti-SIV IgG levels (derived transplacentally) gradually decreased and became undetectable by ELISA and immunoblotting (figures 1, 2). The estimated half-life of SIV-specific IgG was ~4-9 days, similar to the time reported previously for anti-SIV IgG in rhesus macaques [31]. No SIV-specific CTL responses were detected in these 2 uninfected animals. Both animals made normal antibody responses to cholera toxin subunit B and tetanus toxoid, had normal weight gain, and had no clinical symptoms (table 1).

To exclude the possibility that some host factor might have made these 2 animals less susceptible to SIV infection, both animals were reinoculated orally >5 months after birth (i.e., when all maternal antibodies had disappeared; figure 2) with a single 1-mL dose of the same uncloned SIVmac251 virus stock that was used for the initial 2-fold inoculation at birth. After this oral inoculation, both animals became persistently infected, virus had increased to levels similar to those observed in the SIV-infected control animals (figure 3A, B). Plasma viremia in this animal was 10- to 100-fold lower than in the 2 control animals, but by 6 weeks of age, virus had increased to levels similar to those observed in the SIV-infected control animals (figure 3A, B). Plasma viremia in this animal was 10- to 100-fold lower than in the 2 control animals, but by 6 weeks of age, virus had increased to levels similar to those observed in the SIV-infected control animals (figure 3A, B).

The third infant (animal 28481, table 1) became infected despite high levels of maternal antibodies at birth. However, of the 3 newborns with maternal anti-SIV antibodies, this was the only animal with no detectable antibodies directed against the external surface gp120 (figure 2). In addition, these antibodies had no neutralizing activity against the virus used for challenge (table 1) or against autologous virus that was isolated from this animal at 1 week of age (data not shown). During the first 4 weeks of infection, plasma viremia in this animal was 10- to 100-fold lower than in the 2 control animals, but by 6 weeks of age, virus had increased to levels similar to those observed in the SIV-infected control animals (figure 3A, B). Plasma viremia increased at the same time that the anti-SIV IgG antibodies decreased.

The anti-SIV IgG levels declined in animal 28481 at the same rate as they did in the uninfected infants and became undetectable by 10 weeks (figures 1, 2, 3D). This animal did not make detectable de novo anti-SIV IgM or IgA immune responses after the initial 2-fold inoculation at birth strongly suggests that these 2 infants were protected against neonatal SIV infection by maternally derived SIV-specific immunoglobulins.

Table 1. Oral-conjunctival SIV inoculation of rhesus newborns: summary.

<table>
<thead>
<tr>
<th>Animal no.</th>
<th>Neonatal anti-SIV antibody</th>
<th>Postnatal de novo antibody synthesis</th>
<th>Virus load</th>
<th>Disease outcome (pathology)</th>
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<td>Titer</td>
<td>Anti-SIV</td>
<td>Anti-CTB</td>
<td>Anti-TT</td>
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<tr>
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<td>&lt;100</td>
<td>+</td>
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<td>28012</td>
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<td></td>
<td>≥20</td>
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<td>28373</td>
<td>500</td>
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<td>≥40</td>
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NOTE. All animals were inoculated twice (on 2 consecutive days) orally and conjunctivally with 1 mL of uncloned SIVmac251. Animals 28011 and 28012 were born to SIV-negative females; 28481, 28373, and 28468 were born to SIV-immunized females. SAIDS = simian AIDS.

* Measured by ELISA (see figure 1).
† See figure 2.
‡ Antibodies to cholera toxin B subunit (CTB) and tetanus toxoid (TT) were measured by ELISA. At birth, 4 of 5 newborns had maternal antibodies to TT (due to previous vaccination of their mothers), while none had antibodies to CTB.
§ SIV-specific cytotoxic T lymphocytes against viral gag and envelope protein were measured at 2 and 8 weeks after SIV inoculation by chromium release assay.

1 During first 10 weeks of life, calculated by regression analysis. CI = confidence interval. Average growth rate of 50 uninfected control animals was 6.2 g/day (99% CI = 6.0-6.4) [17].

High level of maternally derived anti-TT IgG at birth; detectable de novo IgG response was not observed until after 2nd TT booster immunization at 4 weeks of age.
Figure 3. Newborn rhesus macaques infected with SIV by oral-conjunctival route: time course of viral and immune parameters of disease progression. Solid lines: SIV-infected control infants (28011 and 28012). Dashed line: infant with maternal anti-SIV antibodies that became infected by SIV (28481). Open symbols (F): infants with maternal antibodies (28373 and 28468) that were protected against infection; because these 2 animals had no detectable virus and no de novo antiviral antibody responses, their data for graphs A–E are not presented for purpose of clarity. + = Euthanasia because of simian AIDS. Cell-free (A) and cell-associated (B) virus load was determined by limiting dilution culture of plasma and peripheral blood mononuclear cells (PBMC), respectively [23]. For comparison, shaded areas in A and B represent range of virus levels for 6 animals inoculated intravenously with uncloned SIVmac251 and described previously [17]. SIV-specific IgM (C), IgG (D), and IgA (E) antibody titers were measured by ELISA [24] and are expressed as OD of 1:100 (IgG, IgA) or 1:25 (IgM) dilution. CD4:CD8 T lymphocyte ratio (F) was determined by flow cytometry.

animals (28011 and 28012) were able to mount anti-SIV IgM, IgG, and IgA responses (figure 3C–E, table 1). The presence of maternal antibodies may have suppressed all de novo anti-SIV antibody responses for animal 28481. However, animal 28481 had high levels of maternal antibodies against tetanus toxoid and still produced anti-tetanus toxoid IgM and IgG responses (table 1). In contrast to the 2 control infants, animal 28481 mounted no anti-cholera toxin IgG response (table 1).

Together, these observations of antibody responses to viral and nonreplicating antigens suggest that the effects of maternal immunization on the infant’s immune response may depend on the particular antigen, as is observed in human infants [11].
Animal 28481 died at 13 weeks with symptoms and pathologic lesions of severe simian AIDS (table 1), so the presence of maternally derived anti-SIV antibodies did not delay disease progression in this SIV-infected rhesus infant.

Discussion

Our study provides further support for a mucosal route of HIV infection in human newborns. Contrary to previous reports that efficient oral SIV infection occurs only shortly (within 1 h) after birth [7], in the experiment described here, neonatal rhesus macaques were readily infected by the oral-conjunctival route. Preliminary studies also show that older rhesus macaques can be easily infected orally with SIV (unpublished data). The mucosal location of viral entry following oral infection remains to be determined, but the acidic pH of the stomach may limit the site of entry to the upper gastrointestinal tract (oral cavity, pharynx, esophagus).

Oral infection of neonatal and juvenile macaques with SIV suggests that breast-feeding may be a major route of postnatal HIV-I transmission in developing countries [14, 32–34]. There is also evidence that human adults can be infected after oral exposure to HIV, although the frequency of infection by this route is difficult to estimate [35]. The SIV model will be useful for investigating the early viral and immunologic events after oral exposure to virus in all age groups.

After oral-conjunctival SIV inoculation, the control newborns in the present study developed a fulminant disease course with persistently high levels of viral replication, a pattern similar to that previously observed for newborn rhesus macaques inoculated intravenously with uncloned SIVmac at the California Regional Primate Research Center [17]. The only discernible difference between intravenously and mucosally infected infants was the anti-SIV IgG response: In previous experiments, no rhesus infants infected intravenously made a detectable antiviral IgG response [17, 24]; in contrast, the 2 animals inoculated through the oral-conjunctival route in the present study mounted an anti-SIV IgG response. However, this IgG response did not delay the disease course, as virus levels and rate of disease progression were similar in the 2 animals inoculated by the oral-conjunctival route and those inoculated intravenously (i.e., fatal disease within 3–6 months) [17]. Our results for newborn macaques infected mucosally with uncloned SIVmac are quite similar to those obtained by Baba et al. [7], except that the animals in their study developed disease more slowly. Possible explanations for this difference in disease progression are the composition or dose of the virus inoculum.

The current study also demonstrates that vaccination of pregnant macaques with live-attenuated SIVmac1A11 followed by an intramuscular booster immunization with inactivated SIVmac resulted in transplacental passage of antiviral antibodies that could protect newborns against mucosal SIV infection. Although the number of animals in this experiment was small, the association between the presence of anti-gp120 antibodies and protection from SIV infection is striking.

One can hypothesize that vertical transmission of SIVmac1A11 may have affected the outcome for the 3 infants. However, vertical transmission of this virus would be very unlikely, because infection with SIVmac1A11 results only in a transient, low-level, cell-associated viremia [17–19]. In addition, we found that direct inoculation of fetal or neonatal macaques with a high dose of SIVmac1A11 did not cause disease but resulted in transient low-level viremia, induced antiviral immune responses that were detectable for >1 year [17, 19], and offered protection against challenge with SIVmac251 (unpublished data). The 2 infants in this study that were protected against oral SIV infection at birth had no detectable SIVmac1A11 viremia and had no signs of active immunity to SIV; their anti-SIV antibody levels declined rapidly, as one would expect for passively acquired antibodies. In addition, after maternal antibody levels had disappeared and animals were rechallenged with SIV, both animals became infected and mounted primary antiviral immune responses (IgM, IgG, and IgA), which strongly indicates that these animals had no previous SIV infection. Thus, protection against oral SIV infection at birth was most likely due to the transplacental passage of maternal SIV-specific IgG.

The mechanism and location at which maternally derived anti-SIV IgG can block mucosal infection of the newborns is unknown, but we hypothesize that maternally derived SIV-specific IgG was present in oral secretions of the newborn macaques and inhibited entry of the virus into the mucosa. Traditionally, mucosal immunology has focused on secretory IgA. To our knowledge, there have been no reports describing HIV-specific IgG in oral secretions of newborns of HIV-infected women and correlating these findings to the infection status of the infant. However, previous studies of healthy, uninfected human newborns have found high levels of maternal IgG in their saliva [36]. In addition, it has been shown for HIV-infected adults and for older SIV-infected macaques that HIV- and SIV-specific IgG apparently transudes from serum into the saliva and other secretions and is more abundant than antiviral IgA [37, 38]. Although no saliva samples were collected from the newborn macaques in the present study, it is possible that maternal SIV-specific IgG transuded into the saliva of the newborn macaques. Studies to further characterize and identify the role of HIV- and SIV-specific IgG in mucosal secretions are warranted, as they may provide crucial information for the development of vaccines to reduce vertical as well as sexual transmission.

The study described here is the first to demonstrate that IgG may prevent neonatal SIV infection by the mucosal route. Another study showed that passive antibody transfer protected adult macaques against intravenous challenge [31]. Together, these findings that passive humoral immunity can prevent infection by mucosal and intravenous routes suggest that the levels and the quality of maternal antibodies can contribute to a low rate of vertical HIV transmission. By demonstrating the concept that maternal IgG can prevent viral transmission, our experiments underscore the importance of clinical trials to explore intervention strategies to enhance the quantity and quality of...
maternal antibodies. Such strategies should include active immunization of pregnant women with HIV vaccines and passive immunization by administration of anti-HIV hyperimmune globulin to pregnant women and their HIV-exposed newborns [39].

Our study also suggests that maternally derived antiviral antibodies that lack specificity to the gp120 envelope glycoprotein may not have therapeutic benefits for infants that are already infected at birth. In this experiment, the single neonate with maternal anti-SIV antibodies that became infected had no de novo antiviral immune responses, and maternal antibodies (to viral proteins except gp120) did not prevent the development of a rapid, fulminant disease course. Suppression of anti-SIV antibody responses by maternal antibodies is consistent with observations of other viral infections in human infants [11]. Whether the absence of therapeutic effects of maternally derived antibodies is consistently associated with a lack of anti-gp120 antibodies needs further investigation. Perhaps specific kinds of maternal antibodies may be required to prevent vertical transmission as well as to delay disease progression. In another study, we showed that zidovudine treatment of SIVmac inoculated newborn macaques results in reduced virus levels, enhanced antiviral antibody responses, and delayed disease progression (most animals healthy after 15 months) [23]. Thus, it is possible that a combination of zidovudine and maternal antibodies may substantially reduce infection and delay disease progression. This is currently under investigation in AIDS Clinical Trials Group 185 [40].

Future studies with this newborn rhesus macaque model of pediatric AIDS will further identify the exact mechanisms by which passive antibodies can protect against mucosal infection; in addition, we are currently using this model to determine whether single or repeated administrations of hyperimmune globulin with strong anti-envelope specificity can prevent SIV infection or delay disease progression for infants that become infected.

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References


