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Animal models for perinatal transmission of HIV-1

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1. ABSTRACT

Despite progress in the use of antiretroviral drugs, mother-to-child transmission of HIV still remains a serious medical problem in resource-poor areas. There is a need to find the best method for drug delivery to reduce transmission, while keeping the risk of selection for drug-resistant viral variants low. Even when infection is prevented during pregnancy, the risk of acquiring infection by breast feeding remains significant and in some settings, is unavoidable. The ability of antiretroviral drugs or vaccines to limit transmission by breast milk is unknown. HIV vaccines are still in an early phase of development and have not yet been tested in newborns, in part due to concerns about potential of low immunogenicity due to transplacental transfer of maternal antibodies. Alternative strategies have been proposed to limit transmission using passive prophylaxis by human monoclonal antibody, but to insure product safety, trials have been slowed. Due to such concerns, animal models may provide an alternative for testing efficacy in human newborns. In this review, advances made using such models will be compared for mother-to-child transmission of lentivirus with that of HIV-1. In addition, some perspectives on integrating the data obtained from these models as a groundwork for future clinical work will be presented.

2. INTRODUCTION

Current global estimates for human immunodeficiency virus-1 (HIV-1) infection in children (those under 15 years of age) stand at a staggering 2.2 million infections with nearly 650,000 newly reported just in 2004 (1). It has been estimated that over 90% of HIV-1 infection in children occurs through perinatal transmission, or mother-to-child transmission (MTCT). Transmission from an HIV-1 infected mother to her child can occur *in utero* (during pregnancy), *intrapartum* (labor/delivery) and/or *postpartum* through breast milk. The relative risks of acquiring HIV-1 infection through any of the above-mentioned routes varies from 35-40%, with the *intrapartum* route accounting for approximately 60-70% of HIV-1 infection in infants and the *in utero* route accounting for the remaining 20-30% (2). The risk of acquiring infection increases by another 10-20% if the mother breast feeds her baby for prolonged periods of time (3-9). Understanding the host and virus factors involved may facilitate the discovery and development of better methods to limit or prevent MTCT. Maternal viral load at the time of delivery is the strongest known correlate of transmission (10-12). Other maternal factors such as recent infection, low CD4 counts (9), disease progression in the mother, severe vitamin A deficiency (9), frequent unprotected sex during pregnancy (13), maternal-neonatal Human Leukocyte

Antigen (HLA) concordance (14), and lower concentration of defensins in breast milk (15) may each play a role in increasing the odds of transmission. Antiviral drugs given prophylactically at the time of delivery have been shown to significantly reduce the maternal viral load at the time of transmission, thereby reducing the risk of *in utero* and *intrapartum* transmission (16-20). But administering antiretroviral drugs at the time of delivery may not be sufficient to prevent MTCT through breast milk. Perinatal transmission of HIV-1 is associated strongly with increased HIV-1 shedding observed in genital secretions of pregnant women (21, 22). Among high-risk female sex workers in a cohort in Kenya, hormonal changes during a female's reproductive cycle resulted in increased viral shedding in the genital mucosa, with the highest genital viral load and shedding observed during the late luteal phase and prior to menses (23, 24). This increased genital shedding may also result in increased rates of heterosexual and mother-to-child transmission. Reduction of viral loads not only in the plasma of pregnant women but also in genital secretions is therefore a target for interventions to reduce *intrapartum* transmission. The maternal virus inoculum, the virus that results in HIV infection of the human infant, is difficult to define for a variety of practical and ethical reasons, and importantly, this inoculum is distinct for all mother-infant pairs. Different studies have reported that either the major or the minor variant or in some cases even multiple maternal variants are transmitted to the infant (25, 26).

Although viral load is the major correlate of transmission, there is evidence that maternal cellular and humoral immune status can contribute to lower transmission rates. Immunosuppression is directly associated with increased HIV-1 levels in the genital mucosa (22). Though questions still remain concerning the exact nature of cytokine bias (Th-1 versus Th-2) in pregnancy, it is generally accepted that the balance tips more in favor of Th-2 (27-29). The balance between pregnancy-induced Th-2 bias and HIV-induced Th-1 bias may result in a compromised pregnancy. Mothers who do not transmit have higher frequencies of HIV-1 specific cytotoxic T-lymphocytes (CTL, or effector cells capable of killing target cells with Class I MHC bearing HIV-1 peptides on their surface) than transmitting mothers (30). Studies of neutralizing antibodies (NAbs, those antibodies that can block HIV infection *in vitro*) have been more difficult to interpret. The infant acquires maternal IgG transplacentally and through breast milk consumption, and HIV-specific NAb is typically of the IgG subclass. It has been reported that nontransmitting mothers have higher autologous NAbs (i.e. able to neutralize the concurrent autologous maternal virus) than HIV-1 transmitting mothers (31, 32). Pediatric viral isolates tend to be resistant to maternal NAbs (33, 34) consistent with the concept that they are escape variants. However, there are few studies that have systematically studied the interplay between the developing autologous NAbs in the mother and the infant and their relation to transmission of specific viral variants to the infant. Given that the timing of transmission is difficult to precisely define and the viral sequence identity between maternal and infant isolates, it is also difficult to distinguish whether the infant acquires multiple maternal virus isolates at different times of exposure--during gestation, at delivery and *postpartum* through breastfeeding. It remains to be seen whether the developing immune system in the infant is influenced by the pre-existing maternal immunity directed to circulating viruses. To the extent that neutralization-resistant or CTL-escape HIV variants are transmitted to an infant, these viruses impact the infant's immune system directly and indirectly by killing $CD4^+$ T cells and limiting the infant's capacity to control virus replication.

Despite more than 20 years of research to understand transmission and pathogenesis in adults and children, numerous questions still remain regarding factors involved in transmission of HIV from one host to another. Many of the most critical answers will come from ongoing and planned clinical studies, particularly as more effective drugs become available and promising vaccine candidates are available in adult and juvenile populations. Early news on vaccine immunogenicity in infants is encouraging. Phase I/II HIV vaccine studies done on infants born to HIV-infected women have shown that maternal antibodies do not inhibit infant immune response to the vaccine (35, 36) nor does HIV vaccination modulate infant response to subsequent childhood viral vaccines (37, 38). In fact, most childhood vaccines are recommended for HIV-infected infants and children.

Animal models have provided valuable insights into HIV pathogenesis and vaccines. HIV-1 infection in the human population is characterized by the prevalence of numerous subtypes and circulating recombinant forms, with each individual harboring a unique constellation of viruses, and transmission can occur by a variety of routes, both of which compound the difficulty in understanding parameters involved in transmission. Animal models provide a means to limit variables. They allow the study of these parameters with defined viral sequences, controlled exposure routes, and availability of sampling that can never be achieved in humans. This article will review current animal models of MTCT and their contributions to complementing our understanding of HIV-1 MTCT and disease in infants.

3. ANIMAL MODELS OF LENTIVIRUS MTCT

HIV-1 belongs to the lentivirus genus of the *Retroviridae*, so named because of the slow nature of disease progression in ungulates infected with species-specific lentivirus members. Early after the successful culture of HIV-1 *in vitro*, various isolates were cloned and sequenced, which allowed genetic classification of the virus to the lentivirus family, distinct from HTLV in the genus deltaretroviruses, its original designation (39-49). Investigators launched the search for laboratory species such as mice or rabbits, as well as nonhuman primates that could support the replication of HIV-1. HIV failed to infect either mice or murine cells *in vitro*, and infection of rabbits resulted in a relatively nonproductive infection (50-52). In parallel, there were efforts to develop animal models using other lentivirus family members, particularly feline immunodeficiency virus (FIV) in cats, and a search

for a murine member of the lentivirus family was initiated (53). As of 2006, many of the molecular and biological mechanisms involved in host restriction have been identified (54-57), opening the door to the potential for engineered viruses or hosts. Unfortunately for the field, to date there is no murine immunodeficiency virus (MIV), and engineered mice that can fully support HIV replication are also not yet available. For the purposes of understanding MTCT, important biological differences in gestation between different animal models such as placentation, provide a compelling argument to study models with the greatest degree of similarity to humans, namely the nonhuman primates.

Since the serendipitous discovery of simian acquired immunodeficiency syndrome (AIDS) in a group of rhesus macaques (*Macaca mulatta*) accidentally exposed to simian immunodeficiency virus (SIV) in the 1980s, the use of nonhuman primate models infected with simian viruses have helped in gaining valuable insight into HIV-1 transmission and pathogenesis (58). The primate lentivirus genus includes HIV-1, HIV-2 and SIV (59, 60), and these viruses infect a variety of nonhuman primates, endemic in certain species while leading to pathogenesis in others. The phylogenetic relatedness of SIV and HIV-2 has been used to document the origin of HIV-2 from Sooty mangabeys to humans, and HIV-1 also arose via cross-species transfer from chimpanzees (61-63). HIV-1 replicates well in humans and in chimpanzees (*Pan troglodytes*), but the use of the chimpanzee model has been limited by species protection, ethical considerations, and expense, as well as by the length of time required to develop AIDS, 10 years or greater. To better approximate HIV infection in simian models, chimeric viruses bearing key genes from HIV in the SIV backbone termed simian-human immunodeficiency virus (SHIV) have also been developed (64-66), and SHIVs have been adapted for pathogenicity in macaques by serial transfer. Several macaque species (*M. mulatta, M. fascicularis,* and *M. nemestrina*) can be infected by SIV and SHIV by any of several routes of infection, (*intraveneous*, *intramuscular*, *oral, intravaginal, or intrarectal)*. These infections typically result in detectable acute viremia accompanied by acute or gradual loss of peripheral and/or gut associated $CD4^+$ T cells, followed by a long asymptomatic period involving the establishment of a viral set point and development of antiviral humoral and cell-mediated immunity. AIDS in nonhuman primates, similar to AIDS in humans, is accompanied by immunologic failure and loss of $CD4^+$ T cells to below 200 cells per microliter of plasma. This does not always result in opportunistic infection. Studies in nonhuman primates enable the analysis of virological and immunological parameters in the context of an infecting strain with known genotypic and phenotypic characteristics and within a relatively short time frame of 1-3 years.

The nonhuman primate lentivirus models have been useful in evaluating therapeutic and preventive efficacies of anti-retrovirals, immune-based therapies and vaccines in adults, juveniles, and, more recently, in infants (58). Murine retrovirus and feline lentivirus models of perinatal transmission have been used to study aspects of MTCT that would be challenging to address in macaques, either due to their outbred population or their expense. This section will discuss and evaluate the limitations and promise of current animal models that address MTCT of HIV-1.

3.1. Murine models of perinatal transmission

Our extensive knowledge of the murine immune system makes inbred mice attractive as candidates to study HIV pathogenesis. However, mice are unable to support HIV replication due to restrictions occurring at many levels: lack of cellular receptors on target cells, inefficient viral gene expression, poor assembly and release of virions as a result of murine restriction factors (54, 55). Despite years of effort to overcome these restrictions by modifying mice to express human coreceptors in transgenic mice (67-70), the barriers have not been sufficiently breached to allow HIV-1 replication. Another approach has been to introduce human immune cells into mice lacking immunity, mice with induced severe-combined immunodeficiency (SCID) and reconstituted with human PBMC (SCID-hu) or human thymus or liver cells (SCID-thy) (71-74). Though these models can address questions of infection, the short-lived survival of these transiently reconstituted mice prevents direct breeding and analysis of MTCT. Lack of a MIV has led to the advancement of research on other rodent retroviral infections to examine some of the key questions in MTCT. Perinatal transmission can be studied in mice using Moloney murine leukemia retrovirus, MoMLV-TB, Ts1 (75, 76). Mothers infected with Ts1 at 72 hours post delivery resulted in 100% MTCT in 135 pups, suggesting post-gestational breast milk transmission. While this model, in conjunction with the SCID-hu mice, might be beneficial in dissecting the role that the developing thymus (74, 77-79) plays in perinatal transmission, this model cannot be used to test vaccine strategies directed against the HIV gene products because they will not be effective against MoMLV-TB. Perhaps the most important disadvantage of rodent models in looking at HIV-1 MTCT is that rodent placentation and kinetics of fetal/neonatal immune development differ greatly from humans, making rodents poor models for human transplacental, perinatal and breast milk transmission of viruses.

3.2. Feline models of perinatal transmission

Cats infected with feline immunodeficiency virus (FIV) have the potential to be models for perinatal transmission. Cats are natural reservoirs of FIV, and the information gleaned so far from the cat/FIV model has shown that there are many parallels between HIV-induced pathogenesis in humans and FIV-induced pathogenesis in cats (80, 81). Experimental FIV infection in pathogen-free cats results in an acute infection, followed by a long asymptomatic period associated with a progressive decline in peripheral $CD4^+$ T cells, and finally culminating in immunologic failure, development of opportunistic infections, diarrhea, wasting syndrome and death (81, 82). The feline model of perinatal transmission utilizes one of three types of experimental inoculation of cats: (i) during pregnancy (acute infection model); (ii) prior to pregnancy (chronic infection model); or (iii) after delivery

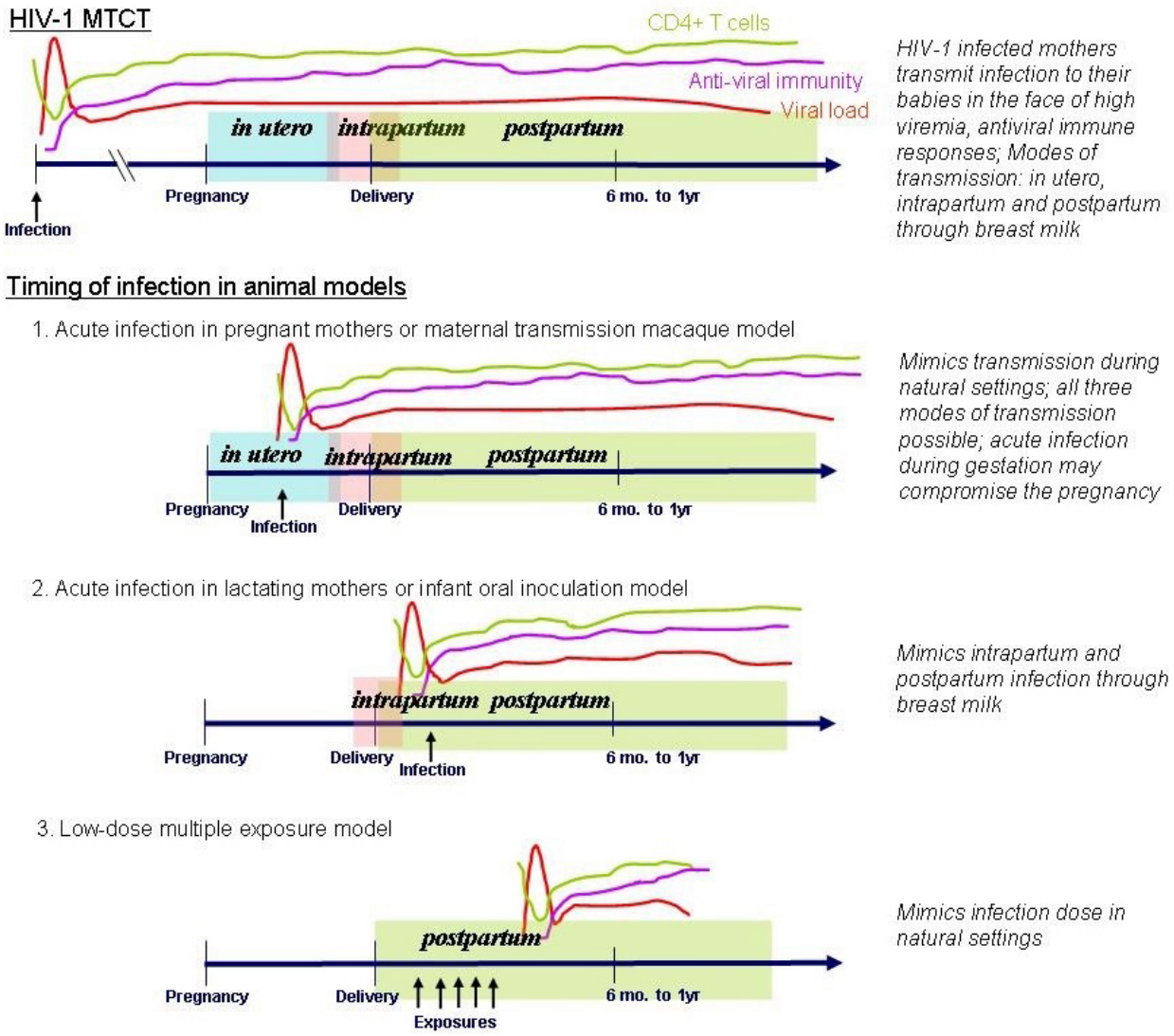

Figure 1. Animal models of perinatal transmission: timing of infection.

(*postpartum* model) (Figure 1). In any of the aforementioned models, queens are impregnated with FIV-negative males and are allowed to deliver vaginally or undergo Cesarean section (C-section). In the acute and chronic infection models, the use of FIV-naïve queens as surrogate mothers after birth facilitates the study of *in utero* and *intrapartum* transmission. In the *postpartum* model, infection of mothers after delivery and allowing the kittens to suckle from their infected mothers enables the study of breast milk transmission in isolation. Similar to HIV infection in pregnant women (83, 84), FIV infection may contribute to compromised pregnancy and spontaneous abortions (85) and can be transmitted vertically. Vertical FIV transmission has been observed with all three FIV clades (A, B, and C) suggesting that transmission is not clade dependent (85-87). Rogers and Hoover showed that term fetuses (n=23) collected by C-section from pregnant queens, and intravenously inoculated with acute phase FIV prior to conception, were found to be 60-95% infected as determined through FIV-specific DNA PCR. No FIV-specific antigens or FIV-RNA were present in any of the fetal tissues examined, suggesting that the infection was occult in nature (87). This rate of *in utero* infection is much higher than that reported in prior studies. Another report by Rogers and Hoover showed that the prevalence of fetal infection increased as the gestational age of the fetus increased (86) indicating that fetal maturity may influence timing of *in utero* infection, and that risk of *in utero* infection may be highest just prior to delivery. In a study by O'Neil *et al*. where queens were infected at least four months prior to conception, 38.5% of 26 kittens delivered vaginally and nursed by their biological mothers were infected either *in utero* just prior to delivery, during delivery, or through milk (88). This transmission rate closely mimics the transmission rate observed in children born to HIV-1 infected breastfeeding women in the absence of any preventive interventions. Transmission of FIV through breast milk occurs very efficiently. Through the

Table 1. Animal models of HIV-1 perinatal transmission: pros and cons

Animal species	Infecting viral strain	Timing of infection (Ref)	Advantages	Disadvantages
Murine	MoMLV-Ts1	Inoculation of lactating mothers 72 hrs post delivery (75, 76)	• Evaluate the role of thymus in mice infected at birth • Larger sample size	• HIV unable to infect mice and lack of murine immunodeficiency virus • Differences in placental ontogeny
Feline	FIV	Inoculating pathogen-free queens: • before pregnancy (chronic model) (85,88) • during pregnancy (acute model) (86,87) • during lactation (*postpartum* model) (88, 89, 150)	• Cats natural reservoir of FIV • Disease profile similar to HIV-1 • Shorter study time frame: gestational age of cats are ~62 days • Number of litter/queen is 2-5, larger sample size with fewer queens • Broad cell tropism of FIV	• Different virus entry receptor; cannot test antiviral strategies against virus-cell attachment and entry • Higher *in utero* TR than observed in humans • Differences in placental ontogeny • Lack of passive transfer of maternal IgG • Can't test HIV vaccine strategies in cats, FIV is >30% phylogenetically distinct from HIV
Non-human primates	SIV, HIV-2, SHIV	Inoculation of • pregnant dams (93-95, 101) • lactating dams (96, 99)	• Study correlates of MTCT in natural setting • Evaluate prevention of infection in the dam as way to prevent MTCT • Evaluate the effect of microbicides on the risk of MTCT • Evaluate mucosal viral and immune factors of transmission, including compartmentalization	• Variable transmission rate • Difficult to evaluate maternal antibodies already present in the infant • Need larger cohort to explore variables associated with MTCT • Tissue tropism/compartmentalization of viruses may be different than HIV-1 in humans
		Oral inoculation of neonatal macaques through: • single-high dose oral exposure (97, 98, 121) • multiple low-dose oral exposures (106)	• Not compromising proven female breeder macaques • Pathogenesis in neonatal macaques similar to HIV-1 infected infants • Good for studying IgG as blocking agents • Flexibility to evaluate • Pre-exposure and post-exposure prophylaxis in infants • The role of oral mucosal inhibitors in preventing oral infection in infants • Initial testing ground for vaccine/ drug therapies	
		• Single-high dose oral exposure	• Can achieve 100% transmission • Can infect with multiple variants and evaluate "sieving" of mucosal transmission	• High infection dose may not recapitulate infection dose in natural settings
		• Multiple low-dose oral exposures	• Recapitulates infection dose in natural settings	• May not observe "sterilizing immunity" in the vaccine arm as macaques will be exposed until infection occurs

two different model systems, acute infection in nursing queens (89) and chronic infection of queens followed by delivery and suckling (88), it has been shown that breast milk transmission in cats increases the overall risk of transmission to newborn kittens by 13.5%. This estimate is, again, similar to what is observed in humans.

Despite similarities in transmission rates and routes, the feline/FIV model also has several key differences that have limited its use for understanding HIV-1 transmission in humans. FIV has a broader host cell tropism than primate lentiviruses, which may impact rates of *in utero* transmission compared to what is observed in humans. It is also important to note that the route of transmission and the extent to which maternal antibodies reach the fetus is determined by placental structure. In humans and higher primates (e.g. chimpanzees and macaques), the placenta is hemochorial; i.e. maternal blood has direct contact with the trophoblast. Hemochorial placentation allows maternal IgG, but not IgM, IgA or IgE to be transferred to the fetus. As a result, in primates, maternal IgG enters the fetal bloodstream and primate newborn infants may have IgG levels and specificity similar to those of their mothers (90-92). In contrast, the feline placenta is endotheliochorial; here, the chorionic epithelium is in contact with maternal capillary endothelium. Thus, in cats, only about 5-10% of maternal IgG levels are transplacentally transferred while the majority of passive antibodies are transferred from mother to kitten via colostrum in the first few days of life (92). Notwithstanding the limitations, the feline FIV model of perinatal transmission has the potential to serve as adjunct testing ground for proof-of-concept experiments and supplement the knowledge gained through other animal models of perinatal transmission and in humans (Table 1).

3.3. Nonhuman primate models of perinatal transmission

The similarities between nonhuman primate and human physiology, pregnancy development, and ontogeny of the immune system make this an attractive host to study fetal and neonatal development and disease. Nonhuman primate models of perinatal transmission can be broadly classified as (i) **maternal transmission models** wherein pregnant dams are infected with the virus and checked for

transmission to infants born vaginally or through C-section and allowed to suckle *postpartum* and (ii) **infant oral inoculation models** wherein newborn macaques are exposed to the virus orally simulating the oral exposure that occurs during delivery and *postpartum* through breastfeeding (Figure 1).

3.3.1. Maternal transmission models

Some of the earliest attempts at mimicking perinatal transmission of HIV-1 were done through experimental infection of female rhesus macaques during gestation and monitoring of the infected pregnant dams for transmission to their infants. These studies evaluated the effect of timing of infection during various stages of gestation (early, mid, or late) on the transmission rate of either SIVdeltaB670 (93) or SIVsmm9 (94, 95) to infants. It was observed that timing of infection in pregnant dams is critical. Infection in the first trimester compromised the pregnancy resulting in a high number of spontaneous abortions. C-section resulted in a decreased infection rate, thus providing one of the earliest clues that the majority of HIV-1 MTCT may occur during delivery and that C-section may serve as a preventive measure in reducing the rate of MTCT. A follow-up study by the same group showed that infection with SIVdeltaB670 during the second trimester did not result in *in utero* or *intrapartum* infection. However, *postpartum* infection was observed in 3/4 of infants in the study (96). To circumvent low rates of transmission, a chronic fetal catheterization model of pregnant *Macaca nemestrina* was developed (35, 97, 98) wherein catheters were introduced into the maternal femoral artery and vein, fetal jugular vein, carotid artery and amniotic cavity. Dams were placed in a tether system allowing complete freedom of movement within the cage, enabling continuous sampling of maternal and fetal blood and amniotic fluid without sedation. While the 100% *in utero* infection observed in the 14 infants born to HIV-2 infected pregnant dams in this model has been useful for evaluating intervention strategies, the procedure may predispose the fetus to infection at the site of the catheter. To evaluate breast milk transmission in the absence of *in utero* and *intrapartum* transmission, Amedee and coworkers inoculated lactating female rhesus macaques (n= 14) with SIVdeltaB670 and followed transmission to infants (96, 99). The observed breast milk transmission rate of 71% is much higher than the rate observed in humans. Not all infants were infected at the same time despite the same timing of acute infection in the mothers, suggesting breast milk transmission occurs throughout lactation. Also, analogous to observations in humans, breast milk transmission in this model was dependent on the breast milk viral load irrespective of the maternal plasma viral load. In this model, early transmission was observed in females with rapid disease progression. Total immunoglobulin levels in plasma and milk were not predictive of infant infection through breastfeeding with the levels comparable between transmitting and non-transmitting mothers (100).

While the use of SIV in pregnant/lactating dams has been useful in delineating parameters in MTCT, the use of SIV precludes the direct evaluation of passive immunotherapy and vaccines that target the HIV-1 Envelope. Chimeric simian/human immunodeficiency viruses (SHIV) have the advantage of ensuring rapid infection, while developing immune responses to the HIV-1 envelope in the context of SIV background. Recently, we developed a maternal transmission model that utilizes *intravenous* inoculation of pregnant dams in their mid-second trimester with pathogenic CCR5 utilizing strain SHIV-SF162P3 (101). Primary infection in the second trimester was well tolerated and four of nine infants born were infected (transmission rate of 44.4%), with one infection *in utero*, and three *intrapartum* and/or immediately post-birth via suckling. Varying levels of binding and neutralizing antibodies were transplacentally transferred to infants. Transplacentally-acquired antibodies were detected in plasma on the day of birth and persisted for 5 weeks or more, depending upon the titer. Infants infected at or after birth controlled acute and post-acute viremia. Maternal transmission models have the advantage of addressing questions pertaining to MTCT in the context of maternal infection and maternal immune responses (Table 1). Additional maternal transmission studies utilizing SIV or chimeric SHIV will serve to increase our current understanding of the mechanisms of maternal-neonatal infection and aid in the development of intervention strategies.

3.3.2. Infant oral inoculation models

Oral infection of neonatal macaques simulates oral exposure through ingestion of maternal genital fluids (at delivery) and breast milk *postpartum* and also results in high plasma viremia concomitant with loss of peripheral $CD4^+$ T cells. Death is usually accompanied by immunologic failure, and the decrease of $CD4^+$ T cells to below 200 cells/microliter of plasma, though not always resulting in opportunistic infection. To facilitate oral exposure, newborn macaques have been exposed to undiluted pathogenic virus stock administered atraumatically by slow dispensing with the help of a syringe or soft pipette in the mouth. One of the challenges in developing animal models is the need to infect each animal reproducibly after a limited number of exposures, which has led to the use of high dose challenges to assure a very high or 100% transmission rate. This high transmission rate is beneficial in an animal model when evaluating intervention strategies, because smaller group sizes can be used to detect statistically significant differences in vaccine or therapy experiments. A 100% infection rate in neonatal macaques can be achieved by using a high dose of pathogenic SIV, HIV-2 287 or SHIVs (102-105). However the high dose that is used to ensure infection may be significantly higher than that faced by a human infant exposed to HIV-1 from its infected mother. Recent efforts to develop multiple low dose exposure infection have met with some success using SIVmac251 in newborn *M. mulatta* (Table 1). Multiple low-dose oral exposures may recapitulate exposure in natural settings as opposed to a single high-dose exposure. Newborns have been infected by exposure to one or more doses of a relatively high-titered virus in tissue culture medium at multiple week intervals. In a new method reported recently by Marthas and colleagues (106), four week old infant

macaques were handheld and bottle-fed thrice daily for 5 consecutive days, exposing the infant to 15 doses of diluted virus. This viral challenge system models colostrum and breast milk exposure and is amenable for use in testing for vaccine or immunotherapeutic efficacy. There are two potential methods to measure vaccine-induced protection in neonatal macaques infected by low-dose multiple exposures. One is to measure sterilizing immunity at comparable oral exposures (number of oral exposures needed to result in infection and inoculation dose). The second is to measure vaccine protection as a function of the number of oral exposures to achieve infection in the vaccinees in comparison to the control groups.

4. UTILITY OF LENTIVIRUS MODELS

Lentivirus models are most useful when they can provide information from experiments that are difficult to control for or unethical to perform in human studies. In the last 15 to 20 years, a great deal of information has been gained about the viral pathogenesis, host immunity, vaccine immunogenicity and efficacy, and therapeutic strategies in lentivirus animal models, principally in the nonhuman primate models. In recent years, several groups have expanded studies into newborn or infant macaques, in an effort to determine which types of vaccines and therapies might be effective at this stage of life. A major finding with significant ramifications was that live-attenuated vaccines that prevented superinfection (i.e. successful infection with a second pathogenic strain in presence of an attenuated viral strain) in juveniles or adult macaques led to rapid pathogenesis in newborns (107). Despite this high degree of pathogenicity in young macaques, the oral infection model has been useful to evaluate preventive therapeutic strategies. The following section will discuss utility of animal models in studying MTCT and how they relate to transmission of HIV-1 from infected mothers to their babies.

4.1. Transmission and Pathogenesis

Nonhuman primate models of lentivirus infection have been particularly useful for studying viral determinants of transmission. HIV-infected mothers are infected with virus from different subtypes, and they harbor diverse quasispecies variants (25, 26). Cohorts of macaque dams or infants can be infected with one viral isolate, thus controlling for effects of viral genotype. One of the earliest observations documenting transmission of distinct maternal variants was accomplished in the nonhuman primate model. Complementary to what was observed later in humans (25), all the mothers in the SIV macaque model were found to harbor a heterogeneous viral population, while their infants contained predominantly one variant. This supports the concept that a selective mechanism or a genetic bottleneck occurs during MTCT (108). Little is known about the specific characteristics of the transmitted maternal viral variants, although it is likely that viral variants derived from localized compartments in the genital tissues are preferentially transmitted. The authors of this study analyzed variants in the maternal blood (PBMCs) and did not compare viral sequences in the maternal genital areas with those found in the infant. Animal models enable invasive monitoring of the fetus and amniotic fluids, methods that are difficult to perform in humans and, in most instances, unethical. Though invasive procedures in animals may predispose the fetus to higher *in utero* infection, they are useful in determining the virus compartmentalization in the uterine and other genital tissues and fluids. It is through such procedures in the SIV macaque model that the relative proportions of HIV-specific neutralizing antibodies to binding antibodies were found to be higher in amniotic fluids than observed in the plasma. This suggests selective passive transfer of high titer virus-specific NAbs (109).

SIV infection of neonatal macaques results in sustained high virus load and rapid progression to disease, which has also been seen in human infants infected with HIV-1 (110, 111). In both SIV- and SHIV-infected macaques as well as in HIV-infected human, the gut is the predominant site of early infection (112-117). Serial sacrifice studies in primate models provide a means to evaluate the virologic and immunologic events occurring in lymphoid tissues such as spleen, thymus, lymph nodes and the intestinal tract. Recent work by Veazey *et al*., in SIV-infected neonatal macaques showed that the spleen and lamina propria in the intestine are primary sites for viral replication (111). These lymphoid tissues were found to harbor memory $CD4^+$ T cells suggesting that priming of neonatal T cells can occur *in utero*. Studies in SIV-infected neonatal macaques have shown that one reason for rapid pathogenesis and higher virus loads in infants could be due to higher numbers of target $CD4^+$ T cells and increased, persistent turnover of activated memory $CD4^+$ T cells compared to adults. In contrast to HIV-infected adults, HIV-1-infected infants tend to have more central nervous system (CNS) involvement, a tendency further supported by the presence of HIV-1 in fetal CNS tissue from SIV infected neonatal macaques (118). HIV-1 infection of the brain has been shown to be associated with dementia. Future studies of CNS HIV infection in newborns and their role in the behavioral development of infected children needs to be conducted, an area accessible for study in macaque models. Similar to disease pathogenesis in HIV-1 infected infants, oral SIV/ SHIV infection in newborn macaques often results in accelerated disease, both in contrast to adult infection. This faster disease progression in neonatal macaques allows evaluation of potential antiviral therapies within a shorter time frame, and more risky approaches can be explored.

4.2. Drug studies

Efficacy of Azidothymidine (AZT, also Zidovudine) in limiting MTCT was first demonstrated in the clinic, leading to adoption of ART and a significant drop in the rate of MTCT in resource-rich settings where breastfeeding could be eliminated and C-section could replace vaginal birth. However, human clinical trials are expensive, time consuming, and can result in patient loss to follow-up. Animal models can be very useful in weeding out less promising antiretroviral strategies and identifying the more promising ones to enter clinical trails. Evaluation of 9-(2-phosphonomethoxypropyl)adenine (PMPA, now Tenofovir) in macaques showed promise and suggested that

this drug could be reevaluated for clinical use (119). Long term post-exposure prophylaxis with PMPA reduced viremia in treated infected infants in comparison to controls. Emergence of PMPA-resistant viruses did not result in viral rebound as has been seen in AZT- or ART-resistant strains (120). In studies performed in *M. nemestrina* with the highly pathogenic HIV-2-287, pregnant dams and infants were catheterized as described above to allow for direct fetal monitoring. Simultaneous sampling of maternal blood, fetal blood, and amniotic fluids in the chronically catheterized pregnant dams allowed the evaluation of triple therapy (Zidovudine, Didanosine, and Indinavir) during pregnancy, and showed reduced *in utero* transmission rates (121). Recent work by VanRompay and coworkers in their SIV/newborn macaque model showed that the status of immunodeficiency can influence the success of an antiretroviral treatment, in this case Tenofovir monotherapy, and may be age dependent (122). Tenofovir treatment initiated during the chronic stage of infection, usually effective in reducing viremia in juvenile and adult macaques, failed to reduce viremia in newborn macaques and yet resulted in prolonged survival despite high viral loads (122). The immunologic abnormalities observed more frequently in HIV-infected infants coupled with the higher replication potential of HIV in infants are key variables in the age-specific lack of response to treatment. Such questions, thus far, can only be adequately addressed through the oral infection of neonatal macaques, where timing of treatment in association with therapeutic benefits can be closely monitored.

4.3. Immune-based interventions

Two groups have examined neonatal macaques orally-exposed to uncloned SIVmac or pathogenic SHIV shortly after birth and have evaluated efficacies of potential vaccines, and/or prophylactic immune-based therapies. Passive immunization of infants with hyperimmune serum from adult macaques protected neonatal macaques from oral exposure with SIVmac251. However, as the antibodies in the hyperimmune serum waned, the infants became susceptible to superinfection suggesting that there is a window during which passive therapy may be beneficial (103). The character of the protective antibody in this hyperimmune serum has recently been shown to include antibody-dependent cytotoxic cell (ADCC) activity, but not neutralizing activity (M. Marthas and D. Forthal unpublished observations) (123-125). The protective outcome in this system is consistent with data from adult macaques treated with passive IgG in the form of neutralizing monoclonal antibody (mAb) cocktails. Triple or quadruple combinations of broadly neutralizing mAbs are necessary and sufficient to confer protection in newborn macaques exposed orally to subtype B SHIVs (SHIV-vpu+, SHIV89.6P) and subtype C SHIV (4, 126-129). Sterilizing protection is time-dependent and can be achieved even when passive immunotherapy is administered after viral exposure, as long as the NAbs target the conserved regions of HIV-1 envelope. These results are similar to those seen in juvenile rhesus macaques, where *intravenous* infusion of mAbs, alone or in combination with HIV immune globulin (HIVIG), protected macaques from intravaginal challenge (130, 131). Juvenile macaques infected with pathogenic SIV and treated post-infection with high doses of neutralizing IgG, or SIVIG, remained disease-free longer than controls, and the treatment also accelerated the development of autologous NAbs by as much as 12 weeks (132). This study suggests that passively acquired maternal IgG might be beneficial to infants, even when maternal virus is transmitted, and deserves further study.

4.4. Vaccine studies

Mice and rabbits are frequently utilized as a "first-step" in HIV-1 immunogen design (133) to study of development of HIV antigen-specific immunity. However, the absence of challenge models has limited interpretation of the findings. Immunogenicity studies in rodents or rabbits are typically followed up in macaques to determine how effective the particular vaccine is in protection from challenge with a primate lentivirus. Vaccination of pregnant macaques has been shown to protect newborns against mucosal SIV infection (134) thus providing support for prevention of MTCT through vaccine-based interventive approaches. Vaccine studies in orally exposed neonatal macaques can model prevention of MTCT in newborns through *intrapartum* or *postpartum* modes. Neonatal macaques immunized at birth and at 3 weeks of age with either modified vaccinia virus Ankara (MVA) expressing SIV Gag, Pol, and Env (MVA-SIVgpe) or live-attenuated SIVmac1A11 followed by oral challenge with pathogenic SIVmac251 showed a delayed progression to disease (135). An interesting observation in this study was the partial effectiveness of the nonpathogenic MVA vector alone, suggesting that innate or other nonspecific immunity may be implicated in limiting infection in newborns exposed to maternal virus. Further experimental work will be needed to identify the mechanisms underlying this observation. Additional work has demonstrated an important principle, that SIV vaccines given to newborn macaques are immunogenic. These macaque studies support the concept that HIV vaccines given to infants within the first few days and weeks of birth can elicit effective immune responses and thus may be utilized in newborns in conjunction with other childhood vaccines.

5. LESSONS LEARNED AND PERSPECTIVES FOR THE FUTURE

Compared to the large body of published literature in juvenile and adult macaques, there have been relatively few studies to date in nonhuman primate infants. Yet these studies have been important in raising questions about safety and in challenging assumptions such as whether results of vaccine studies in adults can be extrapolated to infants. How can animal models best be utilized to contribute to reductions in MTCT? We favor the emphasis of three major areas for future experimentation, all of which can provide valuable insight in areas that are difficult or impossible to assess with clinical work. The first of these is the continued development and use of animal models for MTCT, including breastfeeding exposure. A second area is the comparative testing of vaccines that are in adult clinical trials to prevent and/or modulate infection in newborns. Finally, a third important

area is the testing of novel therapeutics for newborns and infants *versus* placebo.

5.1. Model development

A major area for clinical impact is reducing transmission in resource-poor areas, where eliminating breastfeeding is clinically indefensible. To understand the types of vaccines and therapies that will be effective in preventing breast milk transmission, a reliable model that mimics exposure seen in human infants is a necessity that will be an important advance. As a part of these studies, the development of more sophisticated analyses of differences in breast, vaginal or cervical compartments will yield a better understanding of mucosal viral and immune factors that contribute to risk associated with transmission. Studies can then be performed to systematically examine the role of individual viral variants or the role of NAbs in transmission. An example of this type of study is to examine necropsy samples for tissue distribution of the virus and the potential for compartmentalization in the mother and the infant. Undoubtedly, a suitable animal model of HIV-1 MTCT will help ascertain aspects of fetal and neonatal immunity that will play an important role in the success of prophylactic and therapeutic vaccine approaches.

5.2. Prophylactic and therapeutic vaccines

Because the HIV pandemic cannot be stopped in the near term, universal infant/pre-adolescent HIV vaccines may be the most realistic approach in countries with high incidence and prevalence in young adults. Vaccine studies for other childhood infectious agents demonstrate that newborns are capable of mounting robust cellular responses. Under the appropriate conditions of stimulation, mature cellular responses can be elicited very early in life against intracellular pathogens (136, 137). This is promising as we explore the boundaries of an effective HIV vaccine, particularly in infants. Studies in newborn and infant macaques can help inform the rate at which vaccine immunity can be elicited with different products. Vaccine studies in adult macaques have helped us gain insight into the subtleties of cellular and humoral arms of the immune system, and in recent years have confirmed that for an HIV vaccine to be successful, we will need to target both arms of the adaptive immune system (138-140). It is possible, however, that vaccines may need to be "tailor-made" for infants. We have evidence from other studies in humans that adult and infant vaccine responses can differ significantly and that these differences may be attributed to the nature of the infectious agent (HIV, HSV, HCMV) and the vaccine modality (Th1 versus Th2 bias) (136). A number of phase I/II clinical trails are currently underway in children (141) and results are encouraging but not entirely conclusive. A recent phase I trail, PACTG 326, that employed a canarypox vectored HIV was found to be safe but poor in immunogenicity when compared to immune responses in adult studies (141, 142), thus reaffirming the notion that vaccine response may differ between adults and infants. Some of the approaches currently in multiple Phase I/II trials may be effective in the therapeutic mode in newborns, due to their ability to elicit both innate and acquired responses (135). Nonhuman primate models of HIV-1 MTCT can, therefore, be pivotal testing grounds of infant vaccine strategies that involve the (i) identification of candidate immunogens that induce long-lasting and broad CTL and NAb immunity and (ii) immune augmentation through adjuvants while we are on the road for better and novel therapeutics.

5.3. Novel therapeutics

Antiretroviral treatment of mothers and babies at the time of parturition effectively reduces MTCT. Improvements in preventing MTCT may be achieved by more effective ART or vaccination in infants and young children, or combination strategies. There is a temptation to envision that MTCT can be effectively eliminated by ART treatment of the mother around the time of parturition (143). But we have learned that drug resistant variants can arise after only a limited treatment of the mother (144, 145), which puts the infant born from the next pregnancy at much greater risk for infection with a drug-resistant variant. The use of microbicides has been proposed to prevent heterosexual transmission. Recently, significant protection against a CCR5-using virus, SHIV-SF162P3, was observed in a high-dose vaginal transmission macaque model using inhibitors that targeted HIV-target cell attachment and entry (146, 147). The use of microbicides and disinfection of the birth canal could potentially prevent the infant from exposure to infective cervicovaginal secretions during delivery. However, trials of microbicides are considered unethical for pregnant women, some microbicide products could enhance vaginal and/or cervical inflammation even without clinical signs, leading to enhanced transmission. Consistent with this idea, past clinical trials have shown that microbicides did not result in reducing the rate of MTCT (2, 148). The theoretical potential of this approach can however be explored in an animal model, particularly using antiviral approaches that are less likely to result in inflammation, such as monoclonal antibodies (147, 149). Efforts to determine the effectiveness of passive IgG (HIVIG) were thwarted by an insufficient HIV transmission rate in Uganda. Concerns over safety and potential side effects have appropriately slowed the use of human mAbs as passive prophylaxis in infants. All future clinical work will require that control arms receive the current standard of care, and as a result it may be more difficult, more expensive, and/or more time-consuming to discern improvements in the test arm. Yet the trial sizes will need to be large, as noted in the excellent review by Thorne and Newell (2). If data from animal models can test new concepts directly, by comparison with placebo in lieu of drug treatment, then it may be possible to more quickly identify improvements to treatment that can then be validated in clinical trials. A result of this combined effort may mean the accelerated development of methods to combat infection in HIV-exposed newborns and children and pre-adolescents in their sexually active years.

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Abbreviations: HIV-1: Human immunodeficiency virus type 1, HIV-2: Human immunodeficiency virus type 2, SIV: Simian immunodeficiency virus, SHIV: Simian/Human immunodeficiency virus, FIV: Feline immunodeficiency virus, MIV: Murine immunodeficiency virus, MoMLV: Moloney Murine leukemia Virus, AIDS: Acquired immunodeficiency syndrome, MAIDS: Murine acquired immunodeficiency syndrome, MTCT: Mother-to-child transmission, C-section: Cesarean section, ARV: Anti-retroviral, ART: Anti-retroviral therapy, TR: Transmission rate, HIVIG: HIV immunoglobulin, HLA: Human Leukocyte Antigen, MHC: Major Histocompatibility Complex, CTL: Cytotoxic T lymphocyte, NAbs: neutralizing antibodies, mAb: monoclonal antibody, IgG: Immunoglobulin G, IgA: Immunoglobulin A, IgM: Immunoglobulin M, IgE: Immunoglobulin E, PBMC: peripheral blood mononuclear cells; SCID: severe combined immunodeficiency, PMPA: 9-(2-phosphonomethoxypropyl)adenine, MVA: Modified Vaccinia Ankara, AZT: Azidothymidine

Key Words: HIV-1, SIV, SHIV, FIV, MIV, Mother-to-child transmission, Animal models, Nonhuman primates, Cats, Mice, Feline, Murine, Neonates, Vaccines, Therapies. Pediatric pathogenesis, AIDS, Review

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