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Antibodies for prevention of mother-to-child transmission of HIV-1

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Abstract

Purpose of review—Although antiretroviral (ARV) prophylaxis can reduce mother-to-child transmission (MTCT) of HIV-1 to less than 2%, one-quarter of a million infants continue to be infected with HIV-1 annually. ARV prophylaxis alone will fail to eliminate infant HIV-1 infection because of issues of maternal adherence, toxicities, ARV-resistant virus strains, and acute maternal infection. Effective maternal and/or infant immunization will likely be required to achieve the goal of an HIV-free generation.

Recent findings—This article describes recent studies of antibody responses that protect against vertical HIV-1 transmission. Studies have shown that maternal neutralization breadth is not a critical factor in MTCT, yet the ability of maternal plasma to neutralize autologous virus variants may be important in infant protection. There is also new evidence that infants mount robust and durable antibody responses to HIV-1 envelope following vaccination and can develop broad neutralization during infection. Finally, passive immunization of infants with highly potent and broad neutralizing antibodies may be an effective strategy to protect infants against infection with postnatally transmitted variants.

Summary—Defining the characteristics of maternal and infant antibody responses that protect against MTCT will inform development of effective passive and active immunization strategies that will likely be required to eliminate pediatric HIV-1.

Keywords

antibody; HIV-1; mother-to-child transmission

INTRODUCTION

One-quarter of a million infants continue to become infected with HIV-1 annually, despite considerable scale up of highly effective maternal/infant antiretroviral (ARV) prophylaxis

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Conflicts of interest

S.R.P. serves on the scientific advisory board of Redbiotec. M.A.M. is a member of the Glaxo Smith Klein advisory board for the Belimumab Pregnancy Registry. The remaining author has no conflicts of interest.

[1]. For a number of reasons (including acute maternal HIV-1 infection during pregnancy/breastfeeding, ARV-resistant virus strains, maternal/infant ARV toxicities, and poor maternal adherence) ARV prophylaxis alone will be unable to eliminate pediatric HIV-1 infections. The development of immunologic strategies, such as a maternal or infant HIV-1 vaccine or infant passive immunization with broadly neutralizing antibodies (bNabs), will likely be required to achieve a generation free of HIV-1.

THE SEARCH FOR MATERNAL ANTIBODY CORRELATES OF PROTECTION AGAINST VERTICAL HIV-1 TRANSMISSION

As infants are passively immunized with maternal antibodies via placental transfer prior to birth, the setting of mother-to-child HIV-1 transmission (MTCT) is ideal for investigating the ability of pre-existing, naturally elicited HIV-1-specific antibodies to protect against virus acquisition. In fact, in the pre-ARV era, the majority of infants (60%) remained uninfected despite chronic HIV-1 exposure *in utero*, during delivery, and via breastfeeding, suggesting natural immune protection against virus acquisition. Recognizing this unique setting in which to examine the role of antibodies in protection against virus transmission, several studies have addressed the impact of maternal antibodies on perinatal HIV-1 transmission risk. Although several studies suggested a relationship between maternal antibody responses and vertical HIV-1 transmission risk, others studies were unable to confirm these associations [2]. Reasons behind the ambiguity in these results include small cohort sizes, lack of control for known risk factors of HIV-1 acquisition (such as maternal viral load and $CD4^+$ T cell count), variable timing of sample collection, disparate timing and methods of infant HIV-1 diagnosis, and potential clade-specific differences in virus–antibody interactions. These initial studies of the relationship between maternal antibody responses and MTCT suggested that the magnitude of the maternal HIV-1 envelope (Env)-specific IgG antibody responses, and specifically the IgG response against the third variable loop, predicted reduced transmission risk [3,4]. Subsequent studies did not confirm these associations between the total HIV-1 Env-specific response and transmission risk [5-7], suggesting that the function, rather than the magnitude, of the maternal antibody responses best predict the risk of MTCT. Thus, the humoral immune correlates of protection against infant transmission risk remain ill-defined. This line of investigation remains an important area of research, as defining the characteristics of maternal antibody responses that contribute to protection against MTCT would provide immunologic targets for vaccine development to prevent vertical HIV-1 transmission.

ROLE OF FUNCTIONAL ANTIBODY RESPONSES IN PROTECTION FROM MOTHER-TO-CHILD TRANSMISSION

As the association between maternal HIV Env binding antibody responses and transmission risk was inconsistent across studies, attention was turned to the ability of neutralizing antibodies to block MTCT. A possible role for neutralizing antibodies has been supported by nonhuman primate studies demonstrating that infant passive immunization with a cocktail of HIV-1-neutralizing antibodies provided partial protection against oral simian human immunodeficiency virus transmission [8]. Several studies confirmed that most infant

infections are established by a single transmitted variant [9-11], paralleling that of adult HIV-1 transmission [12], and suggesting that neutralization escape may define the transmitted variant. Moreover, transmitted variants may have characteristics that allowed them to escape this maternal antibody response [9,10,13,14]. Yet, some recent studies of maternal heterologous neutralization in various mother–infant cohorts using state of the art, standardized neutralization assays against clade-matched variants [15,16■] have revealed no association of maternal heterologous virus neutralization and infant transmission. Infants are solely exposed to maternal viruses and are passively immunized with maternal antibodies raised against autologous viruses. Thus, it is potentially unsurprising that neutralization breadth would not be a critical factor in the prevention of MTCT.

A few studies have emerged that revealed particular, highly specific maternal antibody responses that predicted the risk of MTCT in certain cohorts, and these findings may be clues to the types of antibodies that can mediate protection in the MTCT setting. In the study of a Thai mother–infant cohort, neutralizing responses against a particular clade-matched virus strain (CRF01_AE.MBA) predicted the risk of MTCT which may reflect specific epitopes that are exposed on that isolate [17]. Another recent study linked maternal antibody responses against gp41 epitopes with reduced risk of vertical HIV-1 transmission [18]. Finally, antibody-dependent cell cytotoxicity responses against gp120-coated target cells were reported to be of higher magnitude in the breast milk of mothers with high breast milk virus load who did not transmit the virus via breastfeeding compared with transmitting mothers [19]. Yet, the protective mechanism that links all of these identified, highly particular antibody responses is unclear. These antibody responses may in fact be surrogates for an unmeasured, underlying antiviral mechanism that blocks virus transmission from mother to child. One important, yet typically unmeasured antibody response is the ability of maternal antibodies to neutralize autologous viruses. The isolation of autologous maternal variants from large cohorts of mother–infant pairs is resource heavy, and therefore has not previously been attempted. It is possible that these highly specific antibody responses identified to be associated with reduced risk of MTCT in various cohorts are biomarkers of the ability of maternal antibodies to neutralize their own circulating virus strains.

THE POTENTIAL UNIQUE ROLE OF AUTOLOGOUS VIRUS NEUTRALIZING ANTIBODIES IN MOTHER-TO-CHILD TRANSMISSION

The role of autologous neutralizing antibodies in MTCT has yet to be elucidated, but evidence from other perinatally transmitted infections suggests that maternal antibodies could modulate transmission. Infections such as herpes simplex [20] and cytomegalovirus [21] have reduced transmission and disease in the presence of maternal antibodies raised against autologous virus strains; conversely, the highest rates of transmission occur during acute infection. In this latter aspect, HIV-1 is thought to be similar – exposure that occurs during acute infection has been associated with a high rate of transmission [22], and the level of viremia may not be solely responsible [23]. Antibodies arise in HIV-1-infected persons shortly after the transmission event [24] and the initial response is to the transmitting virus and primarily directed against gp41 [25]. Early autologous virus neutralizing antibody responses, that arise within several months of infection, are unable to

contain the ongoing infection as concurrent virus evolution results in escape variants that always stay ahead of the antibody response [26,27]. In some individuals, the coevolution of virus and antibody results in the development of neutralization breadth [28], and during chronic infection, some degree of neutralization breadth develops in many infected persons [29]. Although heterologous virus neutralization does not appear to be important for prevention of vertical transmission, it is possible that neutralization breadth specifically against autologous viruses is sufficient to prevent MTCT, and work is ongoing to investigate that possibility. Data to date have been mixed, with some studies showing a role for antibody-mediated selection of transmitting viruses [9] whereas others do not [30]. Nevertheless, given the persistence of MTCT, determination of an immune correlate that can be harnessed to further reduce transmission is critically important.

INFANT PLACENTALLY-ACQUIRED ANTIBODIES AND PREVENTION OF HIV-1 ACQUISITION

Previous investigations of the role of HIV-1 Env-specific antibodies during MTCT have largely focused on those of HIV-1-infected transmitting and nontransmitting mothers. However, whether antibodies block HIV-1 transmission in mothers or prevent the establishment of HIV-1 infection in infant is still unknown. Interestingly, simian immunodeficiency virus vaccination of pregnant rhesus monkeys can protect their offspring from an oral simian immunodeficiency virus challenge [31], suggesting that maternally acquired antibodies can block virus acquisition in infants. Maternal IgG antibodies are passively transferred across the placenta to the fetus through interaction with the Fc neonatal receptor [32]. As the binding of IgG to the Fc neonatal receptor can be saturated, levels of specific antibodies are sometimes different in infants when compared with their mothers [33]. The transport of IgG across the placenta also depends on gestational age [34] and IgG subclass [35]. Moreover, maternal infections including HIV-1 can impact IgG transplacental transfer [36,37]. Thus, maternal antibodies at the time of delivery may not fully represent the specificity and magnitude of infant antibodies at birth.

The transplacental transfer of HIV-1 Env-specific binding and neutralizing antibodies was recently investigated in 60 mother–infant pairs from the Nairobi breastfeeding trial [16■]. While a strong correlation was observed between maternal and infant HIV-1 Env-binding antibodies; for two out of three viruses tested, only moderate correlations in neutralizing titers were observed among mother–infant pairs. This suggests possible differences in maternal and infant antibody specificities. Accordingly, a small early study investigating HIV-1 Env-specific IgG antibodies in the serum of five HIV-1 infected women and their aborted fetuses reported variations in transplacental transfer between antibodies of different specificity and subclasses [38]. Although the few large studies investigating neutralizing antibody responses in infants have reported no association between infant heterologous neutralization and reduced risk of infection [16■,39], whether the ability of placentally transferred antibodies to neutralize autologous maternal viruses contributes to infant protection remains unknown. Thus, investigations of antibody responses in large cohorts of HIV-1-exposed infected and uninfected infants including epitope-specificity, IgG

subclasses, autologous virus neutralization, and nonneutralizing functions are needed to fully understand the role of HIV-1 Env-specific antibodies during MTCT.

INFANTS CAN DEVELOP ROBUST AND DURABLE HIV-1 ENVELOPE-SPECIFIC ANTIBODY RESPONSES

A pediatric vaccine could be an effective strategy to prevent postnatal HIV-1 infections that continue to occur despite the availability of ARV prophylaxis. However, no pediatric vaccine efficacy trials have been conducted to date, and so whether infants can develop protective antibody responses is unknown. Importantly, because of qualitative differences between adult and infant immune systems, HIV-1 vaccination could induce different antibody responses in adults and infants. The recent identification of antibody responses associated with HIV-1 acquisition risk in the moderately effective RV144 adult HIV-1 vaccine trial [40] provides a unique opportunity to explore if previous vaccines including those tested in infants elicited potentially protective responses.

We recently analyzed samples from the historical Pediatric AIDS Clinical Trials Group (PACTG) protocol 230 and 326 to determine if infant vaccination can induce IgG antibodies against the HIV-1 Env variable loops one and two as this response was associated with decrease risk of HIV-1 acquisition in the RV144 trial [41■■]. In PACTG 230, HIV-1 exposed infants were randomized to receive four doses of vaccine between zero and 20 week of age [42] and were immunized using either a recombinant gp120 (SF-2 strain) with MF-59 as adjuvant (Chiron vaccine) or a recombinant gp120 (MN strain) with alum as adjuvant (VaxGen vaccine). In PACTG 326, HIV-1-exposed infants were immunized with an ALVAC prime/ALVAC+AIDSVAX (B/B)+alum boost vaccine regimen between zero and 12 weeks of age [43]. At week 24 of age, 71–98% of vaccinated infants had detectable anti-V1V2 IgG antibodies (VaxGen 71%, ALVAC/AIDSVAX 86%, and Chiron 98%), indicating that the three vaccine regimens induced potentially protective anti-V1V2 IgG at a frequency similar or higher to the RV144 vaccine in adults [44]. Importantly, at peak immunogenicity the concentration of anti-V1V2 IgG in infants vaccinated with the Chiron vaccine was 20 times higher than in RV144 vaccine recipients. Moreover, as with the RV144 vaccine in adults [45], the Chiron vaccine regimen induced short-lived, potentially protective anti-V1V2 IgG3 antibodies in infants. However, more durable IgG1 responses were induced by the infant vaccine. Interestingly, at week 104 of age, 61% of infants vaccinated with the rgp120+MF-59 (Chiron vaccine) still have detectable anti-V1V2 IgG antibody responses. This relatively durable antibody response is significant as a pediatric vaccine would need to be effective at least throughout the first 2 years of life to cover the breastfeeding period.

Although elicitation of bNabs is thought to be important for an effective HIV-1 vaccine, most vaccines tested to date in adult populations, including the moderately effective RV144 vaccine failed to elicit antibodies that neutralize tier two HIV-1 variants. Similarly, the vaccines used in PACTG 230 and PACTG 326 did not induce bNab responses [41■■]. It was recently reported that, as in adults, bNabs can be detected in the plasma of HIV-1-infected infants several months after infection [46■■]. This finding may indicate that a vaccine capable of eliciting broadly neutralizing responses in adults could also induce

neutralization breadth in infants. Altogether, these recent investigations demonstrate that infants are able to mount potent antibody responses following HIV-1 infection or vaccination. This suggests that developing a pediatric HIV-1 vaccine may be a reachable goal and highlights the need to include infants in future vaccine trials.

INFANT PASSIVE IMMUNIZATION TO PROTECT FROM POSTNATAL HIV-1 TRANSMISSION

A new area of great interest for the prevention of MTCT is the passive administration of bNabs to HIV-1-exposed infants. Early studies in nonhuman primates demonstrated that passively immunized neonatal monkeys can be protected from oral simian human immunodeficiency virus challenge [8,47], yet, the administration of polyclonal hyper-immune globulin preparations to HIV-1 infected pregnant women and/or HIV-1-exposed infants did not reduce the rate of vertical transmission [48,49]. Enthusiasm in the field for passive immunization of infants has been reinvigorated by the isolation of monoclonal antibodies capable of neutralizing the majority of circulating HIV-1 strains. In fact, the potential efficacy of these new generation bNabs in protection against virus acquisition has been established in both adult and infant nonhuman primate studies [50-52]. Recent studies by our group and others have evaluated the ability of these bNabs to neutralize maternal and infant viruses [53■,54■,55,56■]. The majority of infant acute viruses appear to be sensitive to neutralization by bNabs and no difference in neutralization titers was observed when maternal and infant variants were compared. In our study, we measured the ability of eight recently isolated bNabs (PG-9, PG-16, VRC01 3BMC117, NIH 45–46, CH31, VRC03, and VRC04) to neutralize seven clade C postnatal infant transmitted/founder viruses. All variants were neutralized at least by one bNab. Interestingly, PG-9 neutralized all seven viruses whereas PG-16 and VRC01 neutralized six of seven infant postnatal transmitted/founder viruses with infectious concentration$_{50}$ below 2 μg/ml [54■]. Moreover, in 23 Zambian mother–infant pairs, PG-9, PG16, and VRC01 were recently shown to neutralize all variants isolated from 65 to 72% of patients [56■] (Table 1). Clinical trials of passive immunization with bNabs in infants of HIV-1-infected women with high risk of transmission in the USA and in HIV-1-exposed breastfed African infants will define the potential impact of this strategy on MTCT.

SUMMARY

ARV prophylaxis has reduced MTCT in developed countries to below 2%, but this strategy still faces important challenges in areas of high HIV-1 prevalence. The addition of antibody-based therapies such as vaccination or passive immunization to current prevention packages may help achieve the goal of a generation free of HIV-1. The development of these immunologic strategies will require a better understanding of the role of HIV-1 Env-specific antibodies during MTCT and of the mechanism of potential protection. Moreover, the inclusion of infants in the testing of promising strategies is warrant for the identification of potentially efficacious interventions.

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KEY POINTS

- The magnitude and breadth of maternal antibody neutralization of heterologous HIV-1 variants is not likely a key factor in protection against mother-to-child HIV-1 transmission, yet the response against the autologous virus may be important in this transmission setting.
- Infant transmitted/founder HIV-1 variants are predominantly sensitive to neutralization by the new generation broadly HIV-1-neutralizing antibodies, and thus passive immunizations of infants at birth with these agents will likely provide protection to the infant against HIV-1 acquisition in high risk maternal virus exposure settings.
- Infants can mount robust and durable antibody responses to HIV-1 Env immunization that are similar or higher magnitude to those in adults, and therefore should be included in HIV-1 vaccine efficacy trials.

Table 1

Recent studies assessing the sensitivity of maternal/infant transmitted virus to neutralization by new generation broadly neutralizing antibodies

Viruses tested	bNabs tested	Results	Ref
Env variants from four mother–infant pairs (intrauterine and intrapartum transmission)	PG-9, PG-16	All infant viruses (n = 6) neutralized by PG-9 and PG-16	[55]
Env variants from 12 HIV infected transmitting mothers (n = 59); seven HIV infected nontransmitting mothers (n = 26) and 10 HIV infected infants (n = 22).	NIH 45-46W, PGT-128, PGT-121, PG-9, PGT145, VRC01	All infant viruses neutralized at least by one bNab. Except for PGT145, tested bNabs neutralized 77–86% of early infant viruses	[53■]
Postnatal infant transmitted/founder Env variants (n = 7)	PG-9, PG-16, VRC01, VRC03, VRC04, 3BMC117, NIH 45–46	All viruses neutralized by PG-9. PG-16 and VRC01 neutralized six of seven postnatal viruses	[54■]
Env variants isolated from 23 mother–infant pairs (184 from mothers and 71 from infants)	PG-9, PG-16, VRC01, NIH 45-46^{G54W}	65–78% Neutralization coverage for PG-9, PG-16, VRC01, and NIH 45-46^{G54W} PG9 + NIH 45-46^{G54W} neutralized all viruses from 87% patients	[56■]

bNabs, broadly neutralizing antibodies; Env, envelope.