REVIEW ARTICLE

BioDrugs 1999 Jan; 11 (1): 31-41
1173-8804/99/0001-0031/$05.50/0

Current Issues in the Immunoprophylaxis of Vertical Transmission of HIV

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Abstract

Humoral immunity is thought to play an important role in the natural history of HIV infection. It has been hypothesised that the presence of high titre neutralising antibody may protect against the maternal-fetal transmission of HIV-1 infection. HIV-Ig is a passive antibody preparation consisting of highly purified immune globulin containing high titres of antibody to HIV structural proteins. It contains considerable functional antibody in virus neutralisation and antibody dependent cytotoxicity assays. This product (and others) have undergone extensive investigation in preclinical (*in vitro* and animal models) and clinical trials. In a randomised, double-blind trial, pregnant women with HIV infection who were receiving antiretroviral therapy received either HIV-Ig or control intravenous Ig. While transmission rate was 5 to 6% in both treatment and control arms (sample size was too small to show a difference), infected infants who received HIV-Ig had a delayed time to culture positivity versus those receiving intravenous Ig, suggesting that HIV-Ig may have the ability to modify disease but not prevent infection. While this study did not prove an effect of HIV-Ig it did prove an effect of antiretroviral therapy in a population of women with prior zidovudine experience. Passive antibody preparations (HIV-Ig and monoclonal antibodies) may have the potential to decrease perinatal transmission in combination with antiretroviral agents, to levels less than 5%. Special niches where immunoglobulins

and HIV vaccines may play a role, include treatment of infants born to women who do not receive prenatal care, or where the diagnosis of HIV in mother and infant is made only following delivery: a post-exposure prophylaxis strategy.

Globally, the World Health Organization estimates that 3.5 million women, most of whom are of childbearing age, have been infected with HIV-1. More than 1 million of their children have acquired infection perinatally. An estimated 3000 additional women become infected every day.[1] By the year 2000, as many as 5 to 10 million children will be infected, over three-quarters of cases occurring in the developing world, particularly sub-Saharan Africa. Thus, perinatal HIV-1 infection represents a significant global public health problem and prevention of vertical transmission is a high public health priority. Understanding the pathogenesis of perinatal transmission is crucial for the design of new preventative and therapeutic interventions.

1. Mechanisms of and Risk Factors for Transmission

A better understanding of the mechanism and timing of mother-to-child transmission of HIV infection is important to assist with the design of therapeutic interventions to decrease vertical transmission. The mechanisms of viral transmission at the cellular and molecular levels are not known with certainty. Clinical and laboratory evidence suggests several possible routes of infection, including transplacental, fetal exposure to infected maternal body fluids at delivery and breast feeding.

Advanced maternal disease status, as measured by clinical stage, decreased CD4+ cell count and increased viral burden, have been found to correlate with transmission of HIV.[2-11] The amount of maternal virus (viral load) appears to correlate with transmission risk somewhat more reliably than clinical or immunological indicators, though all are less than perfect surrogates.

Recently, with the availability of HIV RNA viral load measurements, researchers have found higher mean levels of HIV RNA among transmitters of the virus than nontransmitters. A study by Thea et al.[12] found mean HIV RNA copy numbers of 7200 and 15 300 among nontransmitters and transmitters respectively, with an odds ratio of 5.4 for transmission among women with viral loads above the threshold of detection. There were no differences in HIV RNA copy numbers when zidovudine recipients and nonrecipients were compared. There was a strong effect of viral load among those mothers with early disease and no effect among those with advanced disease. However, it has been difficult to determine an absolute viral load threshold for mother-to-child transmission, and nearly every study has reported transmission from mothers who had undetectable HIV RNA, as well as mothers with very high levels of HIV RNA who did not transmit the virus. A recent meta-analysis of this subject was presented by Contopoulos-Ioannidis et al.[13] Their review, which included 9 cohorts and 1115 mother-infant pairs, concluded that HIV RNA is a 'strong predictor of the average risk in groups of untreated mothers, but a modest to poor predictor of transmission for individual treated mothers'.[13]

Factors that enhance fetal exposure to maternal blood or body fluids may play a pivotal role in perinatal transmission. Investigators have reported an increased risk of transmission in seropositive women who develop chorioamnionitis,[8,14] or have other sexually transmitted diseases (STDs).[10,14] In addition, several observational studies have revealed an association between the risk of vertical transmission and duration of rupture of membranes.[4,15-18] Clinical evidence that fetal exposure to maternal body fluids may play a role in vertical transmission is provided by observational studies

and meta-analyses that, overall, indicated an increased risk of transmission observed in women who deliver vaginally.[19,20]

Other potential risk factors for transmission include cigarette smoking,[15] low maternal vitamin A level,[21] multiple sexual partners,[22] premature birth,[23] post term pregnancy,[24] positive maternal HIV blood cultures at delivery[16,25] and the use of invasive procedures during labour and delivery.[2,26] Most of the analyses described above were performed before the results of the AIDS Clinincal trials Group (ACTG) study 076 were published (see section 4), when most women were not receiving antiretroviral therapy. A recent analysis of ACTG 185, in which all women received prophylactic zidovudine (ZDV), evaluated risk factors for perinatal transmission in women/infants in this study.[27] Utilising multivariate logistic regression models, this analysis found that only HIV RNA levels both at entry to the trial and at delivery were significantly associated with transmission of the virus. However, since not all women who are infected with HIV and pregnant may have the benefit of receiving available antiretroviral therapy, the 'pre-076' analysis of risk factors will continue to be relevant for many women.

2. Rationale for Immunological Interventions

The maternal humoral and/or cellular immune response to HIV may play a role in preventing perinatal transmission in one or more of the following ways: antibodies might act to neutralise or otherwise destroy the virus, either in the mother or after transplacental or intrapartum exposure, while cell-mediated immunity might reduce maternal viral load and hence the risk of transmission.[28] If antibodies can be identified that neutralise a broad range of viruses, then these antibodies can perform one of three different functions: neutralising antibody can kill extracellular virus; antibody-dependent cell mediated cytotoxicity (ADCC) can kill HIV infected cells by a cooperation between antibody and effector cells; and complement-fixing antibody can involve complement to carry out lysis of HIV infected cells.

Monoclonal antibodies or monovalent recombinant vaccines, if able to produce such antibody responses, could be capable of providing protection. If, on the other hand, neutralisation of a wide range of viral variants without identifiable common target antigens is required, multivalent preparations combining several different monoclonal antibodies, polyvalent anti-HIV sera or multivalent vaccines may be required.

3. The Immune System and Vertical Transmission

Congenital or perinatal HIV infection is acquired by transmission from mother to fetus or infant during gestation or parturition. Several lines of evidence suggest that factors protective against maternal-infant transmission include higher levels or specific types (or both) of endogenous maternal antibodies directed against HIV. While not all researchers have been consistent in their findings,[29,30] a number of studies have indicated lower transmission rates from infected pregnant women with high antibody titre or with high-affinity/avidity to conserved portions of HIV-1 glycoprotein 41,[31] to the CD4 binding site[32] or the V3 loop of glycoprotein 120,[4,33-35] or to p24 *gag* protein.[36]

Maternal neutralising antibody may be an important determinant of protection. Several investigators have reported that nontransmitting mothers more frequently have such an antibody to their own virus than do transmitting mothers, and that transmitting mothers infrequently have neutralising antibody against their child's own isolate.[37-39] Sera from mothers with autologous neutralising antibody frequently have antibodies that also neutralise heterologous primary isolates.[37]

The level and specificity of maternal HIV-1 specific antibody may affect maternal-fetal transmission of HIV infection. However, in the numerous studies published since 1990, decreases, increases and no differences in the rate of perinatal transmis-

sion in the presence of antibody have all been reported.[40]

Maternal neutralising antibody may be most accurately evaluated by testing maternal and infant viral isolates in parallel. This kind of evaluation, which has been done in several small mother-child cohorts, has shown that transmitting mothers had antibody to their own virus less frequently than did nontransmitting mothers.[37,39] Additionally, the serum of transmitting mothers is rarely capable of neutralising their child's viral isolate and, in one case, maternal antibody enhanced infectivity of infant virus *in vitro*. However, in another small study that adjusted for maternal CD4+ cell count, no differences in titres of autologous HIV-1 antibody, viral load and syncytium-inducing phenotype between transmitting and nontransmitting mothers were seen.[41] Studies in larger populations will be required to elucidate the role of HIV-1-specific antibody in transmission. Neutralising antibody may be important in protection against infection from cell-free virus but not cell-associated virus. In an *in vitro* infection system, monoclonal HIV-1 V3 antibody completely prevented infection with cell-free virus, but inhibition was not observed when cell-to-cell transfer of virions was the primary mechanism of infection.[42]

Few studies have evaluated the role of maternal cellular immune response to HIV-1. The presence of maternal HIV-1 specific ADCC has not been associated with protection against transmission, although infected children who had evidence of ADCC in their blood had a better prognosis than those without ADCC.[43,44]

One of the studies which simultaneously measured and provided a correlation between vertical transmission, maternal viral load and plasma levels of CD4 binding site anti-gp120 antibodies was reported by Khouri et al.[32] This study compared 18 women with infected infants and 29 women whose infants seroreverted. Significant differences between groups were observed in the levels of CD4 binding site antibody, as measured by the ability of diluted maternal plasma to inhibit binding of the CD4 binding site monoclonal antibody F-105 to monomeric gp120. A correlation was found between low inhibition levels of antibodies that overlap the F-105 binding sites and vertical transmission. In addition, there was a trend towards lower levels of antibodies that block CD4 binding to gp120 in transmitters compared with nontransmitters. Finally, these nontransmitting mothers had low viral load, as measured by 2 or more negative viral cultures during pregnancy as compared with transmitters.

This class of neutralising antibodies, which appear late in the course of HIV infection, are more broadly neutralising, interfere with the binding of gp120 to the CD4 receptor (CD4 binding site antibodies) and are important in that lack of these antibodies is associated with disease progression in adults (and, as described above, they are correlated with vertical transmission). It can be concluded, however, that 10 years or more into our research on the role of antibody in protection from maternal-fetal HIV transmission, the findings are clearly not conclusive and that such a strategy continues to be only a theoretical possibility.

4. Interruption of Maternal-Fetal Transmission

On 21 February 1994, the AIDS clinical trials group (ACTG) announced the preliminary results from their protocol 076, a randomised, double-blind, placebo-controlled clinical trial of ZDV to prevent HIV transmission from pregnant women to their infants.[45] This trial demonstrated that a combination of prenatal, intrapartum and neonatal ZDV antiretroviral chemoprophylaxis can achieve a 67.5% reduction in transmission of HIV. Since that time, the 076 regimen has been widely adopted for this indication.

A recent secondary analysis[46] reviewed the results of maternal HIV RNA measures at study entry and at labour and delivery. In the placebo group, a large viral burden at entry or delivery or a positive culture was associated with an increased risk of transmission (the transmission rate was greater

than 40% in the highest quartile of RNA levels). In both groups, transmission occurred across the entire range of maternal plasma HIV RNA levels. While ZDV produced only minimal reduction in plasma HIV RNA levels (median 0.24 log), it was effective regardless of the HIV RNA level or the CD4+ cell count at entry. After adjustment for the baseline HIV RNA level and CD4+ cell count, the reduction in viral RNA from baseline to delivery in the ZDV group was not significantly associated with the risk of transmission.

Immunological data obtained at entry into the study were available for 400 mothers. Transmission rates in the placebo group increased as CD4+ cell counts decreased. The presence of a lower proportion of CD4+ cells and a higher proportion of CD8+ cells was associated with a higher risk of transmission in the placebo group, but not in the ZDV group.

In summary, neither the change in the plasma HIV RNA levels from entry to delivery nor a critical level of plasma HIV RNA at delivery accounted for the substantially reduced transmission rate of the ZDV group. Only a fraction of the treatment effect (9 to 17%) could be explained by the treatment-induced change in maternal RNA. Further evidence suggests that the protective effect of ZDV results at least in part from a mechanism other than the reduction of the maternal plasma viral burden.

Most importantly, despite our lack of understanding of the mechanism, data from field studies which have analysed HIV transmission 'post 076' document vertical transmission decreasing to the 5 to 10% range, even where women only received parts of the full 076 regimen.

5. Passive and Active Immunotherapy to Interrupt Maternal-Fetal Transmission

Studies of hepatitis B prevention give credence to the concept that immunoglobulin can prevent chronic viral infections. In a study in Taiwan in the 1970s, Beasley et al.[23] gave high titred hepatitis B immune globulin to neonates whose mothers were chronic hepatitis B surface antigen carriers. There was a 75% reduction in the incidence of chronic infection in neonates who received 3 injections over 3 months, even though 75% of the treated infants had been transiently infected. Antibody thus had appeared to resolve an active hepatitis B infection. One difference in the analogy being presented between hepatitis B and HIV is that while hepatitis B surface antigen positive mothers demonstrate antibody to core antigen, they lack measurable antibody to surface antigen in their plasma, and thus this antibody is missing from the newborn infant; in contrast, with HIV there is measurable anti-HIV antibody to both core and surface (envelope) antigens in the newborn infant from passive maternal transfer.

Nonetheless, based on the results of studies such as the one by Beasley, the development and evaluation of hyperimmune anti-HIV immunoglobulin preparations for prevention or treatment of HIV infection and disease have received special attention.

Several studies in symptomatic HIV-infected adults treated with HIV hyperimmune globulin or plasma preparations,[47-52] and in one child with AIDS who received passive immunotherapy with HIV immune plasma,[53] have shown disappearance of p24 antigenaemia and inhibition of plasma viraemia. In some situations, suppression of virus was sustained and, in the Vittecoq study, was associated with clinical benefit in a group of HIV-infected adults.[51] It is at present unclear, as previously summarised, 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. However, *in vitro* data indicate that HIV immunoglobulins and HIV-specific monoclonal antibodies, especially when used in combination, have potent neutralisation capacity.

6. HIV Immunoglobulin

HIV immunoglobulin (HIV-Ig; manufactured as HIV-IG™ by NABI, Boca Raton, FL] is a prep-

aration of highly purified human immune globulin containing high titres of antibody to HIV structural proteins. It contains considerable functional activity in virus neutralisation and antibody-dependent cytotoxicity assays.[54] This intravenous IgG solution is prepared from the plasma of multiple HIV-seropositive donors from geographically diverse regions of the US who are selected according to strict clinical and biological criteria. Donors are clinically asymptomatic, maintain CD4+ T cell counts ≥400/μl, and are negative for HIV-1 p24 antigen, nonreactive for hepatitis B surface antigen and nonreactive for antibody to hepatitis C virus. The donor plasma contains high titres of anti-p24 antibody (a potential indicator of strong immune response to HIV).

By analogy with the demonstrated efficacy of immunoglobulins for the treatment and prevention of certain viral infectious diseases, studies were planned in the late 1980s (prior to the availability of human monoclonal antibodies), with the hypothesis that HIV-Ig may have similar potential to treat or prevent HIV infection.

6.1 ACTG 185

This clinical trial was designed as a phase III randomised, double-blind, controlled, multicentre study. The target sample size was 800 mother-infant pairs (720 evaluable pairs). Pregnant women with documented HIV infection were eligible for randomisation to HIV-Ig or intravenous Ig between 20 and 30 weeks of pregnancy (inclusive).

The primary question addressed by the trial was whether a combination of HIV-Ig and ZDV would significantly lower transmission in HIV-infected pregnant women with advanced disease compared with women who received ZDV with intravenous Ig.

Treatment consisted of HIV-Ig, 200 mg/kg by intravenous infusion every four weeks up to delivery, or standard polyvalent, HIV-antibody negative intravenous Ig, in the same dose and regimen. The newborn infant was to receive an intravenous infusion of HIV-Ig or intravenous Ig (200 mg/kg) within 12 hours of birth. All women and infants received the '076' regimen of ZDV.

The pharmacokinetic component of ACTG 185[55] reported the safety and pharmacokinetics of hyperimmune anti-HIV immunoglobulin in HIV infected pregnant women and their newborns in the first 28 patients enrolled in ACTG protocol 185, of whom 12 received HIV-Ig and 16 received intravenous Ig. Mean volume of distribution (Vd) and plasma elimination half-life values for the first infusion were 72 ml/kg and 15 days, respectively, compared with 154 ml/kg and 32 days for the third infusions, suggesting accumulation of antibody with repeated administration and duration of pregnancy. Rapid sustained suppression of serum immune complex dissociated (ICD) p24 antigen from baseline (102 ng/L) was observed in HIV-Ig- but not intravenous Ig-treated women, and no increase in either serum ICD p24 antigen or quantitative HIV-1 RNA plasma levels were seen at trough p24 antibody concentrations (28 days after infusion), suggesting a sustained effect from the HIV-Ig infusions.

Following a single infusion in newborns, the mean terminal elimination half-life in HIV-Ig-treated infants was 30 days, mean Vd was 143 ml/kg and mean total body clearance was 4.1 ml/kg/day. Substantially increased serum p24 antibody levels persisted for at least 28 days in HIV-Ig-treated, compared with intravenous Ig-treated, infants, which was deemed to be an effect of transplacentally acquired maternal antibody, as well as HIV-specific antibody received from intravenous infusion at birth. The results of the pilot tolerability and pharmacokinetic study described above, describing a favourable tolerability, pharmacokinetic and antiviral profile for HIV-Ig, gave hope that ACTG 185, the efficacy trial, would provide a successful result. However, the Data Safety and Monitoring Board (DSMB) of this study, at their planned efficacy review in December 1996, determined that because of an unexpectedly low overall transmission rate, the study would possess insufficient statistical power under the existing 800 ma-

ternal-infant pair sample size design to be able to detect an effect of HIV-Ig treatment, and recommended that further enrolment be halted.

Fifteen of 379 evaluable infants were determined to be infected with HIV, with a calculated overall transmission rate by Kaplan-Meier analysis of 4.8%.[56] Seven children were diagnosed as infected in the HIV-Ig arm (4.7%) and 8 children in the intravenous Ig arm (4.8%). Of note, 5 of the infected infants in the intravenous Ig arm exhibited HIV cultures positive at birth and none of the HIV-Ig-treated infants had positive cultures at birth ($p = 0.026$, Fisher's exact test). One interpretation of this finding is that it may represent an effect of HIV-Ig in modifying but not preventing disease in the infants. Such a delay to positivity is an effect similar to that which would be anticipated with other immunoglobulin preparations such as hepatitis B immune globulin (HBIG), which does not prevent infection, but can modify hepatitis B disease. Further analysis of the infant samples is planned to better characterise the level of viremia in infected infants who received HIV-Ig and those who received intravenous Ig.

Preliminary data are available for one additional vertical transmission study of HIV-Ig which is ongoing in Uganda.[57] HIV-Ig was administered at 37 weeks' gestation to 31 mothers and a single dose was given to 29 infants within 18 hours of birth. This was a dose escalation study for mothers and/or infants, with sequential 50 mg/kg, 200 mg/kg and 400 mg/kg infusions. Pre- and post-infusion, there was no evidence of a significant change in CD4+ cell counts or HIV RNA levels. Four of the 7 infected infants reported in this phase I/II study were HIV RNA positive at birth, 1 in the 50 mg/kg dose regimen, 3 in the 200 mg/kg dose regimen, and none in the 400 mg/kg dose regimen, with transmission rates at 6 weeks of 20%, 40% and 11%, respectively. Despite the suggestion of reduced transmission in the high dose group, the sample size for this part of the study was too small to evaluate efficacy.

6.2 Monoclonal Antibody Studies

A recent study by Mascola et al.[58] reported the *in vitro* activity of HIV and a number of monoclonal antibodies (MoAbs; 2F5, 2G12) that bind to distinct regions of the HIV envelope glycoprotein. The antibodies were initially tested against a panel of 15 clade B HIV isolates using a single concentration that is achievable *in vivo* (HIV-Ig, 2500 μg/ml; MoAbs, 25 μg/ml). Individual antibody reagents neutralised many of the viruses tested, but antibody potency varied substantially among viruses. The virus neutralisation produced by double combinations of HIV-Ig plus 2F5 or 2G12, the 2 MoAbs together, or triple combinations of HIV-Ig/2F5/2G12 were generally equal to, or greater than, that predicted by the effect of individual antibodies. Overall, triple combinations displayed the greatest magnitude and breadth of neutralisation.

In several of the experiments presented, the triple antibody combination appeared to completely prevent infection of peripheral blood mononuclear cells by 100% at a viral dose 50% of the tissue culture infectious dose ($TCID_{50}$), i.e. a >99% neutralisation of infectious virus.

The mechanism of synergistic interactions among these 3 antibody reagents, one of which is polyclonal, is likely to be complex. Mab 2G12 inhibits the interaction of gp120 with the beta chemokine receptor CCR5, while Mab 2F5 appears to affect the conformation of the gp41 fusion domain and thus inhibit virus-cell fusion. The synergistic effects seen in these studies are likely to be a consequence of the complementary activities of these 2 monoclonal antibodies together with the functionally diverse spectrum of anti-envelope antibodies present in HIV-Ig.

The improved magnitude and breadth of neutralisation demonstrated by combining neutralising monoclonal antibodies with HIV-Ig suggests that such antibody combinations may be more effective than individual agents when used as passive immunotherapy for HIV. Preliminary unpublished data from this same group, using non clade B viral

isolates, have shown potent neutralising abilities with these clade B generated monoclonal antibodies and HIV-Ig. A second group of researchers, published by Li et al.[59] have done similar studies with a panel of 14 human IgG monoclonal antibodies and HIV-Ig. Their panel included monoclonal combinations including the anti-CD4 binding site, and their findings were similar to that of Mascola, with synergistic neutralisation by combination antibodies *in vitro*. The authors describe studies in rhesus monkeys where CD4-specific antibodies were capable of significantly reducing simian immunodeficiency virus (SIV_{mac}) load in infected monkeys and suggest that combinations of V3 MoAbs, anti-CD4bd MoAbs and V3 loop antibodies are capable of providing conformational changes at neutralising epitopes with resultant synergistic antibody activity.

7. Phase I HIV Vaccine Trials in Pregnant Women and Newborns

ACTG 230, a study administering recombinant-gp120 vaccines to infants born to HIV-infected women, has recently been completed.[60-62] In this trial, infants received the Chiron gp120-SF2, Vaxgen gp120-MN or control vaccine at weeks 0, 4, 12 and 20 following delivery. Vaccines were well tolerated, with an overall transmission rate of 8%. Lymphoproliferative responses to recombinant antigens were detected in 30 to 80% of vaccinees (but not in control recipients), with many responses persisting at 2 years. Humoral responses were seen at 12 and 24 weeks in vaccinees, but not in control recipients. Future trials will evaluate accelerated schedules and administration of candidate HIV vaccines capable of eliciting cytotoxic T cell responses such as the ALVAC™ recombinant HIV vaccines (ACTG 326). This preventive strategy continues to be an important area of future clinical trials research.

ACTG 235 was a phase I safety and immunogenicity study, where a recombinant gp120 vaccine (MN strain) was administered during pregnancy to HIV-infected women with a CD4+ count >400 cells/μl.[63] One-third of patients received placebo (alum) alone. While this study proved the vaccine to be well tolerated, no immunogenicity was detected as measured by HIV-specific antibody responses. These unimpressive results are similar to the experience of other recombinant gp120 and gp160 vaccines administered to HIV-infected adults as a form of immunotherapy.

8. Conclusion

Humoral immunity is thought to play an important role in the natural history of HIV infection. Based on this concept, and on the previous success with this strategy for other infectious diseases, HIV-specific immunoglobulins have been developed and tested extensively *in vitro*, in animal models and in human clinical trials. Passively administered or actively induced antibodies can theoretically be used to prevent or treat HIV infection in several ways. They include pre-exposure prophylaxis with antibody to prevent infection before it has occurred (i.e. the treatment of HIV-infected pregnant women to prevent infection of their babies), post-exposure prophylaxis to prevent or limit HIV infection after exposure (i.e. management of perinatally exposed neonates or of healthcare workers immediately after needlestick exposures to HIV infected blood) or therapeutic immunisation to modify the course of infection in HIV-infected persons. Ideally, antibodies elicited by an HIV vaccine should be able to prevent infection by different transmission routes or, failing that, abort infection, limit transmissibility to others or modify disease. To date, the only effective utility of anti-HIV-specific antibody has been one of therapeutic use, although the results have been only modest in nature.

The astounding success of 076, a 'chemotherapeutic vaccine' has been a good first step to reduce maternal fetal transmission of HIV infection. However, there continues to be a significant transmission risk (5 to 10%) even when ZDV is administered according to the 076 regimen, underscoring the need for development of preventive treatment

regimens of greater effectiveness. Immunoglobulins and vaccines may find a special treatment niche with infants born to women who do not receive prenatal care, or where the diagnosis of HIV in mother and infant is made only following delivery. In these situations, vaccines and immunoglobulins may be an alternative or important adjunct to antiretroviral therapy for post-exposure prophylaxis/treatment of the infant. Such products should be capable of inactivating a broad range of HIV isolates, and should have activity against non clade B isolates. Cocktails of HIV-Ig spiked with a variety of MoAbs (anti-V3 loop, anti-CD4 binding site, anti-gp41), based on currently available *in vitro* data, may be the best candidates for future clinical trials.

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