Reevaluating HIV Vaccine Clinical Trials Policy for Infants

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(See the major article by Fouda et al on pages 508–17.)

The application of antiretroviral therapy (ART) to reduce the incidence of mother-to-child transmission of human immunodeficiency virus (HIV) is, to date, the most significant achievement in HIV prevention [1]. However, despite strategies that have the potential to virtually eliminate HIV infection among infants, transmission of HIV infection to infants continues to occur, particularly during the breast-feeding period [2, 3]. This continuing risk is related to the lack of diagnosis of HIV infection for the infected mother at delivery, seroconversion during the breast-feeding period, and lack of uniform adherence to antiretroviral treatment, both in the perinatal and breast-feeding periods. As we have learned, perhaps slowly and painfully, over the last few years, developing an AIDS-free generation will require interventions that overcome these adherence-related obstacles [4–6]. Moreover, even when optimal adherence to ART is achieved, breast milk–mediated transmission of HIV still occurs, as ART’s effect on cell-associated HIV is less than perfect [7], demonstrating the need for other preventive strategies to avert transmission in the period when breast milk is optimal for infant health. As such, the development of an effective HIV vaccine administered either prenatally or during the neonatal period may be a very useful intervention to eliminate infant acquisition of HIV.

To date, HIV vaccine development in infants has had minimal research funding. This lack of prioritization may be attributed to safety concerns, such as increased risk of HIV acquisition from an experimental HIV vaccine, as well as to perceived theoretical causes of impaired immunogenicity due to the neonates’ immature immune system, blunting of the immune response in the infant because of placental and breast milk transfer of maternal antibodies, and concern for priming an ineffective immune response, thus creating an inability for the infant to develop a potentially effective immune response from a subsequent vaccine regimen (so-called original antigenic sin) [8].

These concerns about risk-benefit ratios to infants enrolled in HIV vaccine trials were exacerbated in 2007 upon release of the data for the STEP study, in which some subgroups of adult male recipients of the MRK Ad5 gag/pol/nef vaccine exhibited an increased risk of HIV acquisition; this was confirmed in the HVTN 503/Phambili study [9, 10]. These data caused many institutional sponsors and regulatory agencies to raise the risk-benefit ratio bar for studies of candidate HIV vaccines in infants, with these sponsors and agencies often articulating that efficacy in adults should be demonstrated before initiating even phase 1 clinical trials in infants. This has led to a paucity of HIV vaccine studies in neonates in the last 5 years [11, 12].

The article by Fouda et al in this issue of The Journal of Infectious Diseases should, in our opinion, alter this conservatism toward the benefit of a potential HIV vaccine for infants. The study uses modern antibody assays developed largely through the extensive correlates of protection program that developed following the RV144 trial [13–17] and demonstrates that vaccination of infants with candidate HIV vaccines may elicit higher antibody responses than those seen in adults. The differences are substantial, and, as such, studies of candidate HIV vaccines in infants may offer important mechanistic insights into vaccine development and illustrate that infants may potentially achieve higher rates of protection against HIV acquisition than adults.

These observations are of interest in that data from recently conducted HIV vaccine studies have demonstrated, in immunocompetent adults, that body mass index markedly influences HIV-specific immune responses, especially T-cell help [18], thus suggesting that current HIV vaccine constructs may, especially if given at similar doses as adults, elicit higher immune responses in infants. The article by Fouda et al seems to corroborate this idea.
Fouda et al analyzed serum specimens from infants enrolled into 2 historical HIV pediatric vaccine trials, PACTG 230 and PACTG 326, that were conducted in the mid-1990s among HIV–exposed infants in the United States. The HIV vaccine regimens selected for analysis include a recombinant protein component, HIV gp120, adjuvanted either to MF59 (in the vaccine developed by Chiron) or alum (in the vaccine developed by VaxGen) alone, as well as a viral vector HIV vaccine (ALVAC) in combination with AIDSVAX with alum. The doses of vaccine were, in some arms, similar to those used in adults.

Several observations emerged from these retrospective analyses. To begin with, infants, especially those who received the full-length gp120 protein adjuvant with MF-59, developed antibody responses that were both robust and, in general, more durable than those of the Thai adults immunized in the RV144 trial. In addition, binding antibodies and antibodies to the V1V2 loop, including those directed to the CH58 epitope [19], were induced after vaccination and appeared to be more durable than those seen in adults in the RV144 trial. Interestingly, serum anti–immunoglobulin A (IgA) responses that were associated with an increased risk of HIV acquisition in the RV144 trial were not seen in any of the infant groups, even those who received ALVAC plus gp120 [13]. The observations that higher antibody responses associated with protection and lack of an inhibitory response are intriguing, both mechanistically and, potentially, clinically. They suggest to us that a trial of an RV144-like regimen in infants should be conducted to corroborate these concepts and to provide context to the Fouda et al observation. Whether this is the RV144 regimen per se or one of the vaccine regimens designed for use in sub-Saharan Africa requires discussion with regulators, community leaders, and funders [20].

Unfortunately, not all immune responses were more robust than adults, as was seen with immunoglobulin G3 (IgG3) antibody response, neutralization, and antibody-dependent cell-mediated toxicity (ADCC) activity. The IgG3 antibody responses, which have been highly correlated with protection against HIV acquisition in the RV144 trial [21], were limited in both frequency and durability, and neutralization responses were narrow in magnitude and breadth. Moreover, no ADCC activity was seen [22]. Data from studies conducted in African HIV-infected lactating women have demonstrated lower neutralizing antibodies and ADCC activity in breast milk, suggesting that IgA-mediated neutralizing and ADCC responses do not play major roles in preventing breast milk–mediated transmission [23]. Results suggesting that high levels of milk IgG–mediated ADCC correlate to a lack of postnatal transmission imply that vaccine protection aimed at inducing an effective protective humoral response could be transferred through breast milk [24]. Even more intriguing is the possibility that the germ-line pathways elicited by infant vaccination may provide novel insights into how to engage the human immune system in eliciting broadly reactive binding and neutralizing antibodies to HIV [25–27].

The study by Fouda et al also provided data on a small group of infants who received just ALVAC alone, and these analyses indicate that the immune responses associated with protection in RV44 were not seen with ALVAC vector alone, demonstrating the value of the gp120 adjuvanted recombinant protein in an HIV vaccine regimen.

The overall message from the analyses by Fouda et al suggests that infants may develop immune responses that are qualitatively and quantitatively different from those of adults and, hence, could be easier to protect with current vaccine technologies than previously appreciated. Of interest, recent studies also suggest that maternal sera may contain high titers of autologous neutralizing antibodies that may be associated with lower rates of perinatal transmission [26, 27]. Observations from transmission events through breastfeeding have shown that there is little or no viral compartmentalization between milk and blood, and as with other routes of infection, a genetic bottleneck restricts viral variants transmitted via breastfeeding to a single or small number [28]. These data suggest that HIV vaccination may be the vehicle that gets us to the virtual elimination of pediatric HIV.

Those in the HIV vaccine field should read the article by Fouda et al carefully and initiate a more robust discussion of how well-conceived studies in infants can provide new insights on HIV prevention. The log jam in HIV prevention research for HIV vaccines in infants should, with appropriate regulation and safeguards, be lifted and well-thought-out studies of candidate HIV vaccines should be initiated in infants as a priority.

Note

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References


