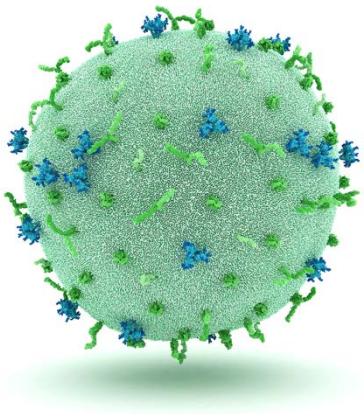

Timely Topics In HIV Vaccines

MEETING REPORT

Prevention Trials in the Population of Infants Born to HIV-Infected Mothers

A Global HIV Vaccine Enterprise, Elizabeth Glaser Pediatric AIDS Foundation, and IMPAACT Network Consultation

22-23 January 2013

Entebbe, Uganda

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Background

With the dramatic progress in the identification of effective interventions to prevent mother-to-child HIV transmission (PMTCT) in low-resource settings and rapid scale up to implement these interventions in the last 5 years, UNAIDS has set a new goal to virtually eliminate new pediatric HIV infections by 2015. Virtual elimination has been defined as a 90% reduction in mother-to-child transmission (MTCT) from 2009 levels and an overall MTCT rate of <5% in breastfeeding populations. However, while > 100,000 new infections have been averted globally between 2003 and 2010, in 2011 there were still 330,000 new pediatric infections, and it is unlikely that the goal of global elimination will be met with current antiretroviral interventions alone.

Additionally, increasing data indicate that for optimal infant survival prolonged breastfeeding by HIV-exposed infants for longer than 12 months may be needed in many low-resource settings. The breastfeeding infant of an HIV-infected mother experiences multiple daily viral exposures starting at birth and continuing for as long as ingestion of breast milk continues. The use of antiretroviral prophylaxis by mother or infant can reduce but does not eliminate transmission risk and relies on strict adherence to daily drug administration. Breakthrough infections at a rate of 2-4% by age 6 months and up to 6% or higher by age 12 months have been observed in breastfeeding infants of HIV-infected mothers who have received triple antiretroviral drug therapy during pregnancy and breastfeeding.

Immunization has been a successful strategy for PMTCT of other infectious diseases, such as the hepatitis B virus (HBV). The HBV vaccine given at birth leads to a 70% reduction in HBV MTCT and the addition of a single dose of HB immunoglobulin (HBIG) at birth results in 94% protection from transmission. Use of an anti-HIV passive immunization approach as an adjunct to antiretroviral therapy/prophylaxis of HIV MTCT could provide additional immediate protection, and an active immunization near the time of birth would provide long-term protection. These combined modalities could then provide protection throughout the breastfeeding period.

While effective HIV vaccines for neonates are not yet available, there is an opportunity to evaluate the efficacy and safety of the passive immunization approach in breastfeeding HIV-exposed infants. Potent monoclonal antibodies have been recently isolated that can neutralize more than 90% of HIV strains of multiple clades and which have demonstrated efficacy in non-human primate (NHP) simian immunodeficiency virus (SIV) models in preventing low-dose oral exposure transmission. One of these monoclonal antibodies, VRC01, isolated by scientists at the U.S. National Institutes of Health (NIH) in 2010, is beginning safety and pharmacokinetic studies in adults in 2013 and could be ready for studies in

neonates by late 2013/early 2014. In studies under consideration, the investigational monoclonal antibody would be used to augment maternal and infant antiretroviral therapy/prophylaxis in infants who are not infected with HIV at birth, but who are at high risk of intrapartum transmission or at continued risk of infection through breastfeeding. The VRC01 monoclonal antibody could be administered subcutaneously in small amounts (e.g., 1 mL) to infants, and because of its long half-life, could be administered once a month or possibly less frequently to the infant for the duration of breastfeeding, with a goal of decreasing residual risk of infection by at least 70%. However, given the evolving landscape of PMTCT interventions, how to optimally and ethically study such new interventions in HIV-exposed infants in low-resource settings, as well as potential availability of the product post-trial and cost of the product, require further exploration.

In response to these issues, the Global HIV Vaccine Enterprise (Enterprise) together with the Elizabeth Glaser Pediatric AIDS Foundation and the NIH-funded International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network convened a consultation on 22-23 January 2013 in Entebbe, Uganda. The consultation was part of the Enterprise's *Timely Topics in HIV Vaccines initiative,* a new strategy series to identify and respond to unresolved and emerging priority issues in the field. The meeting examined issues related to the design and conduct of clinical trials to test the ability of new investigational interventions, such as the VRC01 or other monoclonal antibodies and/or potential future HIV vaccines, to further reduce intrapartum and postnatal transmission in breastfeeding HIV-exposed infants in Africa.

The meeting brought together a broad consultation of approximately 60 stakeholders, including researchers, clinicians, WHO/UNICEF staff, African ministries of health, local community members, ethicists, and others. The morning/early afternoon of 22 January had plenary presentations to discuss the need for new modalities, current PMTCT experience in countries, experience with immunization strategies in infants, and passive HIV antibody immunization animal data, followed by information on the proposed studies of passive immunization with VRC01 antibody to provide a case study to assist in formulating issues for discussion. The meeting then broke into four Working Groups for the remainder of the day to discuss and provide recommendations on 1) logistical challenges; 2) issues related to treatment and provision of standard of care; 3) ethical challenges and long-term plans for VRC01; and 4) future prevention strategies (such as monoclonal antibodies and/or vaccine). On 23 January, the Working Groups formalized their recommendations, which were discussed in plenary discussion session.

Plenary Presentations

The Need for New Prevention Modalities (Lynne Mofenson)

Dr. Mofenson provided an overview of PMTCT strategies in the U.S., including universal prenatal HIV testing of all pregnant women; use of combination antiretroviral drug regimens to suppress viral load with laboratory-guided, individualized patient management (based on HIV RNA and CD4 counts measured at least every 3 months); provision of infant antiretroviral prophylaxis; elective cesarean delivery if HIV RNA >1,000 copies/mL near delivery; and avoidance of breastfeeding. These interventions have led to overall transmission rates of 1-3%; however, since breastfeeding by infected women is not recommended in the U.S., this success does not include issues related to continuing postnatal

transmission risk. Dr. Mofenson noted that in the U.S., 98% of women have antenatal care; 73% start care in the first trimester and 94% before the third trimester; 94% of pregnant women receive an HIV test; 85% of infected pregnant women receive combination antepartum antiretroviral drugs; and 96% of HIV-exposed infants receive antiretroviral prophylaxis. This contrasts with low-resource settings; in sub-Saharan Africa, while 77% of women receive at least one antenatal visit, only 47% have the minimum recommended four visits; only 28% initiate antenatal care in the first trimester and 68% before the third trimester; 38% of pregnant women received an HIV test in 2010; 63% of infected women received any antiretroviral prophylaxis in 2011; and 43% of infants received antiretroviral prophylaxis in 2010. She discussed the current 2010 WHO guidelines for PMTCT and the proposed transition to use of triple antiretroviral drug regimens as the preferred prophylaxis regimen for all women, as well as the new proposal in some countries to initiate life-long antiretroviral therapy in all pregnant women regardless of CD4 cell count or clinical stage. She presented current successes in PMTCT program implementation in South Africa and Uganda, where 6 week infant infection rates of 3-5% have been observed with implementation of the 2010 WHO guidelines, and described the global plan toward the elimination of new HIV infections among children by 2015.

She then discussed data to support the need for new adjunctive prevention modalities including:

- Modeling, which indicates that to achieve a decrease to 72,000 new infant infections annually and MTCT rate of 8%, the following is required: 1) the most effective antiretroviral regimens must be provided to 90% of all HIV-infected women; 2) a reduction 50% reduction in HIV incidence in women is needed; 3) a provision of all unmet need for family planning is needed; and 4) breastfeeding should be limited to 12 months;
- There are continuing new infections in young women in low-resource settings (71% of individuals aged 15-24 years living with HIV in sub-Saharan Africa are women);
- The risk of acquisition of HIV infection may be increased in pregnancy;
- High rates of MTCT are associated with acute infection in pregnancy or during breastfeeding;
- Late presentation/diagnosis and late initiation of antiretroviral drugs significantly reduces efficacy for PMTCT, and late presentation is common in the low-resource setting;
- Although provision of multiple antiretroviral drug prophylaxis ("infant HAART") to infants at high risk of infection reduces the risk of intrapartum infection in a formula-fed population by 50%, there remains a residual 2-3% risk of intrapartum infection with "infant HAART" without accounting for continuing breastfeeding risk;
- Maternal adherence to antiretroviral therapy postpartum has been suboptimal in studies in both resource-rich and –limited countries;
- Optimal infant survival in resource-limited setting requires breastfeeding for longer than 12 months; and
- Even with maternal triple antiretroviral drug therapy during pregnancy and breastfeeding residual postnatal infection rates at age 6 months range from1-4% and up to 6% at age 12 months.

Thus, she concluded that current interventions will not get us to our elimination goals and adjunctive interventions, particularly passive and active immunization, to allow safe breastfeeding for up to 2 years or more are needed.

Implementing PMTCT: Situation on the Ground (Godfrey Esiru)

Dr. Esiru described the Uganda planning process and implementation of transition to provision of triple drug combination antiretroviral drug regimens to all HIV-infected pregnant women regardless of CD4 count and clinical stage. The transition has started in a staged manner in 2012 and it is anticipated it will be implemented country-wide by the end of 2013. Despite additional costs, the new treatment guidelines are viewed as advantageous by the Ministry of Health because they will provide the continuity of treatment through the childbearing age (at 6.2 children/woman, Uganda has the 3rd highest fertility rate in the world) and are anticipated to reduce HIV transmission.

Use of Immunization Strategies to Prevent HIV Infection in Neonates: What Have We Learned (Coleen Cunningham)

Dr. Cunningham discussed lessons learned from immunization to prevent other infectious diseases in neonates and children, which has proven to be effective in preventing infection, acceptable to parents, feasible, safe, and efficacious in reducing childhood mortality. She discussed the difference between active and passive immunization and data regarding immunogenicity, safety and efficacy of vaccines in the neonatal population. She presented recent unpublished data demonstrating that infants are usually infected with a single viral clone; this increases the feasibility that administration of a potent monoclonal antibody at birth may be effective in preventing infection. She then described past experience with HIV vaccine studies in neonates, including studies of active immunization (PACTG 230 and 326, HPTN 027, PedVacc001 and PedVacc002), and passive immunization (PACTG 185 and HIVIGLOB). Immune response has been seen in neonates to recombinant gp120 vaccines (with alum or MF59 adjuvant); ALVACvCP205 expressing clade B genes; ALVACvCP1452 (clade B genes) with recombinant gp120 boost (AIDSVAX B/B); ALVACvCP1521 (clade E and B genes); and BCG HIVA prime – MVA.HIVA boost vaccines. Interference with antibody production to the standard EPI vaccines was not observed in the BCG-MVA studies.

She then discussed the studies of passive immunization with polyclonal antibodies. PACTG 185 evaluated a polyclonal HIV immunoglobulin formulation in a formula-fed population in the U.S., combining the antiretroviral standard of care at the time, AZT prophylaxis (13% dual antiretroviral drugs) as in the 076 study, with HIVIG or IVIG infused monthly during pregnancy starting at 20 weeks gestation and given to the infant at birth. The study was stopped for futility because of unexpectedly low transmission rates; MTCT was 4% in the HIVIG arm vs 6% with IVIG arm, not significantly different (although *in utero* transmission was 0/9 total infections in the HIVIG and 5/13 in the IVIG arm). HIVIGLOB is a polyclonal HIV antibody preparation from Ugandan donors. The HIVIGLOB trial was conducted in Uganda and the product was studied in combination with single-dose nevirapine (the standard of care in Uganda at the time) versus single dose nevirapine alone. HIVIGLOB was given by infusion once to HIV-infected pregnant women at 36 weeks gestation and given at birth to their infants, who were breastfed. There was not a significant difference between study arms at the primary endpoint at 6 months. At birth, transmission rates were higher in the HIVIGLOB arm; however, the single-dose nevirapine arm had an unusually low transmission rate at birth (4%), while the HIVIGLOB/single-dose nevirapine arm had a transmission rate of 9%, which was similar to that seen in other studies of single-

dose nevirapine being conducted at the same site at the same time. Overall transmission at 6 months was 18.7% with HIVIGLOB versus 15% with single-dose nevirapine.

She concluded that infants immunized during the neonatal period can mount measurable humoral and cellular immune responses to HIV vaccines; that studies of active and passive immunization for HIV have demonstrated safety in early studies in infants; and that this immune adjunctive approach deserved further study for prevention of postnatal infection.

Preclinical Studies of Passive Immunization in Neonatal Macaques (J Pablo Jaworski)

Dr. Jaworski described several studies he and his colleagues have conducted in the simian immunodeficiency virus-HIV (SHIV) neonatal primate model. The results have indicated that passive immunization with HIV antibodies, including the VRC01 monoclonal antibody, can protect infant monkeys when given 24 hours prior to challenge; that low doses are effective with repeated low-dose mucosal challenge; and that there appears to be potential benefit of passive immunization in infant animals with breakthrough infection in lowering viral load (free and cell-associated virus) and preventing disease progression. In adult SHIV models, benefit was also seen with breakthrough infections, including delay and reduction in viremia and B cell preservation with more rapid induction of HIV-envelope specific antibody. He concluded these studies support the use of potent HIV antibodies for prevention of HIV infection, particularly in neonates with low-dose repeated mucosal exposure, and that there may be potential attenuation of disease progression should breakthrough occur.

Other Potential Prevention Modalities (Tom Hanke)

Dr. Hanke discussed the PEDVacc001 and 002 studies being conducted in the Gambia and Kenya. This strategy includes a BCG.HIVA prime vaccine with Modified Vaccinia Virus (MVA).HIVA boost. The MVA vector is a non-replicating attenuated poxvirus that has been used in adult HIV vaccine studies, as well as in vaccines against malaria and TB. The immunogen HIVA consists of the HIV-1 Gag p24/p17 capsid subunits of consensus African clade A coupled to a string of overlapping CD8 T cell epitopes. PEDVacc1 is a phase I study in Gambia evaluating safety and immunogenicity of MVA-HIVA in 20 week old infants born to HIV-uninfected mothers. PEDVacc2 is a similar phase I study in Kenya in 20 week old infants born to HIV-infected mothers. Results to date indicate that the MVA-HIVA vaccine is well-tolerated. There were no vaccine-elicited responses detected in *ex vivo* IFN-gamma ELISPOT assays. However, in the cultured IFN-gamma ELISPOT assay there were statistically significantly higher anti-HIV responses between vaccinated and unvaccinated control infants to peptide pool 9 at 1 week post vaccine and peptide pools 1 and 2 at 8 weeks post vaccine in PEDVacc1 (assays for PEDVacc2 ongoing). The MVA.HIVA vaccine did not interfere with antibody induction to the standard childhood vaccines.

Case Study: Proposed Trial of the Passive Immunization with the VRC01 Antibody

Three talks introduced the VRC01, its potential to be used for passive immunoprophylaxis, and a possible roadmap to testing the efficacy in infants born to HIV-infected mothers.

VRC01 Antibody (John Mascola)

Dr. Mascola provided an update on HIV neutralizing antibodies in general, including a review of the antibody epitopes on the HIV-1 trimer envelope. Early monoclonal antibodies were directed to glycan (2G12, neutralizes~30% isolates); gp41 (4E10 neutralizes ~30%; 2F5 neutralizes weakly ~85%); and the CD4 binding site (b12, neutralizes ~40%). He then described how new more potent monoclonal antibodies were identified, including those that target the epitopes at the CD4 binding site, glycan-V3 site, V1V2 on gp120, and MPER on gp41. These new monoclonal products are 10 to 100-times more potent than the early monoclonal antibodies, neutralize ~90% or more of viruses from multiple clades.

He described the isolation and activity of the VRC01 monoclonal, which targets the CD4 binding site, a highly conserved site in the virus. He described the structure of the antibody, and showed how it blocks attachment at the site of initial CD4 binding. Doses of 20mg/kg protect against mucosal SHIV162P3 challenge in NHPs (he cited vaginal and rectal studies). Ongoing studies aim to identify the next generation of monoclonal antibodies with the goals of improving potency; identifying potential combination preparations; and finding ways to extend antibody half-life. VRC07 was found to neutralize 93% of isolates (compared to ~91% with VRC01) at 50 µg/ml. He noted that there is at least a 2 year time lag from the decision to make a new monoclonal antibody and initiation of a phase 1 study in humans. He also noted that while antibodies may be able to be engineered to be more potent, a serious problem is that in the studies to date the antibody then becomes highly auto-reactive. Importantly, in the case of VRC01, the monoclonal is not auto-reactive. Combining monoclonal antibodies is an exciting possibility but to date only VRC01 has been produced in a cGMP manner to allow clinical studies, whereas, a new promising monoclonal 10e8 is not yet slated for clinical production. Finally, he discussed potential modifications of the Fc region of the antibody to increase binding to the neonatal Fc receptor, which might be able to increase the half-life of the antibody. He concluded that while there are some new and promising monoclonal products and it may be possible to test combinations and improve half-life, these products are years from being ready for clinical studies in adults, let alone neonates, and the most promising product that will be available in the 1-3 year timeline would be VRC01.

VRC01: Path to the Clinic (Barney Graham)

Dr. Graham described the clinical development plan for VRC01. He noted that demonstration of passive protection with antibody often preceded the development of a vaccine for active immunization. The only monoclonal antibody approved for prevention of an infectious disease in neonates is palivizumab Synagis®, used prophylactically in infants at high risk of severe disease from respiratory syncytial virus. Since 1986, 30 monoclonal antibodies have been approved by FDA for treatment in humans, most focused on autoimmune disease, malignancy, asthma, angioedema, and infections. He discussed how proof of protection from an antibody product could inform the design of immunogens for an HIV vaccine. He noted that VRC01 has been shown to prevent SHIV infection in NHPs; has no evidence of reactivity to normal human tissue; and has been manufactured as an IgG1 antibody for clinical study evaluation.

The initial development plan for VRC01 began with convening an Advisory Panel of Experts in July 2010, who recommended a focus on PMTCT. Further consultations have been held with experts in monoclonal antibody discovery, manufacture, and clinical development. The initial dosing plan for the product has

been based on clinical experience with Synagis and pre-clinical data in primates. He discussed details of the passive VRC01 studies demonstrating protection of infant macaques, with subcutaneous dosing and high-dose oral challenge – 2/2 protected with 20 mg/kg and 4/5 protected with 5 mg/kg; the one breakthrough infection occurred in an animal with relatively low neutralizing activity (<50 IC50). He showed the pharmacokinetic modeling that has been used to predict required neonatal doses. Phase 1 studies in both uninfected and HIV-infected adults will be initiated in 2013, with potential plans to initiate phase I studies in high-risk neonates in the U.S. in 2014, and the phase IIb study in breastfeeding infants in Africa in 2015. There are ongoing efforts to engineer antibodies to optimize neutralization potency (VRC07), improve Fc-mediated effector functions, and extend half-life, as well as to optimize coverage by using combinations (e.g., 10E08 and VRC07), but these improvements will not be available for Phase I testing for at least 2-3 years.

He then discussed potential biologic and clinical issues for passive prevention modalities in low-resource settings, including safety (noting the VRC01 backbone is similar to other licensed products with favorable safety profiles); interference with other vaccines (noting that since the product targets the virus and not elements of the host immune system, this is not anticipated, but needs to be studied); and viral resistance and fitness (there are no data indicating that virus resistant to CD4 binding site antibodies would be more virulent and suggested they would tend to be less fit given the highly conserved nature of the epitope). He discussed logistical issues, including cold chain requirements (noting the antibody is relatively stable and can be formulated for storage at 4 or -20^{o}C; potentially could be lyophilized to powder which could be mixed with diluents at time of administration); delivery (the product is formulated at 100 mg/mL and hence volume of the dose for infant would be small (e.g., $\leq$1 mL) allowing subcutaneous rather than intravenous delivery); and schedule (will depend on dose and half-life of product, and duration of breastfeeding). He also discussed cost issues, noting that the cost for manufacturing of a fully developed monoclonal antibody product would depend on the scale of manufacturing. At a level between 100 kg and 1 metric ton per year, the cost of goods could be as low as ~$200/gm and that for 6 months of infant monthly administration about half a gram of product would be needed. He estimated that if 30 infants were treated to prevent one infection, then cost would be ~$3000 to prevent each infection and that the lifetime financial cost for care of one HIV-infected infant would be higher than the cost for treating 30 infants with passive antibody to prevent infection. Finally, he discussed post-trial plans for the product assuming efficacy or lack of efficacy is found. Assuming efficacy, a commercial partner would be sought to join a consortium of government and nonprofit organizations to identify ways to manufacture and distribute the product on a large scale. In addition, efforts would be ongoing to improve potency and half-life of the product. He concluded that VRC01 has excellent potency and breadth, favorable biophysical properties, and based on primate data has a high chance of being safe and effective.

Overview of the VRC01 Trials in Infants (Betsy McFarland)

Dr. McFarland described the proposed approach to moving VRC01 from phase I to a phase IIb efficacy evaluation. She noted that broad consultation has occurred within IMPAACT, FDA, IMPAACT community advisory board, and included the current meeting. In an initial survey of 15 IMPAACT African sites, 14 indicated interest in participating in such a trial. Initial phase I safety and pharmacokinetic studies are planned in high-risk, formula-fed infants in the U.S. High-risk has been defined as mothers with no

antepartum antiretroviral drugs or <30 days of antepartum drugs prior to delivery; poor adherence (defined as missing all antiretroviral drug doses for 7 days or more before delivery); high viral RNA in the mother; prolonged premature rupture of membranes (>12 hours); or multi-class drug resistant virus. A single dose of initially 20 mg/kg and, if safe, increased to 40 mg/kg, would be given at birth (N=13 per group). Planned studies include evaluation of pharmacokinetics, safety (clinical, laboratory including CD4 count), development of anti-VRC01 antibodies, and infant HIV diagnostic testing; infant will be followed for longer-term safety for up to 12 months.

Following identification of a safe and appropriate dose, a phase I safety and pharmacokinetic study of repeated monthly dosing in HIV-exposed breastfeeding infants in Africa is planned; mother and infant would receive standard of care antiretroviral prophylaxis (anticipated in the majority if not all sites to be maternal triple drug therapy during pregnancy and breastfeeding and 6 week infant nevirapine). As in the U.S., a phase I study will be conducted; 10 infants will be enrolled with follow-up for up to 12 months. Once safety and dosing information are available, the phase IIb study would then commence, which would be a randomized, double-blind, placebo-controlled trial of monthly VRC01/placebo administration to the infant from birth through duration of breastfeeding in addition to standard of care antiretroviral prophylaxis; initial enrollment of 100 infants with intensive safety monitoring is planned and if no safety issues are identified, a step-back to less intensive laboratory monitoring would be done. The primary efficacy endpoint would be intrapartum/postpartum infection at age 6 months (to allow early determination of efficacy); secondary endpoints would be 6 week, 12 month and 24 month infection rates; HIV-free survival; evaluation of effect on infant immune response to routine immunizations; and exploratory studies on any breakthrough infections to evaluate effect of the monoclonal antibody on CD4, RNA and clinical disease and characterization of virus. All infected infants will be initiated on therapy following diagnosis. Sample size calculations were presented, based on control group transmission rates between 3 and 5% and efficacy rates between 60 and 80%. The current proposed total sample size of 3,186 infants was based on the most conservative estimates - control group MTCT rate of 3% and 60% efficacy. Based on accrual to perinatal prevention PROMISE study, the anticipated monthly accrual (once open at all sites) is 100 patients/month; therefore, the study would complete enrollment in 3 years.

Breakout Groups' Considerations and Recommendations

Breakout groups convened on day 1 to discuss the assigned topics in detail. The resulting considerations were presented and discussed in a plenary session. The groups reconvened on the following day to summarize their recommendations within several key points.

Common considerations

While each breakout group had a specific area to consider, some topics arose in multiple groups and they are summarized in this section.

A compelling need for better PMTCT interventions

Antiretroviral drugs during pregnancy and breastfeeding are highly effective in preventing transmission. However, current strategies do not meet all PMTCT needs. ARV intervention is highly dependent on the daily adherence to treatment, setting a high standard that is difficult for many women/families to

achieve. Several clinicians noted that a large proportion of women and their infants do not remain in care after the infant's 6 week visit. There are women who present late in pregnancy and, therefore, have significant risk for transmission despite initiation of ARVs. Thus, there is a strong justification for continuing to invest in potential new PMTCT interventions if they will provide new technologies that will add to or enhance current strategies.

Advancing an existing product versus waiting for an improved alternative product

A key step for product development is to decide whether it would be better to use currently available products versus deferring until potentially better products are available. All groups felt strongly that the delay in availability of an improved product is an important consideration, which may override its slightly higher potency, and that an extended half-life was a more important property for a second generation product.

Trial Feasibility and Acceptability

Coming for monthly clinic visits to receive the immunization with the study product for the duration of breastfeeding (up to 24 months) presents a challenge for participants. It would be preferable to synchronize these injections as much as possible with already established mother-child health clinic visits, e.g. the immunization and family planning visits, or scheduled visits for their option B+ follow up. However, it was recognized that a product with longer half-life is not yet available. Thus, while the proof of concept may be done with monthly administration, there would be a need to move rapidly toward less frequent administration. A consultation with MedImmune regarding their studies with Synagis should be considered.

The frequent injections to the infants may be a concern for mothers because children will also have safety blood draws and blood draws for toxicity events.

Product feasibility in the context of existing public health systems

Long-term feasibility for the product should consider the potential for public health implementation. While it is recognized that the present VRC01 study requires dosing the monoclonal based on its pharmacokinetic properties, in the long term dosing would be ideally coordinated with and delivered by the same programs that deliver routine immunizations. Such alignment would require longer dosing intervals; therefore, product developers should explore methods to prolong half-life or consider higher doses administered less frequently.

It is critical to ensure that the studied regimen does not interfere with protection from the standard childhood vaccines, and this should be determined in early studies. These studies should not wait until the conclusion of the phase IIb study, as they are an essential decision point for proceeding with a larger efficacy trial.

A roadmap to assure access to the product if it is determined to be effective

Product development must include a pre-determined roadmap leading to availability of the product if it is determined to be effective. Although having product available for immediate clinical use at the conclusion of the study would not be a requirement, there must be an overarching commitment to make every effort to provide rapid, affordable access to the product if effective, with priority given to communities and countries where the study was done and to countries most affected by HIV. At a

minimum, a roadmap for such provision should be outlined prior to initiation of the study. Early discussions with Ministries of Health/regulatory agencies/community should take place.

The product development roadmap should also include a preferred product profile which takes into account the characteristics needed for the intervention to be successful in resource limited settings (e.g. long acting, dosing schedule that can be integrated with current standard of care, preferably no cold chain, cost effective relative to other interventions). However, the consensus opinion endorsed proceeding with clinical trial of an earlier generation product that may not have all the desired characteristics, provided it appeared feasible for subsequent development to meet the preferred product profile. Meeting participants commented on other treatments that are now standard of care in resource limited settings that were previously thought to be impracticable due to either economic or logistical barriers.

However, mothers and infants on study must have immediate access to the product if found effective. There should be consideration of providing the product to current maternal study participants for subsequent pregnancies.

Breakout Group on Logistical Challenges

Chair: Mary Glenn Fowler
Rapporteur: Carolyne Onyango

Population to be enrolled into the study

- The group agreed that the various represented countries have the population of women that could be enrolled into the study. Many women are still reporting to the antenatal clinics (ANCs) late in pregnancy or during the intrapartum period. These women are at high risk of transmitting HIV to their infants as they will either have been on ARVs for a very short period of time and viral suppression will not have taken place, or they may not be on ARVs at all (especially those who present in labor).
- Enrolling women into the study during the intrapartum period was viewed as not optimal by many participants because these women will be grappling with the positive HIV test results and may have difficulty providing adequate informed consent. However, there were a number of group members who felt that this group of women should not be excluded from the study. It was advised to consult researchers that conduct studies enrolling late presenters, like the PROMISE study, who would be able share lessons on how they have been able to enroll the late presenters. However, unlike the PROMISE study where the mothers have a period of 7 to 12 days after birth to be enrolled, the current VRC01 proposal requires the infant to receive the study product within 24 hours of birth.

Incidence and sample size

- Incidence rates of HIV transmission with mothers and infants on ARVs ranges between 3% and 5%. The rate is higher among those who are not on ARVs or who start late in pregnancy (“high risk group”). If the study recruits only the women in the “high risk group”, then it would require a much smaller sample size as opposed to enrolling all women. Moreover, those women who

present early in pregnancy and are adherent to their ARVs already have a lower risk of transmission and they would not benefit from the monoclonal as much as the "high risk group". It was recommended to enroll women from the "high risk group" and consider giving women who present in labor to have a chance to be enrolled in the study.

Enrollment Strategies

- Enrollment of women who appear for the first time in labor and delivery would require additional resources for the study. Human resources are needed to effectively recruit, and financial resources are needed to perform testing during the intrapartum period. Health workers and field workers will be key in maintaining enrollment and retention in the planned study.
- It is important to encourage women identified as being HIV-uninfected early in pregnancy to repeat HIV testing during pregnancy as acute infection during pregnancy poses a high risk of transmission to the infants.
- While disclosure of HIV-infected status to partners is encouraged, it is best not to make it mandatory for enrollment. However, every effort should be made to encourage the women to disclose their status and participation in the study to either a partner or other person of their choice. Disclosure helps the women adhere to ARV medication and to study visits.
- The protocol team should consider strategies to involve men to support their partners to take part in the study.

Protocol Development

- It should be clarified what will happen with participants after breastfeeding cessation: will the mother-infant pair continue with study visits monthly or could these be changed since they may no longer be at risk? At least one extra administration of the product should be provided after reported cessation of breastfeeding because some mothers revert back to breastfeeding.
- Some sites are reporting that there are women on option B+ who are not coming back after delivery or want to stop taking their medications after receiving HIV-negative results for the infant and cessation of breastfeeding, hence not adhering to the counseling guidelines. This should be taken into account when calculating the sample size for the trial.

Communication

- Continue to encourage CAB and community involvement as the protocol is being designed.
- Bring onboard the policy makers, researchers, ethicists, community, drug authorities, and other stakeholders to discuss the study and also the possibility of roll out if the product is safe and efficacious.
- Develop short courses to educate sites (researchers/ doctors/study nurses and midwives/counselors, etc.) about immunology and the interventions to be studied. Specifically, the concept of passive immunization will require specific educational efforts.

Breakout Group on Treatment and Standard of Care

Chair: Chewe Luo

Rapporteur: Coleen Cunningham

General considerations

- The current treatment guidelines are those issued by WHO in 2010 recommending different options for women who are receiving ARV for treatment versus those who are receiving ARV for prevention of MTCT. Women who require ARV for their own care should be receiving triple drug therapy whereas women receiving ARV to prevent MTCT may receive option A, B or B+. Different countries are at different stages of implementation of the guidelines but several have recently moved to implement B+ including Malawi and Uganda.

Standard of care required for the study

- Studies should be designed to test the intervention administered in addition to the national standard of care and should not require a higher level of care in terms of ARV therapy than what is available and delivered to women and children in country. It is anticipated that most countries will provide B/B+ in the near future.
- The study team should not dictate the specific treatment regimen used at each site as different countries may choose different regimens and variations on guidelines. However, close linkages to care are necessary and ARVs should be available, encouraged, and facilitated for the study participants in order to optimize delivery of the national standard ARV. This is important because the intervention being tested is designed to be used in addition to standard of care, which will include individuals who did not receive the full standard treatment regimen, i.e. late presenters.
- It is critically important for the study and the sites to develop targeted strategies to enhance, facilitate, and monitor adherence to ART in study participants. This is important in order to assure the best possible delivery of the national standard ART to women and infants who are on study (we don't want to prove that the intervention works on a suboptimal background) and it is also important for the long-term data analysis as ability to determine which patients are or are not adherent will be important in interpreting the results of the study.

Important study variables that should be collected

- The team should consider incorporating information on how long B or B+ has been implemented in the participating countries and should collect data on maternal ARV history, maternal CD4 (delivery), breastfeeding practice, and adherence to ARV.

Considerations on and recommendations for "high risk" criteria

- Participants raised the question about the proposed criteria to define high risk for transmission, asking "how high risk do we need"? If the goal is to enroll women/infants in whom there is a >3% risk of combined intrapartum and postpartum transmission, it is not necessary to limit enrollment only to women treated in the last month of pregnancy. All women who initiate therapy in the last trimester could be enrolled because a significant portion of those women will not achieve complete viral suppression by the time of labor and delivery.

- The team should consider adding other "high risk" criteria, including replicating virus during pregnancy. Most countries are not providing routine viral load monitoring but viral load measures may become more widely available by the time the study is implemented, especially as less costly point of care testing is rolled out. However, it needs to be determined how to get that viral load results at sites for which the viral load test is not standard of care. The study will have to address the costs for offering the viral load testing for study screening.
- The ability to enroll all HIV-infected women and their infants would logistically be easier, potentially avoiding the difficulty of consenting near the time of labor, and would provide the most generalizable results; however, it would then include infants at lower risk of infection and influence sample size. One participant suggested that perhaps all women who start treatment in the current pregnancy may be sufficiently high risk for study enrollment.

Care for mothers and infants while the infant is on study

- For women and children on study, there should be careful consideration of and support for the sites' ability to directly provide or assure access to general medical services in order to improve health of participants, collection of clinical data, and retention in study. Study participants will be returning to the study site monthly for treatment and the infant will also need medical visits for routine immunizations and the mother (and possibly the father) will require medical care visits for routine post partum care, family planning, ART, and other health care needs. To make study participation feasible for families and to facilitate retention in the study, it will be important to facilitate this care as much as possible. The study should not dictate how that is done at the individual site level but should encourage all sites to deliver the national standard of care medications during clinic visits or directly provide routine clinical care while the participant is completing the research care visit.
- If it's not possible to directly provide the national standard ARV at the research site, trial organizers should provide support and linkages, so that attending multiple visits does not result in an unmanageable burden. For example, can participants avoid waiting in a separate line in each setting, can visits be coordinated, and/or can immunizations be moved to be delivered at the same time product dosing is provided?

Breakout Group on Ethical Challenges and Long-Term Plans

Chair: Helen Rees
Rapporteur: Betsy McFarland

Product acceptability in target population

- There is an established precedence for the use of vaccines in infants and pregnant women. Prevention modalities that are long acting are preferable to those that require daily adherence. Although the community will need education about any new immunization technology, in general the community considers vaccines, which are traditionally viewed as preventative, to be less stigmatizing than medication. HIV-affected communities in resource-limited settings have minimal experience or understanding of passive immunization using monoclonal antibodies. Although passive antibody for protection in infants, such as the RSV monoclonal antibody and hepatitis B

hyperimmune globulin, is used routinely, the group recommended initiating community education in advance of initiating a trial of monoclonal antibody for PMTCT.

Clinical development path

- Anti-HIV neutralizing monoclonal antibody is an agent that has not been tested for efficacy in adults. Some committee members thought that first proving efficacy in adults was the traditional pathway for development and should be followed. However, the majority of the group thought that a study to determine efficacy in PMTCT could proceed without proven efficacy in adults provided there was a pathway to use data from adults to rationally select doses that should be safe and efficacious in infants. The licensed monoclonal antibody (palivizumab) used to prevent respiratory syncytial virus in high risk infants was never tested for efficacy in adults, providing a precedent for this approach. Three considerations provide the rationale for proceeding with PMTCT studies without adult efficacy data. First, there is urgent need for better PMTCT for the at-risk infant population. As a result, there is potential harm in delaying the study of new agents, since there will be ongoing infant morbidity and mortality occurring when a potentially efficacious agent is available for study. Second, PMTCT is particularly suited to use of passive immunization as an intervention since the exposure time is clearly defined. Finally, the mechanisms of transmission in MTCT are sufficiently different from that in adults that efficacy in adults may not translate to efficacy in MTCT.
- There must be a systematic plan for moving from studies enrolling adults to those enrolling infants. Initial studies in adults should determine safety in both HIV-infected and uninfected adults. Pharmacokinetic parameters determined in adults should indicate that dosing regimen will be likely to achieve target levels. With respect to VRC01, the committee supported the sequence of studies as presented to and accepted by FDA: 1) dose escalating studies of safety and pharmacokinetics (PK) in HIV infected and uninfected adults; 2) safety and PK in infants at risk of transmission in the U.S.; 3) safety and PK in infants in breastfeeding populations and then 4) moving to studies to assess efficacy in breastfeeding infants.

The vulnerability of the target population

- Studies of PMTCT, by their nature, are conducted in a vulnerable population. Clinical trials in the current era will, of necessity, have a large sample size and will likely need to enroll mother-infant pairs at higher risk of transmission since the event rate is expected to be low with current ARV interventions. Women with higher risk of transmission are particularly vulnerable, because the factors that increase their risk (e.g. late entry to care, poor adherence to treatment, advanced disease stage) are typically indicators of disenfranchisement. Moreover, the time of labor and delivery is a more vulnerable period for these women. However, the group also emphasized that the mother-infant pairs at higher risk of transmission are also the most likely to benefit from additional technologies to reduce transmission and, therefore, approaches to include them with adequate informed consent and with adequate support to retain them on the study should be supported.

A strong scientific justification for selection of the study product

- In order for an agent to be considered for use in a PMTCT trial, there must be strong pre-clinical data supporting the expectation that the agent will be both safe and efficacious for PMTCT. These should include both in vitro data and data from NHP and other animal models of infection that are relevant to PMTCT. Internal and external review of the available agents should be critical and comprehensive, taking all potentially available products into consideration.

Engaging and educating the community and the study participants to assure informed consent

- The group recommended that the trial sites conduct feasibility studies to improve accuracy of accrual rates, to better understand the circumstances of women with higher risk of transmission, and to determine how best to obtain informed consent. Since VRC01 will represent a technology not previously used for PMTCT in this study population, the investigators will need to proactively educate the community. The product will need to be described to the study participants in understandable lay language that communicates the characteristics of the product. It will be important to engage men in general, and male partners specifically, since partner support will be necessary to recruit and retain many women. Informed consent must also consider the potential social harms, such as inadvertent disclosure of the mother's HIV status.

Access to a pre-defined package of ARV and non-ARV health care

- Ensuring that the health needs of both the mother and the infant are met is an ethical responsibility and is necessary for successful completion of the study. At a minimum, there should be access to national and local standard of care for both mothers and infants in the context of the study, either through care provided at the study site or by rapid, facilitated referral to clinical care facilities. All infants determined to be infected should have immediate access to antiretroviral treatment. There should be a consideration of incorporating infant ARV treatment into the study design. In addition to health care, there should be resources to refer women to community support services for other needs.

Adequate resources to assure successful study completion

- Recruiting and retaining mother-infant pairs with higher transmission risk will require a high level of site resources. This must be recognized by the funding agency for the study and the sites should be consulted in advance prior to finalizing budget decisions. In addition, the group recommended that the debate on the facilities and administrative costs (F&A) that are negotiated with clinical trial sites be reopened for reasons of equity and justice since current rates are not sufficient to build and maintain a sustainable clinical trials infrastructure.

General considerations for study design

- Since the proposed agents will represent a new technology, there must be a safety lead in built into the study design. Products selected for the clinical trials should have pre-clinical results that address the possibility of increasing the risk of HIV acquisition. The study must include a strategy to monitor for this possibility so that it is recognized early if it does occur.
- The study should be designed with careful consideration of the need to complete the study while the study question is still relevant.

- The design must balance recruiting higher risk mother-infant pairs to enrich for HIV transmission events with the feasibility of recruiting these subjects and with the desire to have results that can be generalized at the conclusion of the study.

Breakout Group on Future Prevention Strategies

Chair: Pontiano Kaleebu
Rapporteur: Lynne Mofenson

HIV vaccines

- The number of potential vaccine candidates that might be available for testing in infants within the next 1-2 years is limited, with the most likely candidates being ALVAC or chimp adenovirus combined with gp120 boost. Additional consultations with HIV vaccine researchers should explore in more detail what could be available in this time frame.
- If an attractive vaccine candidate is identified with appropriate safety studies completed in adults, then phase I-IIa trials should proceed in parallel with the monoclonal antibody studies; waiting for the results of an efficacy trial of one modality before testing another modality is neither practical nor beneficial.

Improved monoclonals

- A product that included combination monoclonal antibodies and had a longer half-life would be desirable. However, no other product has reached the stage of large scale production for clinical use and human (adult) studies. Thus, it would be a minimum of 2 to 3 years before human studies of monoclonal antibodies other than VRC01 could begin. Since the VRC01 product is already available, is highly potent, and has shown efficacy in neonatal primate studies, and does not appear to be autoreactive, the studies of VRC01 in neonates should proceed now.
- It should be considered whether using a higher dose of VRC01 would lead to maintenance of levels >50 µg/mL for a longer period to allow dosing every 3 months instead of monthly. For example, it is planned to give a 40 mg/kg dose at birth and then 20 mg/kg monthly – might it be possible to give a 40 mg/kg dose at birth followed by 40 mg/kg every 3 months?

Combination interventions

- The ultimate goal of PMTCT strategies should be a combination active/passive intervention as both immediate as well as durable protection is necessary, and hence research should proceed on both approaches as soon as promising products become available.

Considerations for trial design

- Studies of children with breakthrough infections need to be a part of the design of any active or passive immunization study. The primate data on monoclonal breakthrough infections suggest that there may be a potential persistent effect of intervention in reducing viremia, maintaining B cell function, and reducing clinical disease. Thus, follow-up to evaluate viral set-point and course of disease in infants who are infected (and treated) will be important. Additionally, genetic

sequencing of breakthrough infections to determine whether the infecting virus genetic make-up was affected by the immune product will be critical.

Summary and Next Steps

While the existing approaches to PMTCT are effective, their implementation is challenging and additional modalities are urgently needed, especially in the developing world. Women continue to become infected – and even with optimal implementation of PMTCT meeting the 2015 virtual elimination goal, there would still be 40,000 annual new infant infections. Infants born to women with late diagnosis are at high risk of transmission due to lack of antepartum drugs. Even with optimal prophylaxis, breast milk transmission continues to occur, yet for optimal infant survival we need prolonged safe breastfeeding. Ideally we need an intervention that provides immediate protection to the infant with prolonged protection through at least 2 years of age and that does not rely on daily adherence to maternal or infant drugs. Passive and/or active immunizations can fill these gaps and new potential interventions need to be studied, although only a limited number of options are available currently for testing in infants. Participants identified a number of challenges and important considerations for conducting such studies, covering the areas of logistics, standard of care, and trial design. The need for long-term planning for the tested products have been highlighted, including the need to realistically consider delivery of the studied intervention and its impact on existing public health practices. The group also provided recommendations on the specific trial of VRC01 antibody, which is being considered by the Vaccine Research Center, NIH.

The Secretariat of the Global HIV Vaccine Enterprise has facilitated further discussion of this issue beyond the initial consultation by:

- Posting presentations from the meeting on the Enterprise web site;
- Preparing a full meeting report and posting it on the Enterprise website;
- Holding an open webinar to present the outcomes of the meeting;
- Creating a moderated “Discussion” page on the Enterprise website, hosting commentaries on this topic;
- Facilitating the writing of a paper for a peer-reviewed journal to further discuss this issue and inform the field on the major conclusions from the meeting.