HIV Exposed Infants: Rethinking care for a lifelong condition

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Summary

Each year over a million infants are born to HIV infected mothers though with scale up of prevention of mother to child transmission (PMTCT) interventions, only 210,000 of the 1.3 million infants born to mothers with HIV/AIDS in 2012 became infected. Current programmatic efforts directed at infants born to HIV-infected mothers are primarily focused on decreasing their risk of infection, but this emphasis on maternal interventions has meant follow-up of exposed infants has been poor. Programs are struggling to retain this population in care until the end of exposure, typically at the cessation of breastfeeding, between 12 and 24 months of age. But HIV exposure is a life-long condition that continues to impact the health and well-being of a child long after exposure has ended. A better understanding of the impact of HIV on exposed infants is needed and new programs and interventions must take into consideration the long-term health needs of this growing population. The introduction of lifelong treatment for all HIV-infected pregnant women is an opportunity to rethink how we provide services adapted for the long-term retention of mother-infant pairs.

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I. Introduction

Currently, over 1 million HIV exposed (HIV-E) infants are born to HIV-infected women worldwide every year though the majority of these infants will not become infected. Most are born in resource-limited settings and therefore exposed to increased mortality and morbidity common for children in such regions. In addition, a limited but growing body of evidence suggests that HIV exposure itself may contribute to poor health outcomes as well as a host of unique psychosocial and economic challenges that can have a profound effect on their overall well-being and ultimate outcomes. Access to health care, education, and social services may also be affected due to family and social circumstances. Even when the risk of HIV infection has passed, HIV-exposed uninfected (HIV-EU) infants will continue to be affected by the impact of HIV on their families, to potential long-term adverse effects of antiretroviral drugs, and to a higher risk for acquisition of HIV-related infections through parental exposure during childhood.

The scale-up of prevention of mother-to-child transmission (PMTCT) programs has significantly reduced perinatal HIV infection rates [1]. Programs which have been successful include the implementation of effective provider initiated testing and counseling (PITC) services, increased availability to antiretroviral prophylaxis and therapy (ART) for pregnant women and their infants, improved delivery practices for HIV-infected women, and an enhanced understanding of how to minimize risk of transmission during the breastfeeding period. [2] Despite the increasing access to HIV-related services for women during pregnancy, most need long-term service provision to ensure optimal outcomes. Interestingly, implementing an agreed upon 'package of services' for these women and their infants has been challenging and more efforts are needed to help countries define and implement what these services should be and where and how these services should be offered.

Although the numbers of new pediatric HIV infections will continue to decline as the number of pregnant women and mothers having access to effective PMTCT interventions increase, improving the delivery of services to HIV-exposed infants continues to be a priority for both PMTCT and Pediatric HIV programs in most resource-limited settings. Furthermore, as more adults benefit from ART and have healthier and longer lives the population of HIV-E infants is likely to increase, highlighting the importance and need for countries to strengthen the capacity to provide quality long-term services for this population. These efforts should ideally be complementary to national and international efforts to improve overall child survival as HIV-EU children are still at risk from preventable childhood diseases such as measles, malnutrition, and tuberculosis (TB).

II. Long-Term Impact of HIV Exposure on Infant and Childhood Health Outcomes

The prenatal period and the first few years of a child's life set the stage for long-term physical and mental health. While better understanding of the long-term impact that HIV has on HIV-EU in resource-limited settings is needed, there is evidence that early exposure to HIV has health effects lasting beyond the transmission period. [3] The effects of exposure to

HIV itself must be considered as well as the impact of environmental factors related to birth into a HIV-affected household including orphanhood, stigma, discrimination, and extreme poverty. A brief review of these concerns is helpful as we rethink the types and duration of services, interventions and surveillance needed to ensure optimal outcomes for these children.

Evidence of Increased Morbidity and Mortality

Initial evaluation of increased morbidity and mortality in HIV-E infants in Africa arose from early trials to evaluate PMTCT regimens. A pooled analysis of seven such trails found that risk factors for death among HIV-E infants included maternal death, lower maternal CD4 counts [4], and early weaning [5] (See Infant Feeding paper in this series). Though maternal ART adherence is effective in reducing under-5 mortality, [6] further studies continue to link increased risk of child mortality with poor maternal health and HIV exposure and there is a need to better understand what drives this increased risk of death to develop effective prevention strategies. [7,8]

The reasons for increased morbidity and mortality are likely multifactorial, but there is some evidence that HIV exposure in utero or during the postnatal period affects development of the infant's immune and other organ systems. Moreover, HIV exposure and maternal placental responses to the virus have resulted in modifications or interference with the immune response of HIV-EU infants, resulting in immunological abnormalities and increased susceptibility to childhood diseases. [7,9]

The immune system is underdeveloped at birth and as a result infants and young children may be thought of as immune-compromised regardless of previous HIV-exposure.[10] HIV-infected women or HIV-infected family members are at high risk for co-infection with opportunistic pathogens and are more likely to transmit horizontally to children, resulting in an increased risk of primary acquisition of HIV-related infections in children.[11,12] In addition, HIV-E infants are more susceptible to congenital or acquired infections with TB , herpes and cytomegalovirus (CMV) than their unexposed peers. Globally, CMV is the most commonly transmitted infection from mother to child, occurring in 0.2 percent–2.2 percent of live-born infants in the United States with similar transmission rates likely in resource limited settings. The prevalence of CMV infection among HIV-infected pregnant women is higher than in the general population, with approximately 90% of HIV-infected pregnant women co-infected with CMV [13].

Cotrimoxazole prophylactic treatment (CPT) is currently recommended for all HIV-E infants and while the benefits are clear for HIV infected children the evidence of benefit for uninfected infants is less so.[14,15] The Breastfeeding, Antiretrovirals, and Nutrition (BAN) study demonstrated that the use of prophylactic cotrimoxazole was associated with reduced rates of morbidity and mortality in HIV-EU infants. However, other than temporary protection from malaria, CPT offered no protection against anemia, malnutrition or severe illness and death for HIV negative children.[16,17] Given limited data that CPT may increase risk of diarrheal illness in HIV uninfected infants there is a need to define the optimal duration of cotrimoxazole prophylaxis and possibly reexamine current guidelines. [18]

Growth and Neurodevelopment

Growth stunting is associated with preterm or low birth weight infants both of which occur more commonly in infants born to HIV-infected mothers. [19,20] Additionally, growth stunting is associated with discontinuation or reduction in breastfeeding which significantly effects a child's health and cognitive development. [20,21] Differences in growth between HIV-EU and unexposed children typically present in the first months of life and some studies on postnatal growth show minimal difference in early growth of HIV-EU children compared to unexposed controls.[22]

With the rollout of Option B+ (provision of lifelong triple drug therapy for HIV-infected pregnant women not dependent on CD4 count), the impact of exposure to triple therapy on a child's growth and development needs to be closely examined. Recent evidence from the Mashi and Mma Bana trials in Botswana revealed that both weight for age and length for age were significantly lower in HIV-E infants exposed to ART in utero compared to those that were only exposed to maternal single drug prophylaxis with AZT. [23] It remains unclear whether these differences have a short term impact or whether they predispose the child for subsequent poorer health, obesity, chronic disease or cognitive dysfunction.[24]

The impact of prenatal ARV exposure on neurocognitive development given the association of nucleoside reverse transcriptase inhibitors (NRTI's) with mitochondrial toxicity is also of concern.[25,26] Early reports of birth defects and mitochondrial toxicity from exposure to ARVs remains equivocal and while a French study reported 0.5% of ARV exposed children had mitochondrial dysfunction [27] more recent evidence evaluating outcomes in HIV-EU children found no association between in utero exposure to any ARV and neurodevelopmental outcomes when assessed using a standardized measure of infant development. [28, 29] Similarly evidence suggests that most detectable developmental delays among HIV-EU children are a result of environment factors and not a consequence of in-utero or postnatal HIV exposure and that with improved attention to a child's early developmental and psychosocial needs such delays may be prevented or reversed.[27-30]

Potential for short and long-term antiretroviral -related toxicity

At present the benefits of ART reducing vertical transmission and improving maternal health greatly outweigh the potential adverse effects of ART exposure to children. However as PMTCT coverage increases the number of uninfected infants exposed to antiretroviral therapy (ARV) in utero or through breastfeeding will likewise increase making it critical to continue to monitor for adverse effects. Considerable data link protease inhibitors to preterm delivery and low birth-weight.[31-33]. Hematologic abnormalities may also be associated with exposure to ARV's; both short and long term effects on several hematologic parameters have been noted in infants exposed in utero and post-natally to different ARV's.[34] Firm conclusions about the potential long-term physiologic effects of exposure to ARVs in utero are lacking as significant heterogeneity often exists between studies, however the benefits of antenatal exposure to ARV's must be weighed against an understanding of any risk. Of greatest importance is ensuring the most effective and acceptable regimens are available, as the risks of virologic non-suppression are substantial for both the woman and the child.

As more pregnant women living with HIV initiate ART during pregnancy, many women are likely to become pregnant again while taking the preferred first line regimen containing both tenofovir (TDF) and efavirenz (EFV). There has been concern about the use of EFV in pregnancy due to the association with heterogeneous central nervous system defects in animal studies. However a recent meta-analysis reported only one neural tube defect in infants born to women on EFV-based as compared to non-EFV-based regimens; a lower rate than what is reported for the general population.[35] Therefore, while it appears that the potential risks to the infant with EFV exposure is very low, definitive studies and birth defect surveillance with larger sample sizes are needed (and are ongoing), there is not reason to limit use of EFV in pregnant women. [36, 37]

Tenofovir (TDF) is known to affect bone mineral density and renal function in adults, although the clinical significance of these effects is still not clear.[38-40] Infants exposed to TDF in-utero have been found to demonstrate no growth parameter (e.g., birth weight, length) differences when compared with infants exposed to non-TDF containing regimens. [41] The US Pediatric HIV/AIDS Cohort Study compared infants exposed to combination drug regimens in-utero with and without TDF and found no differences at birth between the two groups (e.g., birth weight, length, or head circumference). However, at one year of age, those infants who were exposed to TDF in-utero were found to have a small but statistically significant difference in length-for-age and head circumference-for-age compared with TDF-unexposed infants. [42] While current literature does not show any serious risks associated with TDF exposure in utero, the evidence is limited and does suggest more research is warranted. The US Antiretroviral Pregnancy Register has seen a rate of all birth defects in infants exposed to TDF in the first trimester of 2.3%, equivalent to the 2.7% prevalence seen in the overall US population. [43]

Impact of living in households affected by HIV

A growing body of evidence indicates that an adverse intra-uterine environment and maternal stressors during early infancy significantly affects a child's long-term development. [44] In addition, HIV affected households may experience various economic and psychosocial stressors that in turn can increase a child's vulnerability.

Limited data that exists examining the psychosocial development and experiences of HIV-EU children making it difficult to isolate the stressors and risk factors associated with HIV exposure. Some studies have demonstrated that maternal stressors associated with the onset of HIV symptoms can affect a child's psychosocial adjustment [45,46] while other studies indicated that it is a mother's illness or physical well being, not maternal HIV status that affects a child's behavior (See Psychosocial paper in this series). [46] Of particular interest, is the relationship between a parent's disclosure of their illness or HIV status and an HIV-E infant's access to healthcare services, psychosocial adjustment and resilience.[46,47] Non-disclosure of a parent's HIV status is associated with increased levels of depression and anxiety among HIV affected children.[48,49]

By virtue of living in an HIV affected household, HIV-E children are often exposed to death, illness and family disruptions at an early age. If there are other children or adults living with HIV in the household the needs o HIV-EU children may not be prioritized, as

food and healthcare may be rationed to care for ill family members. [48] Illness within the family can result in income loss, decreased food availability, frequent relocation and lower rates of school attendance.[50] A study conducted in South Africa to identify the reasons for loss to follow up among HIV-E children underscored the role that poverty and socio-economic conditions played on members of an HIV affected household's long-term access to healthcare.[51] Due to changes in family composition and orphan hood, HIV-E children may also have multiple caregivers or live outside their home of origin and may be treated differently from non -HIV- affected relatives.[50]

In 2011, an estimated 15.2 million children in sub-Saharan Africa were orphaned due to AIDS and it is likely that a significant proportion of these orphans were also HIV-E. [1,52] While more nuanced data on orphan hood and HIV exposure is needed, findings from the literature on the impact of orphan hood on the psychosocial development of children may provide additional clues regarding the stressors experienced by HIV exposed children. Two studies on the relationship between stigma and psychosocial well-being in South Africa and China showed that AIDS orphans reported higher levels of stigma, which was associated with poorer psychological outcomes.[53,54] In South Africa, AIDS orphans engaged in less positive activities and were more likely to experience higher rates of depression, post-traumatic stress, delinquency and difficulties with peer relationships compared to children orphaned by other causes.[55] Similarly, children orphaned by AIDS are less likely to receive social or economic support and therefore do not reap the documented psychological benefits of such assistance; namely lower rates of depression, anxiety, bullying, and behavioral problems.[56]

Resiliency in HIV-affected Children

Resiliency, or the ability to overcome stressors in a psychologically healthy way, amongst AIDS orphans is attributed to caregiver quality, contact with immediate and extended family and school attendance; while risk factors for poor outcomes include bereavement, frequent changes in caregivers, caregiver illness, discrimination as a result of living in another household and exposure to abuse or violence.[56] Studies have shown that male involvement and a mother's status as a member of an association of people living with HIV (PLHIV) can have a positive influence on an infant's health outcomes.[57] These findings highlight the importance of ensuring that HIV-E infants and their families are appropriately evaluated and referred to programs in the community, including those that are aimed at providing support for Orphans and Vulnerable Children(OVC).

III. Programmatic Challenges and Opportunities

Guidance for the care of HIV-E infants has largely centered on recommendations to minimize the risk of transmission through delivery of appropriate antenatal care (ANC) services, encouragement of safe delivery practices, use of ARV prophylaxis and promotion of optimal feeding during breastfeeding (Table 1). The greatest challenge with providing services for these children is addressing some of the issues that affect retention in care through the end of the exposure period. However longer follow-up should be encouraged to address the health impacts of exposure and provide needed support to alleviate or prevent negative outcomes that may manifest after the risk of HIV transmission has passed.

Factors that affect retention of these infants in care are multiple and include those stemming from the health care system itself particularly staffing and infrastructure, as well as social and individual or family factors. There has been limited success in conducting routine and systematic monitoring of HIV-E infants towards the end of breastfeeding. This is illustrated by the lack of data available on the proportion of HIV-E infants with confirmed HIV status at 18 months of age.[1] Quality of early infant diagnosis services and long turnaround times for results may also affect levels of trust in the health care system and influence adherence to follow up care and the use of prophylactic medications [58]

An additional programmatic challenge has been the lack of standardized, easy to use tools for mother-infant pair tracking and site-level and program data collection. Most services for HIV-E and infected infants currently take place within PMTCT program settings, though increasingly the introduction of lifelong treatment for HIV-infected pregnant women and the emphasis on decentralization of care means that more mothers and families could be receiving care in health center settings.

Full integration of HIV services for women and their infants into health centers would require modification of registers used during pregnancy, in delivery units and in postnatal care sites to link women to their infants from the time of ANC diagnosis through 24 months of age or beyond. In addition, the lack of simple medical records for HIV-E infants adds additional challenges faced by health care providers and programs. Some countries have added information related to maternal HIV and HIV-E infant interventions to the hand-held cards that women carry during pregnancy and in under-5 childhood health cards in order to facilitate the identification of exposed infants each time they access the health care system. This allows health care providers to tailor services to address specific needs for mother-infant pairs at each health encounter.

Maternal health is critical to child survival and long-term development, yet care is often provided to mother-infants pairs separately. Currently there is vague guidance on the best service delivery model for HIV-E infants. PMTCT programs generally focus on maternal interventions while pediatric care and treatment programs are designed to care for HIV infected children. While provision of early infant diagnosis in MCH platforms is effective in some settings, longer term care to improve retention and HIV free survival will require a shift in the organization of programs which have historically been vertically implemented in most countries.[59]

Providing specialized follow up care for at risk children, separate from well-child clinics may contribute to stigma and discourage mothers from accessing services. Fear of disclosure may also inhibit caregivers from getting children tested, or even initiating treatment, making identification and follow up of HIV- E and -infected children more challenging. [60] Treatment initiation, as with most child health issues is a family decision; limited male involvement may also be a barrier to providing more comprehensive care to HIV-E infants in order to prevent transmission, ensure HIV-free survival and provide care for optimal development beyond the confirmation of final HIV status.

As many countries are shifting their PMTCT programs towards the use of antiretroviral therapy throughout the duration of pregnancy and breastfeeding, if not for life, there is a need to adapt service delivery models to ensure the long-term retention of women on treatment. This need offers a great opportunity for improving how programs follow and offer services to the infants born to HIV infected women. Ideally, services and interventions for mother-infant pairs should be provided at the same time and preferably in the same setting. Some of these interventions include screening for TB in the child and family members, supporting cotrimoxazole adherence, ensuring all childhood vaccines are provided, and assessing family support needs and establishing linkages with OVC programs to minimize negative psychosocial, developmental and financial effects.

IV. Research Gaps

As PMTCT programming becomes more refined and effective, the number of HIV-EU infants will continue to grow. Gaining a deeper and more nuanced understanding of the impact HIV and ARV exposure in-utero and in infancy has on children's physical and psychological development is crucial to providing better care. ARV toxicity surveillance for pregnant and breastfeeding women and their infants and more robust systems to capture pregnancy outcomes, such as birth defect surveillance or following long-term cohorts of HIV-EU children are a priority to more fully understand the effects of ARVs on this population. This is particularly critical in resource-limited settings where malnutrition and comorbidities are more common and where monitoring capacity is limited. Linked to toxicity monitoring is the potential/need to further investigate the efficacy, safety and viability of alternative ARVs for prophylaxis, particularly as resistance to nevirapine and potentially zidovudine are concerns for children who become infected. Further investigation is needed to understand the the immune-response of HIV-EU infants to determine whether HIV or ARV exposure compromises the ability to ward off future infections and if the benefits of cotrimoxazole prophylaxis outweighs the risks for HIV-EU infants.

Emerging evidence demonstrates that early stress and shocks in utero and for the first two years of life have significant impact on a child's development into adulthood though very few studies have begun to isolate the medium and long-term psychosocial impacts of HIV exposure compared with HIV-infected and non-affected children. More research to explore the interplay between neurological insults and cognitive and psychosocial development is an area that deserves more attention.

Operations research to evaluate the effectiveness of specific programmatic interventions such as integrated follow up of HIV-E infants with growth monitoring, immunization and other well child services should be considered as postpartum follow up of mother infant pairs is weak in most programs. While there is some evidence that these programming shifts have increased rates of EID testing and treatment initiation among infants and young children, determining which interventions individually and in combination have the greatest impact on improving HEI identification and follow up is an area for further research.[61] Considering that post-partum and post-natal care is weak in many programs, identifying the determinants of post natal care uptake –both structural and socio-cultural may provide key

insights into the barriers that impede mothers from accessing post-partum care, which in turn, may point to potential solutions for reducing loss to follow up among HEI.

V. Conclusion/Recommendations

Until recently, the long-term effects of HIV and ARV exposure on uninfected infants and children has received limited attention. Yet, the number of HIV-EU children will expand in the coming years assuming that MTCT rates continue to decline. While pediatric HIV can be considered a neglected disease, the care of HIV-E and HIV-EU infants and children is even more overlooked. Retention and provision of follow-up care to mother-infant pairs through the end of exposure to minimize risks of HIV transmission is critical, as is reinforcing provider initiated testing and counseling at all entry points and training health staff on specific needs of HIV-E during and beyond risk of transmission is also important.

The evidence suggests that the effects of HIV ad ARV exposure extend through childhood and beyond. Providing comprehensive care for HIV-E, HIV infected and HIV-EU children requires a paradigm shift and significant changes to programmatic approaches. Community outreach to highly vulnerable children for active case finding and referral to support services, such as food assistance, cash transfers, and social welfare should be integral to all programs. Strengthening linkages with community-based testing and support services and OVC programs is imperative to increase identification of HIV exposed and infected children and to provide longer term care and support through home visits to all children who are ill.

Essentially, these recommendations call for a shift away from individual disease specific care to family-friendly services that address the spectrum of health needs along different time points, promote safe disclosure and adherence support. Strengthening family and community involvement from ANC, throughout pregnancy and infancy may reduce stigma and discrimination and help to overcome persistent barriers to identifying and caring for these infants.

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Table 1

Summary of Guidance for Routine Care of HIV Exposed Infants (Adapted from WHO Guidelines) [62]

Goal/type of the intervention	Timing of interventions	Recommended Intervention
Prevention of HIV Transmission	Antenatal (maternal interventions)	• Maternal screening for HIV infection at first antenatal visit • Maternal triple ARV prophylaxis for all HIV-infected pregnant women using preferred 1st line adult regimen: TDF+3TC (or FTC)+ EFV • Provision of at least the minimum package of recommended care for antenatal visits
	Intrapartum (maternal and infant interventions)	• Continued maternal support to ensure adherence to ART or HIV specific prophylaxis • HIV testing of women of unknown status presenting at the time of delivery or repeat testing for previously negative pregnant women • Encourage facility-based delivery • Avoidance of unnecessary instrumentation and premature ROM • Non-invasive suctioning of nasogastric secretions in the newborn • Washing away maternal secretions and blood on the newborn after delivery
	Postpartum (maternal and infant interventions)	• Continued maternal ART to prevent breastfeeding transmission and to preserve maternal health. • Infant HIV prophylaxis to be initiated at birth or when HIV exposure is recognized postpartum • For breastfeeding infants, daily NVP for a minimum of 6 weeks should be initiated shortly after birth. Prophylaxis may be extended to 12 weeks in case of late maternal presentation or suboptimal viral suppression; may be restarted if mother interrupts ART during breastfeeding • Infants receiving exclusive replacement feeds 4-6 weeks of daily NVP or twice daily AZT • If infant NVP is not available, 3TC may be substituted
Cotrimoxazole Prophylaxis	4-6 weeks of age (infants)	• Initiation of cotrimoxazole prophylaxis with continued administration until/if HIV infection is excluded
HIV Testing	4-6 weeks of age (infants)	• Virologic HIV testing for infants with known HIV exposure • Serologic testing for mothers of infants with unknown HIV exposure
	9 months of age (infants)	• Serologic testing at time of last immunization (measles immunization) followed by virological testing if serology is reactive
	Symptomatic infant at any age	• Serologic testing for any infant with signs and symptoms suggestive of HIV infection followed by virological testing if serology reactive (presumptive treatment may be initiated in severely ill infants while awaiting diagnostic confirmation)
	End of breastfeeding exposure (12-24 months)	• Serologic testing at least 6 weeks after the end of breastfeeding followed by virological testing for infants with reactive HIV serology
Infant Feeding/Nutrition	Birth - 6 months	• Exclusive breastfeeding for first six months of life with strict avoidance of mixed feeding should be encouraged • Exclusive replacement feeding if AFASS criteria can be met if mother not breastfeeding
	6- 12 months of age	• Introduction of complementary foods at 6 months and continued breastfeeding

Goal/type of the intervention	Timing of interventions	Recommended Intervention
	At 12 months	• Weaning for breastfeeding infants and transition to full family diet if adequate nutrition can be provided.
Additional services for mother infant pairs	Birth to 24 months[*]	• Safe water interventions • Maternal malaria prophylaxis • Insecticide treated bed nets • Growth monitoring and routine childhood immunizations

[*] Some services may need to be extended beyond 24 months, depending on the duration of breastfeeding and other factors.