REVIEW ARTICLE

Challenges Facing Early Infant Diagnosis of HIV among Infants in Resource Poor Settings

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Abstract

The number of children who have HIV continues to grow. Studies have confirmed dramatic survival benefits and mortality reduction for infants confirmed and managed as early as possible after diagnosis. With the advent of the Polymerase Chain Reaction technology, early infant diagnosis of HIV among children is easier and more reliable worldwide. Most HIV programmes in developing countries are donor dependent with less encouraging moves towards sustainability drive by the local health authority. The health systems also face a lot of challenges while implementing these programmes that would promptly identify HIV exposed babies as well as enrolment into care. This review examined challenges facing early infant diagnosis of HIV among infants in Nigeria (*Afr J Reprod Health 2013; 17[1]: 122-129).*

Résumé

Le nombre d'enfants qui sont atteints du VIH ne cesse de s'accroitre. Des études ont confirmé les avantages de survie dramatiques et la réduction de la mortalité pour les nourrissons confirmés et gérés le plus tôt possible après le diagnostic. Avec l'avènement de la technologie de Réaction en Chaine de Polymérase, le diagnostic précoce du VIH chez les enfants à travers le monde est plus facile et plus fiable. La plupart des programmes du VIH dans les pays en développement sont dépendent des bailleurs de fonds avec des tentatives moins encourageantes vers la durabilité d'entraînement par l'autorité sanitaire locale. Les systèmes de santé font face également à de nombreux défis lors de l'exécution de ces programmes qui identifieraient rapidement les bébés exposés au VIH ainsi que leur inscription dans les soins. Ce compte rendu a étudié les défis auxquels fait face le diagnostic précoce du VIH chez les nourrissons au Nigeria (*Afr J Reprod Health 2013; 17[1]: 122-129).*

Keywords: Early Infant Diagnosis (EID), HIV, Dried Blood Spot (DBS), Polymerase Chain Reaction (PCR)

Introduction

The high burden of HIV continues to constitute a major public health concern for the whole world. In sub Saharan Africa, 61% of adults living with HIV are women[1]. More than 90% of the HIV infections among children occur through Mother To Child Transmission MTCT[2]. MTCT of HIV can occur in utero, at the time of labor and delivery, and post-natally through breastfeeding[3]. Worldwide, in 2008, an estimated 430 000 [240 000–610 000] new infections due to the Human Immunodeficiency Virus (HIV) occurred in children[4]. The proportion of mortality among children younger than 5 years of age attributable to HIV was about 7% in Africa as a whole but was estimated to exceed 50% in some of the most severely affected countries[5]. In 2009, an estimated 278,000 children in Nigeria were living with HIV, though the figure has risen to about 360,000 in 2011[6].

In the developed countries, MTCT interventions has decreased the estimated annual number of perinatal HIV-1 infections in the United States from a peak of 1650 infections in 1991[7] to an estimated 111 infections in 2005[8]. Despite the dramatic decrease in rate of MTCT of HIV and in the number of pediatric HIV infections and AIDS cases in the United States, MTCT of HIV has not been eradicated in the United States. For prompt and effective reduction in prevalence of HIV infections among children in developing countries like Nigeria, the timely and accurate determination of the HIV infection status for all children born to

HIV infected women is thus essential.

Early diagnosis of HIV in infants provides an opportunity to strengthen follow-up of HIV-exposed babies after birth through series of interventions classified under PMTCT. In contrast to the early years of the epidemic, HIV-1 infection now represents, with appropriate therapy, a chronic disease; early antiretroviral treatment allows prolonged symptom-free survival with preservation of immune system function. Exclusion of HIV infection is also important for HIV exposed but uninfected children so that opportunistic infection prophylaxis does not have to be instituted or can be discontinued and so that age-appropriate immunizations for HIV uninfected children can be administered. The four prongs of PMTCT include primary prevention of HIV among women of re[productive age group, prevention of unwanted pregnancy among people living with HIVAIDs, prevention of mother to child transmission of HIV during antenatal, childbirth, pauperism and beyond, and holistic care and support for the mother, the baby and the entire family.

HIV-related child mortality rates remain high in sub-Saharan Africa despite growing access to antiretroviral therapy[9,10, 11]. In resource-limited settings, up to 30% of untreated HIV-infected children die before their first birthday and more than 50% die before they reach 2 years of age[12]. Early infant diagnosis (EID) is crucial to reduction of morbidity and mortality in HIV-infected children through the timely initiation of antibiotic prophylaxis and ART[13].

Diagnosis of HIV in Children

Promptly establishing the diagnosis of HIV infection in infants and young children is important for several reasons. First, infants who are infected with HIV have a better prognosis when Highly Active Antiretroviral Therapy (HAART) is started early. Second, prophylaxis for Pneumocystis jiroveci pneumonia is recommended for infants who may be infected with HIV. Infants who are not infected can stop taking medications such as trimethoprim-sulfamethoxazole, and reducing the risk for side effects. Third, families will generally be anxious for the results of definitive HIV testing. Both clinical and laboratory-based methods for the diagnosis of HIV-1 infection in children have been developed

WHO and the United Nations Children's Fund developed the "Integrated Management of Childhood Illness" strategy in 1992 to provide guidelines for the clinical diagnosis and management of sick children at the primary care level [14]. Integrated management of childhood illness (IMCI) is an evidence-based, cost-effective and comprehensive child health strategy developed by WHO/UNICEF to improve child survival in resource poor settings[15]. Its guidelines were adapted to include a validated HIV component to identify and manage HIV infected and exposed children. According to these guidelines, every mother bringing a sick child to a health facility is asked whether she has had an HIV test, and if she reports having tested HIV positive, the child is identified as HIV exposed. All children should also be routinely checked for common signs and symptoms found to be most predictive of HIV infection[16]. If three signs are present, the child is classified as *suspected symptomatic HIV* and the care-giver advised that the child should have an HIV test. The IMCI strategy aims to reduce child morbidity and mortality and to enhance child growth and development, and has been shown to improve the quality of care and to increase the utilization of health facilities[17].

The WHO has released a revised case definition of HIV-1 infection for surveillance purposes and a revised clinical staging classification of HIV-1–related disease in adults and children[18]. The WHO has also released revised guidelines or clinical criteria for the presumptive diagnosis of severe HIV-1 disease (among HIV-1–seropositive, HIV-1–exposed children younger than 18 months to allow for the early initiation of antiretroviral therapy[19]. However, evaluations of clinical staging systems for the diagnosis of HIV-1 infection in children in sub-Saharan Africa, especially in young infants, have suggested limited sensitivity[16,20].

Laboratory-based methods for the diagnosis of HIV-1 infection can be divided into 2 groups: immunologic and virologic [21]. Immunologic assays detect the antibody response to HIV-1 or the extent to which the immune system has

deteriorated as a consequence of HIV-1 infection. Virologic assays detect HIV-1 genetic material or components of the virus. Virologic assays, especially HIV-1 NAATs, and HIV-1 DNA PCR assays, represent the gold standard for diagnostic testing of infants and children younger than 18 months.

With such testing, the diagnosis of HIV-1 infection (as well as the presumptive exclusion of HIV-1 infection) can be established within the first several weeks of life among non-breastfed infants. Important factors that must be considered when selecting HIV diagnostic assays for pediatric patients and when choosing the timing of such assays include the age of the child, the potential timing of infection in the child, whether the infection status of the child's mother is known or unknown, the antiretroviral exposure history of the mother and the child, and characteristics of the virus[21].

For children 18 months of age and older, diagnosis may use the same antibody tests (e.g. rapid test or ELISA) as for adults. In this case, a positive test means HIV infection while a negative test means no HIV infection. However, antibody test must be repeated in children who are breast-feeding because of continued exposure. For children under 18 months of age, **a**ntibody test is not diagnostic unless it is negative. Thus, appropriate HIV-1 diagnostic testing for infants and children younger than 18 months differs from that for older children, adolescents, and adults Positive antibody test is not diagnostic in children less than 18 months due to presence of maternal antibodies, usually maternal antibodies starts to clear from about 6 months but can last till 18 months [21]. If the infant is breast-feeding, the test will need to be repeated 6 weeks after all breast-feeding has stopped. A special and more valid (though more sophisticated but reliable) test is thus required for detection of the virus and diagnosis of HIV infection.

In uninfected babies, antibodies decline over the first 18 months of life. Thus, if a baby tests antibody negative at any age, they are considered uninfected. However, infected babies continue to produce antibodies and will remain antibody positive after 18months of age, thus meaning that a positive antibody test may be indicative of infection in a child over 18 months. Therefore, routine serologic testing of these infants and young children is generally only informative before the age of 18 months if the test result is negative. Virologic assays, including HIV-1 DNA or RNA assays, represent the gold standard for diagnostic testing of infants and children younger than 18 months[21].

The specialized Polymerase Chain Reaction (PCR) technology

DNA PCR is a sensitive technique used to detect specific HIV proviral sequences in DNA of patients' peripheral blood mononuclear cells (PBMC). Extracted DNA from patients' PBMC is incubated with a thermostable DNA polymerase, deoxynucleotide triphosphates, and oligo-nucleotide primers that correspond with the portion of the HIV genome to be amplified. By 4 weeks of age, the DNA PCR test results are positive in more than 90% of infected infants. In infants older than 4 weeks of age, sensitivity of DNA PCR is consistently high, ranging between 91% and 99%[22,23]. Polymerase chain reaction (PCR)-based HIV DNA and HIV RNA assays [24] have become the most widely used assays, even in resource-limited settings, for both diagnostic and monitoring purposes[25-29].

The use of Dried Blood Spot-PCR methods in infants has been demonstrated to be both highly sensitive and specific; enabling EID in even resource-limited settings[13]. The PCR technology is a special test that detects the virus (DNA), and not antibody. However it uses specialized equipments and requires special skill to handle. This accurate technology is not just anywhere in resource poor setting, but specially placed in some specialized reference laboratories mostly in teaching hospitals. Dried Blood Spot specimen are usually collected by trained health personnel in health facilities, and transferred to the laboratory after appropriate drying, storing and packaging. The need to increase access to these technology-even rural areas is central for an effective EID program.

HIV exposed Infants less than nine months old are required to go for PCR diagnosis. Infants 9-18 months may have both rapid test and PCR performed on them and managed based on PCR

result. According to the 2007 Nigerian national paediatric ART guidelines, if the mother breastfed in last 6 weeks, infant is not infected at present but at risk through breastfeeding. A re-test is usually ordered for 6 weeks after stopping breast feeding.

EID Challenges

Analyses of observational cohorts have shown that the response to ART is very good: survival in children starting ART is about 93–95% at 12 months and 91–92% at 24 months[30-32]. Recently published data, confirming dramatic survival benefits and mortality reduction for infants started as early as possible after diagnosis of HIV on ART suggest a need for EID of HIV[33-35].WHO revised the recommendations for initiation of ART in infants with HIV infection and now recommends ART to be started as soon as HIV infection is diagnosed[36]. However, very few infants are gaining access to early diagnosis, the necessary prerequisite to 'timely' ART. In 2009, only an estimated 15% of HIV-exposed infants needing testing are tested in the first two months of life as reflected by WHO in data from 54 reporting countries[37].

Most EID programmes in Nigeria were being provided as part of PMTCT programs, and are mostly funded by implementing partners or NGOs receiving grants from donor agencies like the United States Agency for International Development (USAID).WHO recommended implementation of provider-initiated HIV testing, even for babies[38]. However, a key component of EID programmes being effectively carried out by these implementing partners is the retention of the mother-baby pair, and prevention of loss to follow-up of mothers and their infants between the time of mothers' HIV diagnosis in pregnancy and return after delivery for early infant diagnosis of HIV. This may facilitate timely initiation of pediatric antiretroviral treatment for eligible children. Any departure from these basics may constitute challenges to HIV care in children. Programmatically, this EID program faced a lot of challenges hindering effective early diagnosis and identification of HIV in children and subsequent placement of positive infants on ARVs. Some of the challenges are as follows.

1. **Poor training for health care workers**: In Nigeria, most health care workers have not had formal training on EID. Many who had the training sponsored mostly by NGOs or as additional course do not routinely step down the training to fellow staff at work. The resulting knowledge and skills gap is so wide that the few specially trained health care workers are being over-worked. Situation is worsened by frequent and indiscriminate transfer (out) of specialized trained staff from one unit to the other without taking such skills into consideration. It is hereby recommended that EID lecture topics as part of PMTCT of HIV should be incorporated into the training curriculum of health care workers in Nigeria. In addition, NGOs should scale up EID trainings to allow more health care workers to benefit from the training. Trained health care workers should also assume the responsibility of doing step down and on the job trainings to other health care workers at the health facility level.
2. **Difficulty in identification of HIV-exposed and infected infants for referrals**: This is more pronounced in an environment that contributes a lot to the PMTCT gap. Parents of healthy children often do not see the need to have them tested. It is thus important for health care workers to have high index of suspicion for HIV in children. No system for PMTCT babies for follow up for EID of HIV through the PCR technology. Exposed children are however expected to be identified from all hospital units dealing with children most especially children emergency wards, children clinics, immunization clinics, paediatric surgical ward and the general out-patient department.

Such children should be referred to the EID unit. Babies not referred may continue to live until when he or she becomes symptomatic or fall sick. Many have died while others are orphaned and have no one to bring them back to the clinic for care. Stigma and fear of discrimination may have forced mothers of many exposed babies to abandon their children to the extent of not coming around for EID follow up clinics. It is hereby recommended that health care workers should adopt the

Strategy of Provider Initiated Counseling and Testing (PICT) , in which case all suspected babies will be promptly referred by the health care workers to the laboratory for EID services

3. **Weak referral linkages**: Referrals is a vital component of a successful EID programme. From time to time, children are being suspected of being infected with HIV. Examples include malnourished babies, babies who are not thriving and those with suggested symptoms and signs. Health care workers need to link them to an EID clinic, through proper filling of forms and relevant registers. In this environment, many referrals are being done verbally. Poor attitude to documentation among some health care staff prevent many from accessing these services as a result of the health system giving in appropriate referrals. There may be a need for tracking of defaulters to reduce systematic loss to follow up of exposed babies. Health care workers also need to show more commitment to prompt and proper referrals and documentation issues, including proper filling of forms and registers for referrals and feedback
4. **Inadequate information to track patients:** Consequence to stigma and discrimination against HIV positive clients and members of their family, many clients would not honour referrals for EID, some may not return for the results of their babies while others may not go for follow up to paediatric ART clinic if the baby turns out positive. It is common instances that many HIV positive mothers give false contact addresses, fake telephone numbers and non-specific identities so that they could not be traced or followed up during tracking exercise-all for a fear of being stigmatized with HIV. The author recommends stepped up awareness campaign to the general public on HIV/AIDs and clarifying the myths and misconceptions associated with the disease. These efforts which could reduce stigma and discrimination against people living with HIV/AIDS should also be directed to the work place and the health sector
5. **Poor Community and Private sector participation in PMTCT programme:** The general awareness of EID even among HIV positive clients is still low. Situation is worsened in environment where most deliveries or births occur outside orthodox hospital settings [39]. In the health system, many PMTCT clients presents late for antenatal care while key stakeholders in the communities have no role to play despite that they are well positioned to make referrals as well as suspect infected babies for referrals for EID programme.

   Considering the fact that a significant proportion of Nigerian population patronizes private hospitals most especially in the current era of National Health Insurance Scheme[40], it is disheartening to find out that private hospitals may not yet be fully involved in provision of EID services despite that they offer maternity services to women. This may be because NGOs may not have been carrying them along in training, funding and logistics related to EID programmes. There is a need to encourage active collaboration between the organized health system, and private hospitals, the TBAs and other community structures in order to identify roles and redirect the spectrum of services available towards benefitting the lives of HIV positive clients and their families.
6. **Reducing Donor funding for EID activities:** There is no doubt that donor funding for HIV programmes generally is reducing, probably due to global financing crises, shift in priorities of donors competing demands and the need for host countries to sustain ongoing financial efforts among other reasons. The author believed that successive Governments in Nigeria have taken little or no step towards sustainability drive and payments of counterpart funding. Continued funding may thus depend on effective management of existing resources, payment of counterpart funding and a good monitoring and evaluation system, all of which are required in EID programmes. It is hereby recommended that Governments at all levels should increase budgetary allocation to health, give higher funding priorities to HIV programmes as well as payment of counterpart funding in order to foster the desired sustainability drive in HIV programming.
7. **Poor Logistic management system:** A constant supply and availability of EID kits and

consumables are central to an effective EID programme. Out of stock syndrome would only lead to more loss to follow up. In situation where reagents expires, get out of stock, or not requested for or where expired kits are found, effective logistics system need to be put in place. Health care workers need to be conversant with Logistic management system to ensure constant management of supplied kits and consumables. This is easier now that basic requisition are been carried out with the help of the computer and internet. All stakeholders in logistics management should rise up to their responsibilities towards ensuring zero tolerance to stock outs of bundle kits and consumables. These include government's proper funding of health and its logistics systems, implementing partners effectively forecasting logistics problems and acting accordingly including proper monitoring and evaluation, and health care workers at facility level collaborating with implementing partners towards solving common logistics problems.

8. **Inadequate sample transportation and transfer**: A good EID programme requires effective transfer of collected samples from health facilities to reference laboratories. The PCR technology that analyzes these samples is often far from the collection points in most developing countries. It is thus important that an arrangement exist to transfer the collected sample under some specific environmental conditions to and from the reference laboratory. Many cases of samples not getting to reference laboratory, samples taking up to few weeks before eventual delivery and results not reaching referring health facilities have been observed. This may put a lot of pressure on mothers or care givers of these children as they eagerly await results of the PCR test.

   On the average, the turn-around time is prolonged beyond the expected average of six to eight week. Cases of mothers abandoning PCR results of their babies, opting for antibody testing for their children within six months of birth among others have been reported. The use of the new DBS results transfer computers linking the health facilities and reference laboratory could assist in resolving these challenges. Results could be sent directly from PCR laboratory as soon as ready while the health facility awaits the hard copy of the results. The availability and affordability of such technology may be a factor to contend with in many developing countries with erratic and unstable electricity supply needed to power such computers. It is hereby recommended that implementing partners should make more EID machines and consumables available to more health facilities instead of concentrating them at specialized referral sites or facilities. In order to circumvent logistics problems being created by inefficient blood sample and results postage system through couriers, the use of mobile phones which is available in every household in Nigeria could be employed. In this case, processed results could be sent as special text messages between PCR laboratory and the health facilities in order to reduce the turn-around time for results.

9. **Poor counseling by health care workers:** Within the context of HIV, babies are still exposed while still be breastfeeding. This infant feeding method is more or less a universal practice in this part of the world. The 2010 Nigerian national guidelines following WHO rapid advise on PMTCT now encourage breastfeeding for exposed babies under ARV cover would greatly assist in circumventing many of the cultural and societal factors contributing to mixed feeding. Many health care workers may be biased in their Infant feeding counseling sessions towards replacement feeding based on traditional teachings on HIV prevention.

   This is worsened by aggressive marketing of cow milk products in various children welfare clinics in health facilities. It is thus important for health care workers to be objective in counseling, presents all information related to clients infant feeding method and lay emphasis of ARV cover. This is possible when health care workers have received adequate and quality counseling training. This has a lot of implication for the new national guidelines of breastfeeding in the context of HIV as more children will require drugs, more monitoring and for a longer period

of time. It is hereby recommended that Government and implementing partners should organize counseling training (formal and on-the job) sessions for health care workers in order to improve their quality of counseling given to their clients

10. **Stigma and discrimination against HIV exposed babies and positive clients:** One major reason why women may not want to come for PCR, attend to referrals or associate themselves with EID program is the avoidance of the possibility of being stigmatized by people who may wish to find out about her own HIV status or that of her baby and reasons for coming to a HIV clinic. This could affect coming back for results, adherence with ARVs regimen most especially if indicated before results are ready and mother's cooperation with the health system.

    Mothers who are already receiving and complying with ARVs are more likely to bring their exposed infants for EID and care [41]. The many faces of stigma and discrimination against people living with HIV/AIDs may have pushed many infected clients into seeking religious and supernatural solutions, and many of these clients may have been lost to follow up through this means. It is thus important for stake holders in HIV care to sensitize the communities towards reduction of stigma and discrimination.

In conclusion, the introduction of early infant diagnosis techniques is an important step in the fight against HIV/AIDS in Africa. By identifying infants who need services as early as possible, these children will have a better chance of maturing into healthy adults. Strategies for early identification of HIV-exposed and infected infants should be organized within the context of well-child care. Widespread and efficient use of early infant diagnosis resources will also help funding agencies and program implementers to analyze the results of PMTCT programs.

Contribution of Authors

The design, literature and review work and write up of this article are original efforts of the author.

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