EARLY INFANT DIAGNOSIS

IATT Laboratory & Child Survival Working Group

IATT
THE INTERAGENCY TASK TEAM
The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children

I: Background/Rationale

In 2010, in response to emerging data showing dramatic survival benefits of early ART initiation among HIV-infected infants and children, WHO issued the revised Recommendations on the Diagnosis of HIV infection in Infants and Children[1]. Key elements include:

- HIV virological testing to be used to diagnose HIV infection in infants and children below 18 months of age.
- All HIV-exposed infants to have HIV virological testing at 4-6 weeks of age or at the earliest opportunity thereafter.
- Infants with an initial positive virological test result to start ART without delay, and, at the same time, a second specimen to be collected to confirm the initial positive virological test result.
- Infants with signs and symptoms suggestive of HIV infection to undergo screening with HIV serological testing and if positive, follow with virologic testing to confirm infection.
- Well, HIV-exposed infants to undergo HIV serological testing at around 9 months of age (or at the time of the last immunization visit). Infants with reactive serological assays at 9 months to receive a virological test to identify HIV-infected infants who need ART.
- Children 18 months or older, with suspected HIV infection or HIV exposure, to have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults.

Early diagnosis of HIV infection is essential for ensuring timely initiation of ART and reducing the high morbidity and mortality that occurs among HIV-infected children who do not receive treatment[2]. Using a pooled analysis of data from 12 studies in sub-Saharan Africa, Marston et al estimated that without treatment, net survival at one year would be 52% among infants infected perinatally (with 20% having demised by 90 days) and 78% among infants infected during breastfeeding[3].

While disease progression is particularly rapid in the first few months of life in those infants infected perinatally, early initiation of ART has been shown to significantly reduce the risk of mortality[2]. Infants and children who present with more advanced disease have a far worse prognosis even if ART is initiated[4]. It is critical for HIV-infected infants to be diagnosed as early as possible in order to begin life-saving treatment before the virus has had a chance to take its toll.

Although mother-to-child transmission rates have been reduced to less than 5% in some low and middle-income countries 330,000 children were still newly infected in 2011 as only 57% of the estimated 1.5 million pregnant women living with HIV in low and middle-income countries received effective antiretroviral drugs to avoid vertical transmission to their child[5]. Mothers with advanced disease, such as those with CD counts less than 350 cells/mL are at highest risk for transmitting the virus to their children but of the estimated 620,000 women who were eligible for ART for their own health in 2011, only 190,000 (31%) were initiated on ART[6]. Overall PMTCT coverage rates for the 21 priority countries in sub-Saharan Africa was only at 61% during pregnancy and delivery and further decreased to 28% during breastfeeding[5]. In 2010, among 65 reporting countries, only 28% of infants born to mothers living with HIV received an HIV test within the first two months of life[6].

While early treatment is known to dramatically decrease morbidity and mortality from HIV infection, ART coverage of HIV-infected children still remains low at 28% and in 2011 out of the estimated 3.4 million children living with HIV globally, 230,000 died from AIDS-related illnesses[5].

1 WHO recommendations on the Diagnosis of HIV infection in Infants and Children. 2010

2 Violari et al. for the CHER Study Team. N Engl J Med 2008; 359:2233-2244

3 Marston et al. Net survival of perinatally and postnatally infected children: a pooled analysis of individual data from sub-Saharan Africa. International Journal of Epidemiology, 2011,40:385-396

4 KIDA-ART-LINK Collaboration. Low risk of death but substantial program attrition, in pediatric HIV treatment cohorts in sub-Saharan Africa. JAIDS. 2008. 49(5):p523-31

5 Together we will end AIDS. UNAIDS. 2012

6 UNAIDS Progress Report Summary. 2011. EID coverage rates at the end of 2011 were not reported in the more recent UNAID Progress Report, 2012

Clearly there is more work to be done to identify HIV infected infants earlier and initiate lifesaving treatment. An effective EID program is the first step to ensuring the survival of this vulnerable population.

II: EID Challenges

An effective EID service should be able to:

- Identify all HIV-exposed infants and their mothers, provide appropriate HIV testing services, and return the HIV test results to the caregiver in a timely manner.
- Retain HIV-exposed infants and their mothers in care to ensure the mother-infant pair successfully navigates the EID cascade to the point of a definitive diagnosis, without being lost to follow-up
- Identify all HIV-infected infants and link them to treatment services to ensure timely initiation of ART.

Challenges to development of an effective EID service include:

1. Integration of infant and young child HIV testing into all routine MNCH services

Although EID can be offered at any point of contact with a health facility, EID has often been integrated into immunization services. However, high national coverage rates for first DTP in many countries have not yet been translated into high virologic testing rates for HIV-exposed infants in the first 2 months of life. At the site level, infrastructure and human resources constraints present significant challenges; there is a lack of capacity of staff at immunization services to conduct HIV screening, particularly when the mother requires HIV testing. Rapid tests are under-utilized as a method of screening for HIV exposure when the maternal status is unknown.

2. Sample transport and return of results

Weak, non-standardized sample transport networks contribute to long turnaround times between date of sample collection and date of return of result to the site, resulting in further loss to follow-up. While new technology, including automated nucleic acid PCR testing and use of SMS to return results to facilities has been shown to reduce this turnaround time, delays can still occur at the facility and laboratory level without effective data management systems in place. This problem is compounded by lack of communication and equipment (e.g. access to email/ faxes or lack of equipment in working order) between facilities and laboratories (e.g. the facility doesn't know who to contact to get result or doesn't have a functioning telephone to make contact). Facilities often designate specific days and hours when DBS can be collected and PCR results provided to the caregiver, which further increases the time between sample collection and when the caregiver receives the PCR result.

3. Retention and loss to follow-up

As with the PMTCT cascade, infants are lost to follow-up at every step of the EID cascade with some studies showing that up to 85% of infants are lost by 1 year[7]. Busy clinics, long wait times, stigma, excessive turn-around times, weak referral systems, lack of integration of services, infant death prior to receiving a PCR test or accessing HAART, and poor follow-up all contribute to the poor retention rates. Relatively recent implementation of national adaptations of the 2010 WHO Recommendations for PMTCT which include ARV prophylaxis to the mother or infant throughout breastfeeding (Options A,B) provides an ideal opportunity (although not yet fully utilized) to improve retention of the mother-infant pair within care, ensuring that all HIV-exposed infants receive a final definitive diagnosis and HIV-infected infants initiate ART; initiation of lifelong ART to all pregnant and breastfeeding HIV positive women (Option B+) provides a similar and potentially even greater opportunity.

7 Sherman, G "PMTCT from research to reality- results from a routine service" *S Afr Med J*, 2004; 94(4): 289-92

4. Provision of the full package of care to HIV-exposed infants

To reduce morbidity and mortality among HIV-exposed and HIV-infected infants, a comprehensive package of care should be offered to these infants and their mothers which includes HIV testing, co-trimoxazole prophylaxis, counseling on infant feeding, clinical monitoring, and appropriate ARV prophylaxis at the service site that cares for mothers and infants together (MNCH). Although progress has been made on scaling up provision of infant HIV testing at 6 weeks of age, maintaining this continuum of care for the HIV-exposed infant throughout the period of breastfeeding has been difficult for most countries, resulting in few infants receiving complete co-trimoxazole prophylaxis and even fewer receiving a final definitive HIV diagnosis after cessation of breastfeeding.

5. Initiation of ART among HIV-infected infants

Many HIV-infected infants fail to initiate ART due to failure to identify HIV-exposure and/or subsequent infection; loss to follow-up of the mother-infant pair before diagnostic results are returned; weak linkages between EID and pediatric HIV care and treatment; non-availability of pediatric-appropriate ARV formulations, lack of integration of pediatric ART into adult ART services or decentralization of pediatric ART programs; and inadequate staff training on pediatric HIV. It is imperative that PCR-positive results are prioritized for rapid notification and infants promptly referred to treatment.

6. Effective data tools and data management systems

Although increasing PMTCT coverage means more HIV-infected women are identified during the antenatal period, documentation of serostatus often doesn't carry forward to the peri- and post-natal periods. Use of patient-held health cards (mother and infant) which document maternal and infant HIV exposure status, and HIV care and treatment details such as maternal and infant ARV prophylaxis and infant co-trimoxazole, is essential to the provision of optimal HIV care to HIV-exposed infants.

National standardized registers and patient records for HIV-exposed infants can aid clinic staff in accurately identifying exposed and infected children. Busy clinics, human resource constraints, lack of training and a lack of prompts in immunization/other child health registers for staff to check for and document infant HIV exposure status can result in HIV-exposed infants never being identified despite multiple facility visits, and previously identified HIV-exposed infant-mother pairs leaving the facility without being recognized.

National unique patient identifiers for both the mother and the infant (i.e., an identifier for the mother and a separate identifier for the infant) would allow infants to be identified as they moved between health services and between facilities. Maintaining information about the relationship between the two identifiers (i.e., a tag indicating that one is the mother and the other her infant or vice versa) would also allow follow-up on infants whose mothers were HIV positive but for whom no HIV test has been done.

Lack of national, standardized comprehensive data tools and/or inadequate staff training on how to correctly use them prevents reliable monitoring and evaluation of the EID program at site, district and national level, resulting in limited quality improvement activities. Linkages between EID databases (health facility or laboratory-based) and PMTCT and pediatric ART programs would facilitate tracking of HIV-exposed infants to ensure all HIV-exposed infants received a definitive diagnosis after cessation of breastfeeding and infected infants initiated ART promptly.

7. Testing algorithms

Recent findings in the context of current PMTCT protocols coupled with more sensitive HIV assays (viz. Roche CAP/CTM version 1.0 assay), demonstrate that 76% of all early vertical transmissions of HIV (viz. intrauterine and intra-partum infection) are detectable at birth[8]. Additionally, these findings showed that more HIV-infected children were diagnosed at birth than at 6 weeks of age because of the loss to follow up and deaths that occurred by 6 weeks of age.

8 Lilian RR et al. Early diagnosis of in-utero and intra-partum HIV infection in infants prior to 6 weeks of age. J Clin Microbiol 2012;50(7):2372

Additionally, evidence is emerging that provision of 3 or more drugs to mother and/or infant delays diagnosis of DNA positivity in non-breastfed infants to beyond 6 weeks of age[9]. In the current context of Option A, B, and B+ for PMTCT, these data suggest that current infant testing algorithms which recommend an initial PCR test at 6 weeks of age may fail to correctly diagnose some intra-partum and early post-partum transmissions at 6 weeks of age.

Where most deliveries/births occur in a facility, PCR testing at birth could lead to improved case finding using a testing algorithm that includes 1st PCR test at birth, a second PCR test at 10-14 weeks of age to detect intra-partum and post-partum transmission and subsequent rapid testing of all HIV-exposed infants at 9 months of age and again after cessation of breastfeeding. Rapid HIV tests could be used to exclude HIV infection at a single clinic visit from 4-6 months of age[10] and infants with a positive rapid test would require PCR testing to detect HIV infection.

Testing at birth is a strategy that needs to be further explored, and does not obviate the need for current testing approaches.

III: Promising practices from Kenya and South Africa

Kenya

1. **Collaboration between implementing partners, coordinated by the Kenya Ministry of Health.** Successful implementation of the EID program in Kenya required concerted collaborative efforts on the part of all stakeholders, under the coordination and leadership of the Ministry of Health (MOH). Coordination of activities across all levels of health facilities resulted in strong service delivery and successful implementation.

2. **Use of an HIV-Exposed Infant Follow-up Card,** which was able to monitor and track the infant to establish the appropriate required clinical interventions, while providing a record for HIV-exposed infants who may test negative at 6 weeks, but then develop clinical symptoms suggestive of HIV infection thus requiring repeat testing at a later visit. The HIV Follow-up Card tracked information about ARV prophylaxis, the parent profile, immunization history, laboratory history, and overall nutrition and development. It also provided infants with a unique HEI identification number that would allow tracking of laboratory results as well.

3. **Development of a national EID database** to aggregate clinical data from the facilities, as well as test results from the laboratories. Data was reported monthly into the system, and could then be used by health partners and the MOH to evaluate the success of the programs. Reporting from facilities was not always consistent, and required time and effort on the part of the implementing partners and the MOH to ensure accurate assessments of the program were being captured.

4. **Automation of DNA PCR testing.** The manual system of DNA PCR testing that was used for many years was not designed to run the high volumes that are being delivered to some centralized testing facilities. The manual system required laboratory technicians to be heavily involved in the sample analysis process, and is therefore prone to greater error. With the restrictions in human resources, and the great demand to analyze samples, automating the laboratories is credited as being a key component of Kenya's ability to scale up access to EID testing services. Automation also facilitated the reporting of data from the labs into the EID database more efficiently.

9 Shapiro IAS 2011

10 Sherman G. The performance of five rapid HIV tests using whole blood in infants and young children – selecting a test to achieve the clinical objective. Paed Infect Dis J. 2012;31(3):267-272

5. **Development of an online EID dashboard.** With the automation of the laboratories, it became easier to collect data from the laboratories and import them into the database. The Kenya MOH worked with partners to build an online EID dashboard – where the information from the EID database would be available online, real-time, for all partners and stakeholders. This type of transparency helped drive the program across all levels. Partners were given login accounts and could see details about the health facilities they supported, and could easily generate reports for their donors. The MOH could see the turnaround time for samples in each of the 4 laboratories, which helped to improve efficiency in the labs, and identify facilities that needed help.

6. **Use of SMS printers.** One of the major bottlenecks in Kenya highlighted by the dashboard was the long turnaround time for sample results to return to facilities; average time was 45 days but could be up to 60 days in some regions. The short message service (SMS) printer system allowed laboratories to send results back to health facilities through an SMS system: due to the automation of the laboratories, this was an effortless process of clicking 'send' for results to be disseminated. The average turnaround time for facilities with SMS printers became 7 days. This system also provided the health facilities with access to the laboratories, so they could track samples, and allowed laboratories to prioritize result delivery for infants who needed to initiate treatment.

South Africa

1. **Strengthening the role of the laboratory network in EID.** The South African laboratory network plays a key role in EID in the following ways:

   - provides training by an EID nurse trainer and updated job aides (booklets/posters) that demonstrate how to collect suitable DBS specimens
   - provides consultation regarding diagnostic dilemmas where diagnostic testing may deliver discrepant results
   - distributes monthly reports detailing
     - the number of PCR tests per healthcare facility by age and test result
     - early PCR testing (in infants aged 2 months and less) as a proxy of early transmission rates and against estimated targets of HIV-exposed infants to monitor EID coverage at a district level
   - provides clinicians (on an adhoc basis due to the challenges of maintaining patient confidentiality and limited modes of communication) with reports containing patient identifying details to track PCR positive patients into care prior to their 10-week visit and recall patients for repeat samples where PCR samples have been inadequate for testing or where indeterminate lab results were obtained.
   - provides a results hotline to access HIV PCR results telephonically if, for whatever reason, the hard copy report has not reached the facility

IV: The way forward

Laboratory networking

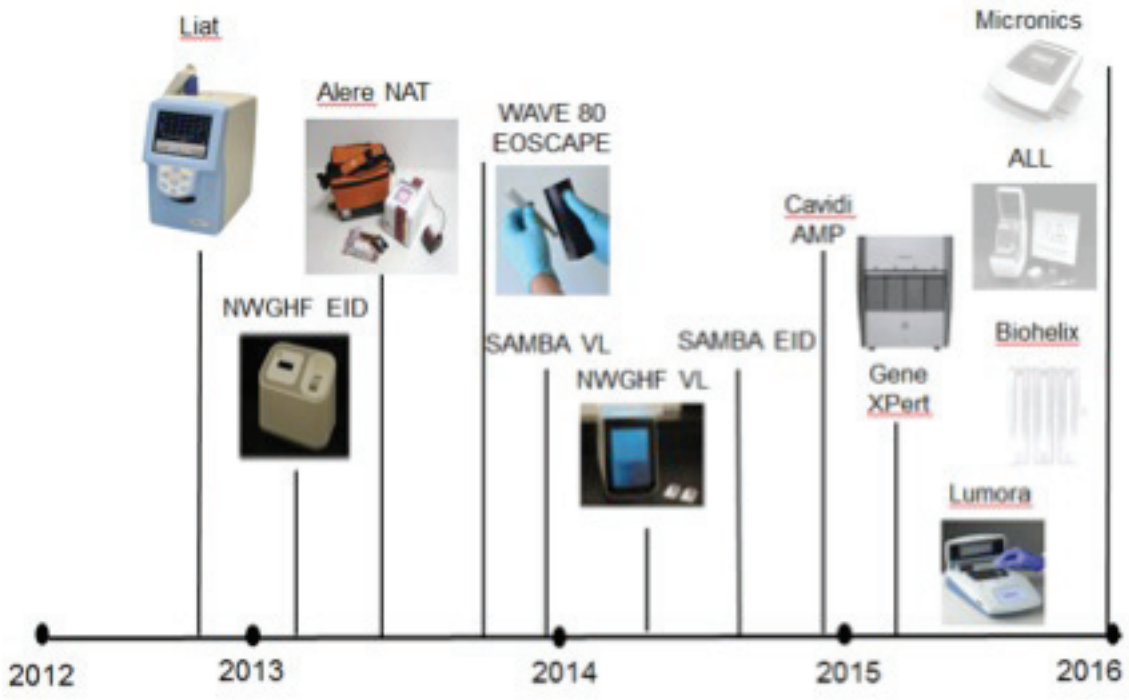
Laboratories are designated as national, regional or sentinel based on the types of samples they can collect. Forming an EID- laboratory network in each country is essential. To ensure that all HIV exposed and infected infants are diagnosed and receive appropriate prevention and timely treatment services, an EID-laboratory network should be built in two dimensions. In one dimension, the EID- laboratory network should be embedded within the national laboratory tiered system in which the national reference laboratory supports regional EID and all sentinel laboratories in the country by providing technical and programmatic guidance and assistance. Regional laboratories should then support the sentinel or hospital EID laboratories by providing technical assistance.

In another dimension, all regional and sentinel laboratories should be cross-linked geographically. A strong laboratory network will allow all infants to have access to EID testing through PCR testing of DBS

New technology and short message system (SMS) printers

There are no Point of Care (POC) tests currently available for EID testing, although several are under development. The most effective placement of the POC instruments to optimize HIV diagnosis has not yet been determined. It is anticipated that technologies in the pipeline will have lower instrument and per-test costs, and lower throughput requirements compared to laboratory-based systems.

Figure 1: Technology pipeline – POC VL and EID (estimated - timeline and sequence might change)[11]



The potential advantages of POC testing include: reduced reliance on sample transport networks by decentralizing lab access; increased testing of HIV-exposed infants; reduced costs per test; same day results for prompt clinical decision-making; improved patient retention.

However, there are technical issues to be considered with the placement of POC devices, such as reagent stability, adequate standard operating procedures (SOPs) to ensure maintenance and service plans, remote connectivity, remote quality control and quality assurance management, laboratory information systems (LIS) and on-site waste disposal.

It will be critical to develop adequate certifications of competency coupled with regular re-certification and re-trainings whenever applicable. Additionally, data gathering for surveillance is more difficult when testing is decentralized. Test readers (automated machines where diagnostic tests are inserted, and results provided to the technician numerically or otherwise) for EID should be developed to address these problems. The aim of test readers will be to improve the standard of test interpretation, provide a degree of QC, and minimize transcription errors. Test readers with connectivity can improve supply chain management, data management and strengthen surveillance efforts.

In addition, mobile phones can be adapted as disease surveillance tools using short message service (SMS) technology, and are being used to improve treatment adherence, send appointment reminders, and support community mobilization and outreach. For EID, the SMS technology was adapted to reduce the turnaround time for EID test results using SMS printers.

11 UNITAID (2011) http://www.unitaid.eu/resources-2/news/949-2nd-edition-of-unitaid-diagnostic-technology-landscape-report-published

V. Key Recommendations:

1. **Use of maternal and child health cards which document HIV care including maternal HIV status, maternal and infant prophylaxis and infant co-trimoxazole. Additional information could include DBS sample identifiers, allowing the health care worker to trace specimens to the laboratory and retrieve results.**

2. **Promotion of routine HIV screening of mother-infant pairs at every point of contact with the health facility to improve case finding. Routine screening will require coordination within the site to ensure tracking of DBS and return of results in a timely manner; in addition, documentation will be critical to avoid collection of multiple unnecessary DBS from infants as they contact different points of the facility. However, consideration must be given to the appropriateness and cost-effectiveness of such an approach in regions/ countries with low prevalence.**

3. **Development of a national EID technical working group to coordinate efforts and ensure effective collaboration at all levels. This can also help to leverage the resources being directed towards implementation of new PMTCT guidelines (e.g., extended prophylaxis throughout breastfeeding) to strengthen retention of the mother-infant pair. Collaboration and coordination across the HIV program and MNCH services will be critical to ensure appropriate service delivery models are implemented that effectively identify and retain mother-infant pairs in care.**

4. Standardization of sample transport systems and develop standard operating procedures; leverage pre-existing transport systems where possible (e.g., CD4 sample transport).

5. Roll-out of SMS printers in selected sites where challenges with sample transport and long turnaround times are expected to persist.

6. Investment in community engagement to improve both identification and retention of mother-infant pairs within HIV care and treatment services. Mentor mothers play a key role in PMTCT; with new PMTCT guidelines recommending provision of ARVs throughout breastfeeding, they are likely to assume even greater importance in the efforts to retain mother-infant pairs within this cascade of HIV care and treatment.

7. Strengthening and integration of data collection and data management systems at all levels to improve patient care and basic program monitoring and evaluation. Use of electronic medical records is not uncommon in larger sites within national ART programs but is rare within PMTCT. As more countries move towards Option B and B+, consideration should be given to incorporating PMTCT into ART electronic records. This would facilitate the transition from one service to another and optimize care for both mothers and their HIV-exposed infants. It also would have the added benefit of allowing more complete monitoring and evaluation (M+E) activities for ART. Close coordination is required between DNA PCR testing laboratories, national M+E departments, and program planners to ensure optimal use of EID data.

8. Education of healthcare workers in the use of rapid tests is required; HIV antibody detection assays are poorly interpreted in children aged less than 18 months.

   Not all rapid tests meet all the needs of HIV testing of infants less than 18 months old: highly sensitive rapid tests are best reserved for determining HIV exposure among infants while rapid tests with higher specificity and lower sensitivity are best used for excluding HIV infection.

   For the purposes of procurement and training, ideally programs should select rapid tests that are equally effective for diagnosing HIV infection in adults and children aged greater than 18 months.

9. Development of national unique patient identifier numbers which enable mother-infant pairs to be followed across different services, facilities and regions within a country. Both the mother and the infant should be assigned a separate unique identifier, and a tag used to maintain the relationship between the two identifiers. (Use of one identifier for the mother-infant pair would limit the flexibility of its use, especially if the two were to become physically separated).

10. Revise current infant testing algorithms to allow for HIV testing of infants at birth in appropriate contexts (high facility delivery rate) e.g. POC instruments in labour wards in order to identify more HIV-infected infants, including those that would otherwise die before the 6-week test or never present for testing.

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