Scale-up of Early Infant HIV Diagnosis and Improving Access to Pediatric HIV Care in Global Plan Countries: Past and Future Perspectives

Shaffiq Essajee, BMBCh, Ravikiran Bhairavabhotla, PhD,† Martina Penazzato, MD, PhD,* Karusa Kiragu, PhD,‡ Ilesh Jani, MD, PhD,§ Sergio Carmona, MD,‖¶ Bharat Rewari, MBBS,# Charles Kiyaga, MBBS,** John Nkengasong, PhD,†† and Trevor Peter, PhD‡‡*

Abstract: Investment to scale-up early infant diagnosis (EID) of HIV has increased substantially in the last decade. This investment includes physical infrastructure, equipment, human resources, and specimen transportation systems as well as specialized mechanisms to deliver laboratory results to clinics. The Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive, as well as related international initiatives to prevent mother-to-child transmission of HIV and treat children living with HIV have been important drivers of this scale-up by mobilizing resources, creating advocacy, developing normative recommendations, and providing direct technical support to countries through the global community of international stakeholders. As a result, the number of early infant diagnosis tests performed annually has increased 10-fold between 2005 and 2015, and many thousands of infants are now receiving life-saving antiretroviral therapy because of this improved access. Despite these efforts and many success stories, timely infant diagnosis remains a challenge in many Global Plan countries. The most recent data (from the end of 2015) suggest a large variation in access. Some countries report that almost 90% of HIV-exposed infants are being tested; others report that the level of access has stagnated at 30%. Still, just over half of all exposed infants in Global Plan countries receive a test in the first 2 months of life. We discuss the key factors that are responsible for this scale-up of diagnostic capacity, highlight some of the challenges that have hampered progress, and describe priorities for the future that can help maintain momentum to achieve true universal access to HIV testing for children.

Key Words: HIV, early infant diagnosis, global plan, sample transportation, point-of-care virological testing

(*J Acquir Immune Defic Syndr* 2017;75:S51–S58)

From the *World Health Organisation, HIV Department, Geneva, Switzerland; †UNICEF, New York, NY; ‡UNAIDS, Geneva, Switzerland; §Instituto Nacional da Saude, Maputo, Mozambique; ‖National Health Laboratory Service, Johannesburg, South Africa; ¶University of the Witwatersrand, Johannesburg, South Africa; #World Health Organisation, New Delhi, India; **Ministry of Health, Kampala, Uganda; ††Centers for Disease Control, Atlanta, GA; and ‡‡Clinton Health Access Initiative, Boston, MA.

The authors have no funding or conflicts of interest to disclose.

Correspondence to: Shaffiq Essajee, BMBCh, HIV Department, World Health Organisation, Avenue Appia 20, Geneva 1211, Switzerland (email: essajees@who.int).

INTRODUCTION

Providing early antiretroviral treatment (ART) to HIV-positive infants is a global public health priority. These children are among the most vulnerable of those living with HIV, and without access to treatment they are at very high risk of mortality, particularly those who acquire HIV through in utero or perinatal transmission. Up to 50% die by the age of 2 years, with the greatest mortality in the first few months of life.[1–3]

Fortunately, the annual number of new HIV infections in infants is falling. Since the launch of the Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive (Global Plan), the number of new pediatric infections among the global plan countries has fallen from 400,000 in 2009 to an estimated 110,000 at the end of 2015.[4,5] A key factor in this success has been the rollout of lifelong antiretroviral therapy to HIV-positive pregnant and breastfeeding women (Option B+). In 2015, among the 21 Global Plan countries of sub-Saharan Africa, which account for 90% of the global burden of pediatric HIV—74% of HIV-positive pregnant women were either already on ART or were started on ART during antenatal care.[5]

Although this success is laudable, we are far from eliminating pediatric HIV as a global public health problem. Providing antiretroviral therapy to HIV-positive infants (and delivering appropriate preventive care to HIV-exposed infants) remains a moral and ethical obligation, and it is dependent on prompt and accessible diagnosis, as well as linkages to treatment and care. It is estimated that half of all HIV-exposed infants presently receive an early infant diagnosis (EID) test within the first 2 months of life.[5] Although reaching this level of coverage in just a few years is an achievement, especially considering that coverage was estimated at 15% at the end of 2009, critical gaps remain that sour the success of the Global Plan in reducing mother-to-child HIV transmission.

There is a new urgency to scale-up EID and new approaches to testing that is prompted in part by renewed global pediatric treatment goals, revised World Health Organization (WHO) guidelines, and the availability of novel technologies to improve test access.[6,7] This article reviews the progress and challenges with EID scale-up over the past decade, and examines new strategies to scale-up EID in light of the global 90-90-90 targets and UNAIDS′ 2020 Fast-Track

goals to increase antiretroviral therapy access to 90% of children identified with HIV and reduce new HIV infections among children to fewer than 20,000 per year.[8,9]

GLOBAL PERSPECTIVES ON EID SCALE-UP: THE EARLY YEARS OF ROLLOUT

Until 2005, antiretroviral therapy for children in most resource-limited settings was available only in research settings or specialized clinics because the drugs and expertise needed to treat children were limited to tertiary urban settings. Rates of mother-to-child HIV transmission were high, and diagnosis of HIV in children was often guided by clinical criteria. Only a few countries, such as Botswana and South Africa, had national programs providing EID testing to HIV-exposed infants.[10] Most public health programs lacked the means to identify infants in need of treatment and also lacked information on transmission rates to assess the effectiveness of early efforts to reduce MTCT, thereby constraining appropriate allocation of PMTCT resources and funding.[11] Although rapid HIV assays were available and, in keeping with WHO guidance, could be used to make a presumptive diagnosis in HIV-exposed infants with signs of advanced HIV disease, this was rarely implemented in practice.[12] Some programs were able to test exposed infants at 18 months, when serological tests can reliably detect or exclude HIV in exposed children, but because of the known high early mortality from HIV and high rates of loss to follow-up, this information was not useful for evaluating the impact of programs to prevent mother-to-child HIV transmission or identifying HIV-positive infants at highest risk for rapid disease progression. Although the need for EID was recognized, achieving full scale-up was seen as being virtually impossible. The main limiting factors were high cost, technological complexity, lack of political will, challenges of incorporation into public health programs, and poor engagement with manufacturers of testing technology.[13,14]

The landscape changed dramatically in 2006. Funding from UNITAID, the United States President's Emergency Plan for AIDS Relief (PEPFAR), the Children's Investment Fund Foundation (CIFF), the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), the ELMA Foundation, and other donors enabled scale-up of access to EID in many countries. UNITAID in particular provided catalytic funding to support the procurement of EID commodities. This intervention laid the foundation for large-scale EID programs and has become a model for increasing access to critical health products that have a limited or challenging market and therefore face significant early market barriers.[15]

Many delivery innovations emerged and went to scale during the term of the UNITAID grant from 2006 to 2011. These included the bundling of laboratory supplies for polymerase chain reaction (PCR) testing (such as gloves, pipette tips, and PCR amplification tubes) to reduce procurement complexity and stock shortages; systems to transport dried blood spot (DBS) samples to a small number of centralized EID laboratories via sample transport networks; and use of SMS-enabled printers to facilitate the rapid return of results to collection sites. The funding also enabled volume-based price negotiations that brought down the cost of laboratory instruments, test reagents, and consumables to less than US $12–15 per test.[16] Under the UNITAID donation —and with the critical support of governments and technical partners, particularly the US. Centers for Disease Control and Prevention (CDC)—EID testing facilities were built, laboratory standard operating procedures were put in place, forecasting and procurement systems were improved, and thousands of frontline health workers were trained in the collection, storage, and shipping of DBS samples.

By serendipitous coincidence, UNAIDS and PEPFAR launched the Global Plan as the UNITAID grant began to wind down in 2011. Although there was no longer earmarked funding for EID commodities, the Global Plan created an unprecedented level of advocacy, because EID was not only a means of identifying infected infants but also a direct measure of the efficacy of efforts to prevent mother-to-child HIV transmission. As countries designed and costed their strategies to prevent new HIV infections among children, there was a concomitant concern that only 1 in every 10 children living with HIV was receiving antiretroviral therapy.[17] For that reason, the Global Plan specified in its 10-point framework the need to ensure that EID and pediatric treatment were prioritized. It set targets for a 50% reduction in AIDS-related pediatric deaths through scale-up of pediatric treatment, and it called on countries to secure reliable access to diagnostic commodities, provide training and mentoring of providers, and ensure robust and reliable data systems at the facility level. The plan also called on communities and networks of women living with HIV to join the effort, particularly to help identify other children in the family who may not have been tested for HIV.

EID SCALE-UP SUCCESSES TO DATE

Overall, the results of EID scale-up over the past 10 years are encouraging. Data from the 21 sub-Saharan African countries of the Global Plan indicate that by the end of 2015, 51% of HIV-exposed infants were reported to have received an EID test within the first 2 months of life (up from less than 10% a decade earlier).[5] In some countries, such as Lesotho and South Africa, coverage has reached levels seen in higher income countries (Fig. 1). Put in terms of the market, the significant scale-up in the number of EID test kits procured and conducted over the past decade demonstrates success in the implementation of EID as a testing service (Fig. 2).[18]

The Global Plan also renewed focus on the need to provide treatment for children living with HIV. This focus was synergistic with the emergence of a range of child-friendly fixed-dose combination drugs. It began in 2006 with the approval of a pediatric stavudine-based fixed-dose combination, and it continues to date with the approval in 2015 of a pellet formulation of lopinavir/ritonavir.

The importance of programs starting to provide treatment for HIV-positive children cannot be overstated. Access built confidence among providers and communities that holistic HIV care and treatment for the whole family was possible. The effort to scale-up effective services to eliminate new HIV infections among children and keep their mothers

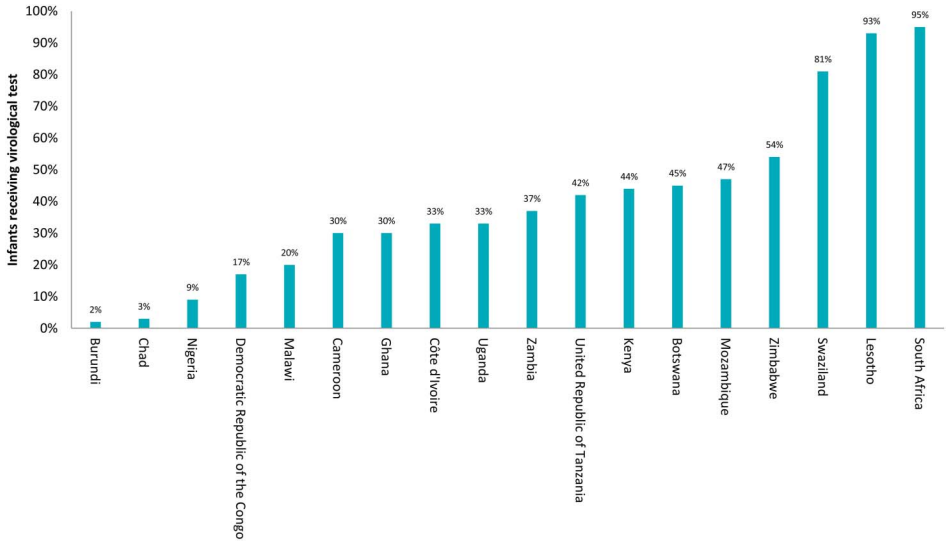

FIGURE 1. Percentage of infants born to women living with HIV receiving a virological test within 2 months of age, 2015.

alive (which was spurred by the Global Plan), combined with the push to increase access to pediatric antiretroviral therapy saved the lives of hundreds of thousands of children in sub-Saharan Africa. EID was an intervention at the heart of both programs.

The UNITAID Pediatric Initiative helped address many of the upstream problems with EID, such as high costs of equipment and reagents and the lack of laboratory capacity for PCR testing. At the same time, the Global Plan enabled national programs to tackle some of the downstream issues of implementation, including expanding access to testing beyond urban centers and improving meaningful linkage to treatment for HIV-positive children.

The annual Global AIDS Response Progress Reporting (GARPR) mechanism began collecting data on access to EID in part to facilitate monitoring of the Global Plan. Each year, the Global Plan report provides detailed data on EID scale-up that enables countries to track their efforts and compare themselves with others—an important tool for ongoing advocacy to increase the reach of EID testing services.

REMAINING CHALLENGES

Despite considerable progress, there still is an urgent need for further scale-up of EID services as a tool to increase pediatric antiretroviral therapy coverage. Low access to EID persists: countries such as Angola, Burundi, Chad, the Democratic Republic of the Congo, and Nigeria have EID coverage rates below 15%.[5] In fact, most Global Plan countries provided EID to less than half of HIV-exposed infants as of 2015.

There are 3 important reasons for this ongoing unmet need:

- Mechanisms to track mothers and infants who do not return for testing are weak, so infants who are not brought for testing at 6 weeks are often lost to follow-up.
- Systems issues still hamper effective delivery of EID services, including stockout of laboratory reagents, delays in sample collection, and delays in results return.
- Infants may be brought for testing eventually, but often this is after the first 2 months—too late to be counted in national EID statistics, and also later than optimal for initiation of treatment and prevention of early mortality among HIV-infected infants.

Rates of retention and linkage to treatment and care among those tested can be low. It can take weeks to return EID results to mother–infant pairs, which may contribute to preantiretroviral therapy loss to follow-up, which currently ranges between 30% and 80%.[19–21] This statistic highlights

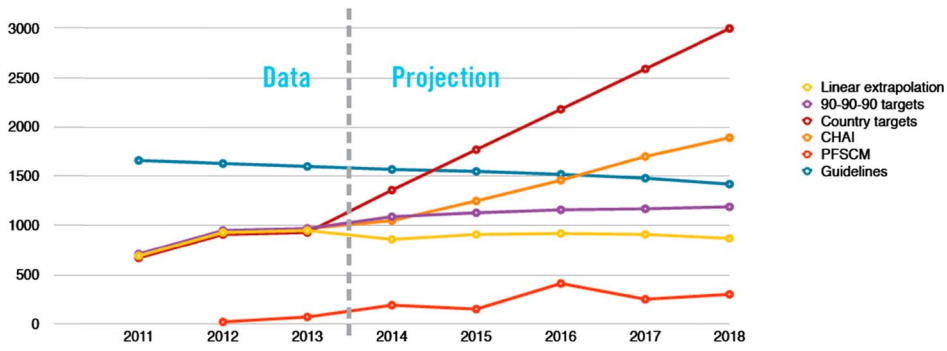

FIGURE 2. Projected global numbers of EID tests procured each year using different scale-up scenarios.

the need to improve retention and integration in the continuum of care and to improve the laboratory–clinic interface.[22]

Most EID is currently conducted on the infants of mothers enrolled in programs to PMTCT; efforts are needed to identify children whose mothers did not receive those services or those who miss testing when they are under 2 months of age. Increased provider-initiated testing and counselling (PITC) in high-yield settings (such as pediatric wards, nutritional rehabilitation centers, and in the families of HIV-positive women) is also crucial. Recent studies have found high percentages of HIV-positive infants and children at these often-overlooked entry points.[23] In addition, it is important to ensure that HIV-exposed infants who test negative by virologic testing at 6 weeks receive a final serologic test after the HIV transmission risk ends; this will provide definitive confirmation that the child is HIV negative.[24] Finally, weaknesses in the continuum of care to PMTCT contribute to low EID coverage and poor linkage to treatment, including low antenatal care attendance in some countries, late presentation, human resource constraints, and lack of male partner involvement. Each of these factors contributes to loss to follow-up, especially in the postpartum period.

LOOKING FORWARD: WHAT WE HAVE LEARNED AND PRIORITIES FOR THE FUTURE

Funding from foundations, industry, and governments has developed a pipeline of new EID technologies for both central laboratories and decentralized point-of-care settings that will support future phases of EID expansion, despite the small relative size and uncertainty of this market.[6] The first point-of-care EID products became available in 2015; as of mid-2016, WHO had prequalified 2 products, enabling these instruments and reagents to be procured using donor funds.[25] The global effort to scale-up EID over the past 10 years also has laid a foundation for a point-of-care test market. This is important proof-of-concept for the viability of new technologies to test for other diseases if similar supportive conditions prevail.

EID is the first example of a molecular nucleic acid testing service implemented on a large scale in public health programs with limited laboratory infrastructure and resources. This scale-up has established undeniable evidence of the feasibility of nucleic acid testing in such settings, and it has helped build test delivery systems that include PCR-enabled laboratories, skilled personnel, sample transport logistics, data management solutions for result delivery, and mechanisms to respond urgently to positive test results (Table 1). EID has strengthened health systems in ways that may facilitate other future nucleic acid testing of public health importance (eg, viral load testing for HIV and hepatitis C, and early diagnosis of emerging viral infections, such as Ebola and Zika).

Critical assessment of EID as a clinical service, however, has identified shortcomings in delivering EID and ensuring linkage to care to prevent loss to follow-up further (Fig. 3). Innovative approaches have expanded conventional laboratory network access, improved turnaround times and efficiencies through mHealth and eHealth interventions (such as SMS messaging and SMS-enabled printers), strengthened sample logistics, and promoted faster testing at laboratories (Boxes 1 and 2). These approaches need to be scaled up. Similarly, although the focus of EID testing has been on testing HIV-exposed infants at 4–6 weeks of age, the feasibility of EID testing at birth has recently been demonstrated.[26] Testing at birth or soon after birth may enable early identification of infants who were infected in utero and who

TABLE 1. Challenges of Delivering Services in a Low Prevalence Epidemic Context: Learning From India

Challenge	Specific Problem	Solution
1 Low prevalence in a vast geography	There are 35,000 HIV-positive pregnancies among 29 million pregnancies overall, resulting in detection of only one-third of HIV positive pregnant women and even fewer exposed infants tested	Prioritizing districts based on PCR positivity rates in the last 3 years, Coordination with MNCH for testing at subcenter level, involvement of private sector, as 40% of deliveries happen in private sector
	Each site has very low volumes for PCR so very few samples per site	Sites designated specific days for sample collection to avoid lengthy delays. Moved from 1 DBS and 1 whole blood sample for confirmation to 2 DBS samples testing; this simplifies sample transport
2 Low and fragmented access to obstetric care makes it difficult to identify and track HIV-positive pregnancies, or to follow HIV-exposed babies	Socioeconomic barriers to access including low ANC attendance and low rates of hospital delivery	Incentives such as the Janani Shishu Suraksha Yojna have been implemented to increase hospital delivery. This scheme is designed to provide pregnant women who access Government health facilities with a package of free services to promote institutional delivery.
	Women seek delivery services at different sites from ANC services	An electronic software platform has been created to track all cases
3 Delays for in-country regulatory approval since the commercial EID assay was labeled as "research use only"	Lack of progress in rolling out the service because of lack of clarity around the legalities of testing	Until regulatory approval was obtained, all positive DBS samples were verified using whole blood assays and a testing platform approved by the Indian Council of Medical Research; this allowed the service to roll out even before regulatory approval was obtained

ANC, Antenatal Clinic; MNCH, Maternal Newborn and Child Health Services.

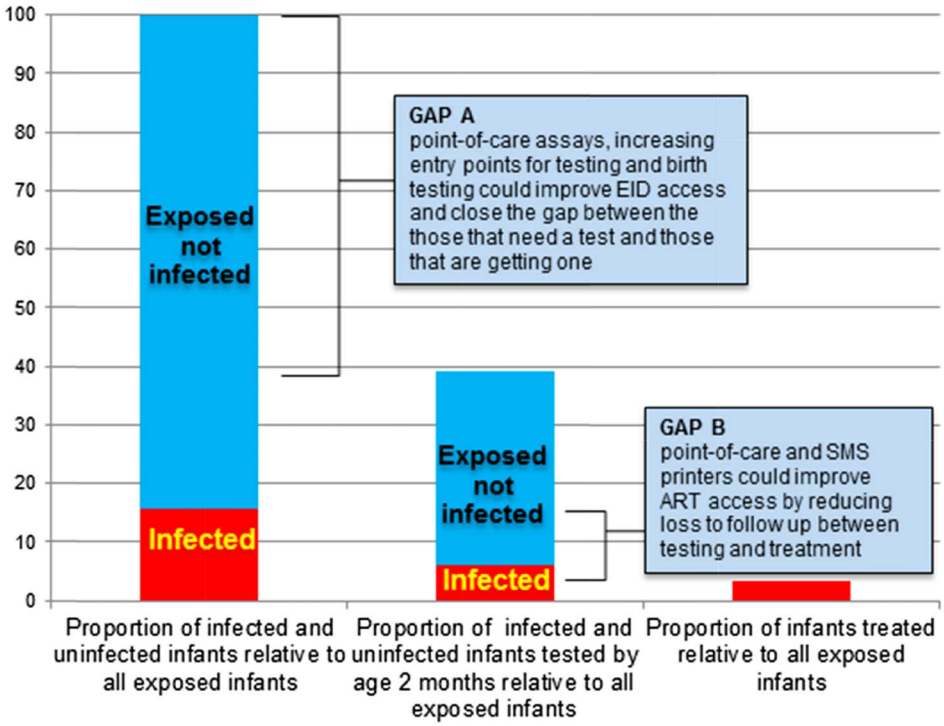

FIGURE 3. Illustration showing the estimated proportions of exposed and infected infants tested using EID and started on treatment. Estimates based on 2014 data from the Global AIDS Response Progress Report, WHO, Geneva, Switzerland, 2015.

BOX 1. Country Perspectives: Lessons From the Field—Mozambique: An Evidence-Based Approach to Harness Partnerships, Innovations, and Evidence to Strengthen the Health System

The implementation of EID in Mozambique began in 2005. Initially, just one research laboratory in the capital city, Maputo, performed the PCR-based HIV DNA testing technique for only a few specialized clinics where most HIV-exposed infants were being seen. Fewer than 1000 children, mostly those with symptoms suggestive of HIV disease were tested annually. In 2007, with increased global availability of PMTCT and pediatric antiretroviral therapy, several other clinics in the country started to benefit from EID. From 2009 onwards, additional laboratories were established to respond to the rapidly increasing demand for EID.

In the past 10 years, new partnerships and health system innovations have boosted scale-up of EID in Mozambique. They include the following:

- Use of SMS technology to expedite delivery of EID results. To reduce the time needed to deliver laboratory results to patients, printers connected to the mobile phone network were placed in health facilities nationwide. The Ministry of Health and a mobile phone company established a partnership to develop and implement this innovation, with the company donating SIM cards, airtime, and technical assistance to the health system. Another partnership—between the Ministry of Health, bilateral and multilateral organizations, implementing partners, and local governments—facilitated the purchase of printers and supported training.
- Dashboard for information management. All EID laboratories installed a custom-made database for information management. This enabled periodic monitoring and analysis of key system indicators. All stakeholders have access to an online dashboard, where system indicators can be graphically represented and used to guide changes in policy and procedures.

Currently, 5 laboratories in the country perform EID testing using conventional molecular biology technology. In 2015, 72,547 EID tests were carried out in Mozambique, with DBS specimens collected from 1159 health facilities nationwide. Overall this translates to 47% of all HIV-exposed infants receiving an EID test in the first 2 months of life.[5] Despite a great deal of progress, access to (and efficiency of) EID remains a challenge: systemic issues persist with the supply chain of reagents, equipment maintenance, and slow turnaround times for results. Ultimately, the number of children who benefit from lifesaving antiretroviral therapy remains below expectations with coverage estimated at around 57% of all children in need.[5]

In Mozambique, the introduction of point-of-care EID assays will be guided by scientific evidence and the experience obtained during the implementation of point-of-care CD4 technologies. Recent evaluations have identified several point-of-care EID technologies with good performance when used by nurses at primary health-care facilities. One point-of-care technology is being evaluated further in 2 ongoing studies: the first is measuring its performance in newborns, while the other is investigating its effect on retention in care and antiretroviral therapy initiation rates. At the same time, tools are being developed to guide the deployment of point-of-care EID assays in Mozambique's national health service. In the near future, EID in Mozambique likely will be performed using a hybrid network that strategically implements both laboratory-based and point-of-care technologies to deliver results to patients in a more efficient manner.

BOX 2. Country Perspectives: Lessons From the Field—Uganda: Centralized Testing Yields Program Benefits

Uganda began EID testing in December 2006. At the time there was no capacity for molecular diagnostics in the public health system. Therefore, the Ministry of Health collaborated with 8 regionally-based implementing partners with EID laboratory capacity. UNITAID provided laboratory reagents and other associated consumables; the partner laboratories charged the program only for overhead.[33]

Because of the high overhead costs (US$22.2 per test) and long test turnaround times, in 2010 the national EID subcommittee evaluated the laboratory network in terms of cost and efficiency and compared the findings with other laboratory network models. After this evaluation, the model of a single centralized laboratory to serve the entire country was deemed more efficient and cost effective.[34]

The national EID subcommittee also evaluated the systems of sample transport being used by different stakeholders to move samples from the testing facilities to any 1 of the 8 EID laboratories. This evaluation found that various systems were being used, and they were largely ad hoc, inefficient, and expensive. In some cases no model existed.[33]

In 2011, the Central Public Health Laboratories (CPHL) adopted the single centralized laboratory model. To increase access to this centralized laboratory, a hub-based sample transport system was set up. Both of these innovations improved efficiency and cost effectiveness of the previous semidecentralized laboratory network and ad hoc, fragmented sample transport network. Test turnaround time decreased from 1 to 2 months in the old model to 1–2 weeks. Overhead cost decreased from US $22.20 per test to US $5 per test.[34,35]

Over the same period, a clinic improvement system was established to address the findings of an EID evaluation that showed that loss to follow-up from the number of HIV-positive infants identified to those who were alive and on treatment was very high (close to 77%). Challenges ranged from low numbers of mothers returning to the clinic to collect results, low rates of treatment initiation among infants found to be HIV-positive, and among infants found to be HIV negative, low numbers remaining in care to receive follow-up testing at the end of breastfeeding, as recommended in the national testing algorithm.[33] The clinic improvement system had the following 5 key components:

- Delivering a package of services that included co-trimoxazole prescribing, infant feeding counselling, and EID.
- Establishing a well-equipped EID care point at every participating facility, where all testing, care, and follow-up of exposed infants are done.
- Improving tracking tools to follow infants longitudinally and monitor care indicators.
- Establishing a triplicate referral form to improve linkages between EID and antiretroviral therapy services.
- Strengthening and standardizing counseling at all points in the EID process.

The intervention was piloted in 21 health facilities in 8 districts in 2009. It resulted in a 42% increase in samples collected, a 43% reduction in the age at first test, and a 33% reduction in overall loss to follow-up of HIV-positive infants from 77% at baseline to 51% at 6 months after implementation.[34]

are at greatest risk of rapid disease progression. Programs need to consider the clinical impact and utility of at-birth testing.[27,28]

Point-of-care EID offers additional opportunities to improve access to infant diagnosis and reduce loss to follow-up along the care cascade. Point-of-care EID platforms can be used at all points in the health service where there is a sufficient volume of tests. This may include laboratories, clinics, and community settings. The performance of point-of-care EID technologies has been evaluated: a joint multisite evaluation of the first commercially available point-of-care and near-patient technologies conducted by the EID Consortium in multiple African countries suggest that these tests are as accurate as laboratory EID assays.[29] Furthermore, point-of-care testing may increase retention and linkage to care, and enable same-day treatment initiation, as has been demonstrated with other point-of-care tests (such as CD4 and tuberculosis diagnosis).[30,31] To sustain the benefit to patients, their use should be combined with improvements in clinical services. Furthermore, introduction of these new technologies must be considered in the context of maximizing the investments already made in existing laboratory systems. Point-of-care testing for EID is a promising innovation, but in itself, it may not enhance outcomes for infants living with HIV unless there are parallel efforts to improve clinical service delivery (including training of service providers) and increase access to essential commodities for infant antiretroviral therapy (such as lopinavir/ritonavir).

New Approaches to Monitoring and Assessment

The strongest rationale for continuing investment in EID is the potential to reduce early mortality, particularly in infants who are infected in utero, for whom disease progression is especially rapid.[2,32] For this reason, while identifying HIV infection is the first critical step, outcomes cannot be improved if infants are not effectively linked to care and started on treatment in a timely manner. Thus, the performance of infant testing strategies should be viewed in the larger context—beyond that of test performance, quality, and coverage—and should focus on EID as a tool for early treatment and preventing mortality and morbidity.

After 10 years of investment in laboratory-based EID and given the intensive effort needed to scale-up new interventions such as SMS results delivery and point-of-care diagnostics, a case needs to be made that shows how innovations can address current access challenges. New

BOX 3. Country Perspectives: Lessons From the Field—South Africa: Breaking New Ground in One of the Most Established EID Programs in the World

South Africa has been providing EID to HIV-exposed children since 2000, and it has one of the oldest and largest established EID programs globally. This was accomplished through a network of HIV PCR laboratories managed by the South African National Health Laboratory Service (NHLS), which implemented a centralized EID program that is currently supported by 10 accredited referral laboratories. These molecular laboratories are linked to a strong sample referral network that has made EID testing accessible to 4000 health facilities across the country.

South Africa has been a leader in new programmatic approaches for EID delivery. For example, the early implementation of DBS within the South Africa EID program led to the more rapid adoption of DBS EID as the global standard of care. In addition, management of the national EID service by a single organization (the NHLS) has become a model for many countries, and it has permitted centralized data warehousing and analysis of program performance. This, in turn, has guided implementation science in the field. South Africa also conducted early evaluations of EID performance at different times after birth and was the first to implement birth EID testing as a national policy. This pioneering experience served to inform global policies around the timing of testing, leading to the introduction of birth testing as a recommendation in the revised WHO "Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection" released in 2016.[6]

The scale of South Africa's program also has positioned the country as the backbone of the market for current and future EID tests. South Africa Mozambique and Uganda are all part of a regional EID consortium that undertakes independent multicentre field evaluations of point-of-care technologies. This forum has the potential to accelerate the implementation of novel EID platforms.

solutions should not be considered in isolation but rather as an integrated set of efforts to improve the care continuum. An updated monitoring and evaluation framework for diagnostics is needed, one that measures progress along the care continuum and clinical impact in addition to access to EID testing itself.

Maximizing the value of EID requires a package of interventions to be in place for HIV-exposed infants: one that includes EID, postnatal prophylaxis, and early treatment for those infected. The prospect of long-term HIV remission with initiation of early treatment in infants is tantalizing if as yet unrealized opportunity. Although the evidence for this remains sparse, there are studies ongoing; as findings emerge, it will be important to build such concepts into the rationale for EID testing, especially as rates of mother-to-child HIV transmission decline and resources for HIV programming become increasingly constrained.[33]

As innovations in EID are implemented, documentation is essential to inform normative guidance. The most recent WHO HIV treatment guidelines recommend innovations such as birth testing and point-of-care EID on the basis of their theoretical benefits because of a paucity of evidence and absence of field experience. As a result, there is limited guidance on how to implement these innovations in different epidemic settings. For example, experience with nucleic acid testing at birth has thus far been limited to South Africa, which began implementation in November 2014, initially focusing on high-risk infants before moving to national scale-up in 2015 (Box 3). Documentation of the challenges and opportunities observed with birth testing in South Africa will be important for understanding the resources and service delivery elements necessary to ensure effective introduction.

Smart approaches to implementation—such as within the Clinton Health Access Initiative (CHAI)/UNICEF and Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) point-of-care projects supported by UNITAID and the—should involve robust collection of data as innovations are scaled up. Thorough documentation and assessment will enable better understanding of the optimal combination of platforms and potential impact on program and patient outcomes. Such data could in turn be linked to robust costing and modeling exercises to inform guidance that can be used to develop cost-effective and context-specific services.

CONCLUSIONS

Despite the success to date of EID scale-up, significant weaknesses in access and impact remain. EID (and pediatric HIV care) stand on the brink of major changes that could improve access and quality of care. Developments on multiple fronts include: (1) diagnostic technology innovations (point-of-care tests); (2) service delivery innovations (ie, more comprehensive testing strategies, such as birth testing and routine testing at additional entry points); and (3) stronger political impetus and targeted funding opportunities for scale-up of testing. Looking forward, the lessons of the past 10 years can help make best use of the global community's newest tools to expand EID scale-up and improve pediatric treatment.

As PCR positivity rates go down, EID may seem less of a lifesaving assay, but the legacy of EID will remain. PCR for HIV infant diagnosis is the first example of a molecular assay that has been successfully introduced as a public health testing service on a global level. This has important implications for the diagnosis and management of conditions such as tuberculosis and viral hepatitis, as well as emerging epidemics like the Ebola and Zika viruses.

REFERENCES

1. Bourne DE, Thompson M, Brody LL, et al. Emergence of a peak in early infant mortality due to HIV/AIDS in South Africa. *AIDS*. 2009;23:101–106.
2. Newell ML, Coovadia H, Cortina-Borja M, et al. The Ghent International AIDS Society (IAS) working group on HIV infection in women and children. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet*. 2004;364:1236–1243.
3. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008;359:2233–2244.

4. UNAIDS. *Countdown to Zero. Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive, 2011–2015*. Geneva, Switzerland: UNAIDS; 2011.
5. UNAIDS. *On the Fast-Track to an AIDS-Free Generation*. Geneva, Switzerland: UNAIDS; 2016.
6. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recommendations for a Public Health Approach*. 2nd ed. Geneva, Switzerland: World Health Organization; 2016.
7. UNITAID. *HIV/AIDS Diagnostics Technology Landscape*. 5th ed. Geneva, Switzerland: UNITAID; 2015.
8. UNAIDS. *90–90–90: An Ambitious Target to End the AIDS Epidemic*. Geneva, Switzerland: UNAIDS; 2014.
9. UNAIDS. *Fast–Track: Ending AIDS by 2030*. Geneva, Switzerland: UNAIDS; 2014.
10. Creek T, Tanuri A, Smith M, et al. Early diagnosis of human immunodeficiency virus in infants using polymerase chain reaction on dried blood spots in Botswana's national program for prevention of mother-to-child transmission. *Pediatr Infect Dis J.* 2008;27:22–26.
11. Stringer EM, Chi BH, Chintu N, et al. Monitoring effectiveness of programmes to prevent mother-to-child HIV transmission in lower-income countries. *Bull World Health Organ.* 2008;86:57–62.
12. World Health Organization. *Antiretroviral Therapy of HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a Public Health Approach*. Geneva, Switzerland: World Health Organization; 2006.
13. Bolu O, Allread V, Creek T, et al. Approaches for scaling up human immunodeficiency virus testing and counseling in prevention of mother-to-child human immunodeficiency virus transmission settings in resource-limited countries. *Am J Obstet Gynecol.* 2007;197:S83–S89.
14. Creek TL, Sherman GG, Nkengasong J, et al. Infant human immunodeficiency virus diagnosis in resource-limited settings: issues, technologies, and country experiences. *Am J Obstet Gynecol.* 2007;197:S64–S71.
15. UNITAID. *Annual Report 2007*. Geneva, Switzerland: UNITAID; 2007.
16. Clinton Health Access Initiative. *HIV Early Infant Diagnosis Market Analysis*. New York, NY: Clinton Health Access Initiative; 2016.
17. United Nations Children's Fund. *Children and AIDS: A Stocktaking Report*. New York, NY: United Nations Children's Fund, 2007.
18. World Health Organization. *HIV Diagnostic Tests in Low- and Middle-Income Countries: Forecasts of Global Demand for 2014–2018*. Geneva, Switzerland: World Health Organization; 2015.
19. Chatterjee A, Tripathi S, Gass R, et al. Implementing services for early infant diagnosis (early infant diagnosis) of HIV: a comparative descriptive analysis of national programs in four countries. *BMC Public Health.* 2011;11:553–562.
20. Hsiao N-Y, Stinson K, Myer L. Linkage of HIV-infected infants from diagnosis to antiretroviral therapy services across the Western Cape, South Africa. *PLoS One*. 2013;8:e55308.
21. Nuwagaba-Biribonwoha H, Werq-Semo B, et al. Introducing a multi-site program for early diagnosis of HIV infection among HIV-exposed infants in Tanzania. *BMC Pediatr.* 2010;10:44–54.
22. Ciaranello A, Park J, Ramirez-Avila L, et al. Early infant HIV-1 diagnosis programs in resource-limited settings: opportunities for improved outcomes and more cost-effective interventions. *BMC Med.* 2011;9:59–64.
23. Cohn J, Whitehouse K, Tuttle J, et al. Paediatric HIV testing beyond the context of prevention of mother-to-child transmission: a systematic review and meta-analysis. *Lancet HIV*. 2016;3:e473–81.
24. World Health Organization. *Recommendations on the Diagnosis of HIV Infection in Infants and Children*. Geneva, Switzerland: World Health Organization; 2010.
25. *Two Cutting Edge Technologies for HIV Detection in Infants Receive WHO Prequalification [press release]*. World Health Organization. Available at: http://who.int/diagnostics_laboratory/cutting-edge-hiv-prequal/en/. Accessed November 14, 2016.
26. Mazanderani A, Kufa-Chakezha T, Sherman G. *Introduction of Birth Testing into the South African National Consolidated Guidelines*. CROI; February 22–25, 2016; Boston, MA. Abstract 783.
27. Lilian RR, Kalk E, Bhowan K, et al. Early diagnosis of in utero and intrapartum HIV infection in infants prior to 6 weeks of age. *J Clin Microbiol.* 2012;50:2373–2737.
28. Penazzato M, Revill P, Prendergast AJ, et al. Early infant diagnosis of HIV infection in low-income and middle-income countries: does one size fit all? *Lancet Infect Dis.* 2014;14:650–655.
29. Carmona S, Wedderburn C, MacLeod W, et al. Field performance of point-of-care HIV testing for early infant diagnosis: pooled analysis from six countries from the EID Consortium [LBPE008]. Poster presented at: XXI International AIDS Conference; July 18–22, 2016; Durban, South Africa.
30. Vojnov L, Markby J, Boeke C, et al. Point-of-care CD4 testing improves linkage to HIV care and timeliness of antiretroviral therapy initiation in a public health approach: a systematic review and meta-analysis. *PLoS One*. 2016;11:e0155256.
31. Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011;377:1495–1505.
32. Marston M, Becquest R, Zaba B, et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. *Int J Epidemiol.* 2011;40:385–396.
33. IMPAACT P1115. *Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission*. International Maternal Pediatric Adolescent AIDS Clinical Trials Group. Available at: https://clinicaltrials.gov/ct2/show/NCT02140255. Accessed November 14, 2016.
34. Kiyaga C, Sendagire H, Joseph E, et al. Consolidating HIV testing in a public health laboratory for efficient and sustainable early infant diagnosis (early infant diagnosis) in Uganda. *J Public Health Policy.* 2015;36:153–169.
35. Kiyaga C, Sendagire H, Joseph E, et al. Uganda's new national laboratory sample transport system: a successful model for improving access to diagnostic services for early infant HIV diagnosis and other programs. *PLoS One*. 2013;8:e78609.