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LESSONS LEARNED FOR STRENGTHENING EARLY INFANT DIAGNOSIS OF HIV PROGRAMS

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LESSONS LEARNED FOR STRENGTHENING EARLY INFANT DIAGNOSIS OF HIV PROGRAMS

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ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
EID	Early Infant Diagnosis
HFG	Health Finance and Governance
HIV	Human Immunodeficiency Virus
KEMRI	Kenya Medical Research Institute
NASCOP	National AIDS and STD Control Program
PMTCT	Prevention of Mother-to-Child Transmission
POC	Point-of-care
WHO	World Health Organization

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EXECUTIVE SUMMARY

Early infant diagnosis (EID) testing of HIV-exposed infants is an essential step to initiating lifesaving treatment for HIV-positive infants and preventing mother-to-child transmission for HIV-negative infants. Whether infected in utero, at birth, or in the months thereafter via breastfeeding, infants who are promptly diagnosed and started on antiretroviral therapy (ART) can achieve viral suppression of HIV and go on to live full and healthy lives. While the importance of EID testing is known and reflected in national and international commitments like the UNAIDS 90-90-90 goals, EID programs face several challenges that can limit their effectiveness. This report uses Health Finance and Governance project experiences in Kenya and peer-reviewed literature to identify key EID program challenges and approaches to solving them in sub-Saharan Africa, where the majority of testing is needed.

A literature review focused on EID programs in sub-Saharan Africa identified patient loss to follow-up, test result turnaround time, and failure to initiate ART as the main challenges to program effectiveness.

Caregivers and infants may be lost to follow-up at any point in the EID care cascade, with pre-enrollment, pre-testing, and while awaiting results as the major bottlenecks. Lack of integration or inadequate referral mechanisms between maternal, child, and HIV care and testing services leaves gaps for patients to be lost to follow-up. Late maternal HIV diagnosis also appears related to mother-infant pairs exiting the EID cascade. Interventions that strengthened linkages to testing immediately after birth, used community-based approaches and expert patients to provide counseling and referrals to care, and promoted accountability for EID outcomes at the health facility level appeared to help mitigate loss to follow-up in several countries and subnational settings.

Once patients initiate testing, long turnaround times from when a sample is collected to when results are received can negatively impact retention in care and the clinical effectiveness of ART when initiated. National EID programs rely on centralized or regional laboratory or networks to collect samples from health facilities, conduct testing in the labs, and deliver results back to the facilities, where patients return to receive them. Depending on a wide variety of factors, the process can take anywhere from days to months. Countries have invested in transportation interventions like courier networks and overnight delivery, and technological interventions like web- and SMS-based notification systems to speed up all stages of turnaround and decrease delays in result receipt and clinical response. Point-of-care (POC) testing can reduce turnaround times to the span of a single facility visit, though national level implementation of POC testing is unrealistic at current prices.

Under modern HIV care guidelines, all patients testing HIV-positive, including infants, should immediately initiate ART, but some do not. Loss to follow-up before receiving EID results is a major reason some infants never begin ART, but caregiver's denial of results, lack of understanding, other sociocultural factors, and even the absence of a referral by health providers can lead to inaction on results. Similar to loss to follow-up interventions, countries used community- and peer-based counseling efforts, provider trainings, and EID focal persons at facilities to improve ART uptake for HIV-positive infants. Reducing loss to follow-up and turnaround times, whether through previously mentioned interventions or POC testing, can also improve likelihood of receiving and acting on results.

In Kenya, HFG worked with the Kenya Medical Research Institute to measure the costs of EID testing using lab- and POC-based approaches, and also to calculate EID turnaround times at a sample of facilities in Siaya County. Lab-based testing costs an average of $25.05 per test, which is lower than most previously reported costs from Kenya and elsewhere in Africa. Costs of POC-based testing are higher

and more complicated to estimate due to higher reagent costs, different procurement requirements, and variability linked to demand for testing, but could range from similar to lab-based testing at high-demand facilities to several times more expensive at low-demand facilities. Based on a sample of 288 patient records, the average turnaround time from sample collection to result receipt was nearly 43 days, and the average age at receipt was 113 days. Infants with positive test results were returned to facilities to collect results 5 days earlier than those with negative results, and all HIV-positive infants in our sample initiated ART, typically the same day. Both the costing activity and turnaround time analysis were aided by data from Kenya's National AIDS and STD Control Programme dashboard for EID testing, which reports current data on a wide range of indicators and serves as a useful tool for program managers and researchers.

HFG's research in Kenya and the literature review of EID programs in sub-Saharan Africa suggest that progress is being made on EID's major challenges. Every country has unique national and subnational circumstances that modify the interrelated challenges of loss to follow-up, turnaround times, and ART initiation, but there are a wide variety of approaches with demonstrated successes to learn from. This report aggregates recent examples that can serve as a starting point for health facility and lab managers, health system planners and policymakers, and others seeking to develop or strengthen EID programs.

Overall, countries should feel empowered to experiment with the interventions best suited to their challenges, priorities, and resources. Where lab-based networks are already well established, prioritizing adherence to testing and treatment guidelines for current patients while conducting outreach to draw in underserved populations likely makes more sense than deploying new technologies. Conversely, in countries without robust networks, or regions wholly disconnected from them, POC and near-POC technologies may be good short-term solutions while labs and their supporting infrastructure are developed. Whatever approaches countries choose, monitoring and evaluation components such as the data dashboards used in Kenya and elsewhere should be included to promote accountability, transparency, and the sharing of best practices between countries, development partners, and other organizations working toward the global goal of ending the AIDS epidemic by 2030.

1. INTRODUCTION

1.1 Background

The first step in UNAIDS's 90-90-90 targets is to ensure at least 90 percent of people living with HIV know their status, which can only be confirmed through testing. For children and adults, rapid diagnostic tests are sufficient for initial testing, but for HIV-exposed infants in the first weeks and months of life, the presence of maternal antibodies can confound these tests. The solution is infant virological testing, more commonly known as early infant diagnosis (EID) testing, which can establish whether detected virus copies are of maternal or infant origin (UNICEF 2018).

Diagnosis of HIV enables initiation of antiretroviral therapy (ART) and is thus a crucial component of efforts to end the AIDS epidemic. Whether infected in utero, at birth, or in the months thereafter via breastfeeding, infants who promptly start ART can achieve viral suppression of HIV and go on to live full and healthy lives. World Health Organization (WHO) guidelines, which had previously recommended EID testing for HIV-exposed infants at six weeks of age, supported by prophylactic therapy, now recommends the addition of at-birth testing when feasible (WHO 2016a). Developments in national HIV care guidelines, laboratory testing networks, and new point-of-care (POC) testing technologies are enabling more countries to implement at- or near-birth EID and thus lifesaving ART for all HIV-positive infants.

Without ART, mortality among perinatally infected infants can exceed 10 percent by two months of age, 40 percent by three months, and as high as 68 percent by two years (Marinda et al. 2007; Bourne et al. 2009; Marston et al. 2011; Becquet et al. 2012; Kim HY et al. 2012). By comparison, in a South African trial, initiation of ART at a median of 7.4 weeks after birth was associated with 9.8 percent mortality by 13 weeks of follow-up, 3.7 percent between 13 and 26 weeks, and 3.1 percent between 26 and 52 weeks; mortality among infants who initiated ART at a median of 28.2 weeks after birth was 40.6 by 13 weeks of follow-up, 19.7 between 13 and 26 weeks, and 6.8 between 26 and 52 weeks (Violari et al. 2008). While continued research is needed on optimal drug regimens and dosing for infants, there is great potential for ART initiation within the first weeks of life, and as early as the day of birth, to prevent or delay disease progression and save more lives, making early diagnosis critical (Persaud et al. 2013; Innes et al. 2014; Luzuriaga et al. 2015).

Need for EID testing is greatest where adult HIV prevalence is highest, particularly among reproductive-age women. In 2014, more than 75 percent of EID testing occurred in sub-Saharan Africa, and the WHO projects that South Africa, Uganda, Zimbabwe, Mozambique, and Kenya will be the five largest markets for the more than 2.8 million tests required globally by 2020 (WHO 2016b). Given the scope of the epidemic in sub-Saharan Africa, as well as the currently large unmet need for testing, this document focuses on testing challenges and approaches to solving them in sub-Saharan Africa, though EID testing is of course needed wherever HIV-exposed infants are born.

Because EID testing has long required the use of sophisticated technologies, pre-test preparation, and post-test interpretation by highly trained laboratory personnel, complex lab-based testing networks became the standard approach to testing. Equipped with a steady supply of electricity and water, high-throughput testing platforms, and skilled technicians, and supported by sample transportation networks, such labs perform EID and other important testing for millions of people, but it is clear that coverage gaps and other challenges remain. Innovative approaches, ranging from community outreach to lab-

network reforms to new POC technologies, will be needed to solve the underlying issues and close the coverage gaps.

1.2 Objectives

Using evidence from peer-reviewed literature, institutional publications, international guidelines and recommendations, and the Health Finance and Governance (HFG) project's experiences assessing the HIV viral load and EID testing program in Kenya, this report aims to describe the latest approaches to strengthening EID in developing country contexts, including through the use of POC testing. Specific to POC testing, it will also contribute to ongoing discussions around the feasibility of implementation, the plausible range of effects on diagnosis and outcomes, and the factors that will influence costs and cost-effectiveness of use.

This report is intended to benefit health facility and laboratory managers, health system planners and policymakers, and local and international organizations seeking to develop or strengthen EID programs and end the AIDS epidemic.

2. METHODS

2.1 Literature Review

A literature review was conducted to gather information on EID programs in sub-Saharan Africa, where the majority of new infections occur. Documents on EID programs, guidelines, and innovations were also collected from international health organizations. The findings of this review describe current challenges EID programs face at the national and subnational levels, novel approaches to improving programs, and progress on the implementation of POC technologies. The costs and cost-effectiveness of program interventions, POC technologies, and confirmatory testing are also described.

Peer-reviewed literature was found using multiple databases and is limited to articles published after 2011 to provide up-to-date information on EID developments. Search terms included "early infant diagnosis," "infant HIV diagnosis," "infant point-of-care diagnosis," "EID cost-effectiveness," and related terms. Institutional literature and international guidelines were collected from organizations' websites. While programs from many sub-Saharan African countries were reviewed for challenges and health indicators, the interventions and studies described in detail come from Kenya, Malawi, Mozambique, Nigeria, South Africa, Tanzania, Uganda, and Zambia, which were all identified as focus countries of the *Global Plan Towards the Elimination of New HIV Infections among Children by 2015 and Keeping Their Mothers Alive* (UNAIDS 2011). Examples are presented to summarize the range of EID-strengthening interventions in use across sub-Saharan Africa, not to exhaustively describe all interventions or endorse any particular approach.

2.2 HFG in Kenya and the NASCOP Dashboard

HFG worked with the Kenya Medical Research Institute (KEMRI) to conduct a costing study of HIV viral load and EID testing in the country's western counties in 2016. Trained data collectors visited primary and secondary health facilities in Siaya County and their supporting KEMRI lab in neighboring Kisumu County to understand how patient samples are collected and move through the testing network and measure all required inputs for viral load and EID testing, including human resources, medical supplies, reagents, equipment, transportation, trainings, quality controls, and overheads. KEMRI provided clarifying information where needed, as well as data on inputs for POC testing and on input costs. Beyond the lab-based testing KEMRI conducts in Kisumu and throughout the country, POC testing is now available in some areas through donor-supported pilot programs, though the programs had not started at the time data were collected. Full methods and findings of the costing activity are described in *Costs of HIV Viral Load and Early Infant Diagnosis in Kenya* (Cintron et al. 2017).

Following the costing study, HFG built a model to evaluate the cost-effectiveness of POC viral load testing compared to lab-based testing (Mangone et al. 2018). Data from peer-reviewed literature, Kenya's National AIDS/STD Control Programme (NASCOP) Dashboard, and primary data on viral load result turnaround times collected from the costing study sites were used to inform the model. While the NASCOP Dashboard reports on a vast number of indicators useful in understanding the viral load and EID landscapes in Kenya, their turnaround time measurement only spans from sample collection to result dispatch. Thus, HFG revisited facilities to collect additional turnaround time data spanning from sample collection to when patients/caregivers receive results, broken down by each event in the process. Issues with the data, such as records indicating a patient received their result before it had been

tested at the lab, or missing dates, were resolved as best as possible by cross-referencing facility and lab records and following up with staff. Records with irreconcilable issues were excluded from turnaround time calculations, which were used in modeling the likelihood of a patient experiencing an extended delay in result receipt. Full methods on how the data were collected, cleaned, and used are described in *Economic Evaluation of Nationally Scaled Point-of-Care Diagnostic Platforms for Viral Load Monitoring in Kenya* (Mangone et al. 2018).

2.3 Synthesizing Lessons Learned

Findings from the literature review, data and knowledge gained from the costing and cost-effectiveness activities, and publicly available data from the NASCOP Dashboard inform the discussion and recommendations included in this report.

3. FINDINGS

3.1 Literature Review – Key Program Challenges

The past decade has seen substantial increases in the number of HIV-exposed infants who are tested and initiated on ART, but an estimated 49 percent of infants in *Global Plan* focus countries still do not receive appropriate tests to determine their HIV status within their first two months of life (UNAIDS 2016). Countries face numerous obstacles to scaling up EID programs and to ensuring that all infants who are diagnosed then start ART as soon as possible. Our review of recent literature on EID programs revealed that there are still high rates of loss to follow-up throughout the EID care cascade, delays in turnaround times between sample collection and the receipt of results, and a low rate of HIV-positive infants initiating ART.

3.1.1 Loss to follow-up

Assessments of EID programs have shown that high rates of loss to follow-up occur throughout the EID cascade, from before testing occurs all the way to retaining HIV-positive infants on ART. The earliest form of patient loss can happen before they are even enrolled in EID programs, as seen in a cohort study in Mozambique, where only a quarter of HIV-positive mothers ever returned with their infant for EID after receiving a referral from prevention of mother-to-child transmission (PMTCT) services at birth (Cook et al. 2011). For patients who do reach enrollment, early dropout is the next risk. In a cohort study from the early years of EID testing (2006 to 2008) in Kenya, 26 percent of the cohort was lost to follow-up within two months of enrollment and nearly 20 percent of infants who were enrolled long enough to initiate testing never returned to receive their results (Hassan et al. 2012). Only 32 percent of the cohort were still in care at the same facility by 18 months of age. A multi-country review from the same time period also reported that many infants who initiated testing never returned for results in Cambodia, Namibia, Senegal, and Uganda (Chatterjee et al. 2011).

Caregiver's barriers to accessing EID services have been identified as contributing to loss to follow-up or substandard practice in care. In Kenya, a study found caregivers had incomplete or inaccurate knowledge of mechanisms of mother-to-child transmission, effectiveness of prophylaxis, and the necessity and timings of EID testing (Hassan et al. 2012). Health service providers also had knowledge gaps and felt they lacked adequate training on EID. Another study in Kenya found maternal education, feelings of partner support, feelings of stigma from providers, and distance to health facilities were associated with the timing of EID initiation (Goggin et al. 2016). In Cameroon, late HIV diagnosis during pregnancy was significantly associated with caregivers not completing the EID process, and caregiver's explanations for not returning for results included fear of results, forgetting appointments, and having to travel to a different facility (Tejiokem et al. 2011). Late maternal HIV diagnosis and late or no ART/prophylaxis initiation were also associated with loss to follow-up from the EID cascade in Ethiopia (Kebede et al. 2014). Qualitative research from South Africa suggested late or absent HIV testing during pregnancy, lack of counseling for mothers after diagnosis, and providers being unaware of mother's HIV status all contributed to missed opportunities for initiating EID testing (Feucht et al. 2016).

Inadequate referral mechanisms within facilities and patient tracing efforts, especially for those who do not return to health facilities to pick up test results, also contribute to loss to follow-up. The absence of a streamlined process for mother-infant pairs from sample collection to ART initiation creates

opportunities for them to be lost, and gaps in the documentation of patient records makes it difficult for providers to flag when infants do not return (Chatterjee et al. 2011; Feucht et al. 2016). Ultimately, loss to follow-up at various points in the EID cascade prevents infants from receiving the care they need, even when EID services are available.

3.1.2 Turnaround time

While the WHO recommends that all HIV-exposed infants undergo virological testing at 4-6 weeks of age and begin ART without delay if infants receive positive test results, lengthy turnaround times between sample collection and the receipt of results makes it difficult to achieve these recommendations (WHO 2016a). Turnaround times vary between and within countries due to laboratory and health facility network structures, staff training, laboratory equipment capacity, and sample transportation networks. Poor data quality and a lack of systematic documentation of samples and test results' arrival to laboratories and health facilities make it difficult to measure turnaround time from sample collection to receipt of results (Chatterjee et al. 2011). Studies and national reporting systems may also define turnaround times differently and at different points of the EID process. The lack of a standard definition of turnaround time makes it difficult to compare programs or measure improvements.

Different approaches to the transportation of samples from health facilities to laboratories and test results from laboratories back to health facilities have significant impacts on turnaround time. Namibia, which has invested in overnight transportation, has an average turnaround time of samples from facilities to laboratories of 1.4 days (Chatterjee et al. 2011). Conversely, difficult terrain conditions and low sample numbers contribute to the approach of a clinic in rural southern Zambia to only send samples to a central laboratory in Lusaka approximately once a month, resulting in significantly longer turnaround times by default (Sutcliffe et al. 2014). Various transportation systems are used across Tanzania, contributing to substantial turnaround time differences between districts. Districts that provided financial support for the systematic delivery of samples to laboratories and results back to health facilities by using postal couriers had significantly shorter turnaround times than districts that sent samples to laboratories with health personnel whenever they traveled there (Chiduo et al. 2013). Delays in turnaround due to transportation were also seen in Uganda and Ethiopia, where poor courier systems, loss of samples, and laboratory issues inhibited timely results delivery (Chatterjee et al. 2011; Kebede et al. 2014).

Laboratory processing times, which were not commonly reported, also contribute to delays in turnaround. Sample processing took on average 3.3 weeks in Uganda and over a month in Zambia, both of which were among the longest total turnaround times seen in the literature (Chatterjee et al. 2011; Sutcliffe et al. 2014). While specific reasons for the extended processing times in Uganda and Zambia were not provided, laboratory issues reported in Ethiopia included light interruption, DBS processing errors, and overloading test batches (Kebede et al. 2014).

There are also delays in returning results to caregivers, although this portion of the result turnaround process is not always included or made explicit when reporting turnaround times. In Zambia, it took on average 45 days from the time results were available at a clinic for caregivers to return and receive them (Sutcliffe et al. 2014). Delays occurred because caregivers missed appointments or clinics failed to locate results when caregivers returned.

3.1.3 ART initiation

As previously noted, there is considerable loss to follow-up of HIV-positive infants before they initiate ART, and challenges in retaining them in treatment afterward. Loss to follow-up, long waiting times in health facilities, and delays in receiving results due to slow turnaround are all barriers to HIV-positive infants initiating appropriate treatment. This is a critical step in the EID cascade, considering that the main goal of diagnosing infants as soon as possible is to begin treatment as soon as possible and thus reduce HIV-related morbidity and mortality. Systemic challenges to infants accessing treatment after diagnosis therefore reduce the impact of EID programs.

Rates of ART initiation are considerably low, even in countries with high EID coverage and where a high proportion of infants are tested and referred to ART. In Senegal, Uganda, and Cambodia, only 22, 37, and 38 percent of infants testing positive for HIV initiated ART (Chatterjee et al. 2011). In Namibia, which has an otherwise strong EID program and whose guidelines recommended ART initiation irrespective of age before it became the official WHO recommendation, only 70 percent of infants initiated ART within six months enrollment in care. One reason for failed ART initiation can be caregivers never returning to receive test results. In Malawi, 40 percent of caregivers initiated testing but never returned for results, including 13 percent of HIV-positive infants (Dube et al. 2012). Among the HIV-positive infants that did receive their status, 42 percent never initiated ART. Inadequate training of health service providers may also act as a barrier to care, as seen in South Africa where infants with positive tests results were sometimes not referred for ART initiation (Feucht et al. 2016). Other reported barriers to ART initiation included CD4 requirements, referrals to other departments or facilities for ART services, fear or denial of results by caregivers, facilities losing results, and appointment delays (Chatterjee et al. 2011; Hassan et al. 2012).

3.2 Program Interventions and Advances

To address the challenges of high loss to follow-up, lengthy turnaround times, and low levels of ART initiation, countries have attempted a number of different interventions and service delivery changes for EID. Interventions mainly focus on either improving referral mechanisms to address loss to follow-up and increase ART initiation, or implementing technological changes to reduce turnaround time. POC technologies, newly validated by the WHO, represent a great potential change in terms of both intervention approaches, though evidence of their effectiveness and impact on HIV-related morbidity and mortality are still limited. It should be noted that interventions targeting one or more of the identified challenges are likely to have spillover or bidirectional effects on the others – decreasing loss to follow-up may decrease turnaround time by increasing the number of samples available at a facility for batching and testing without delay; conversely, decreasing turnaround may decrease loss to follow-up and increase ART initiation because caregivers are more likely to get test results at their first return visit after testing; finally, increasing ART initiation might itself decrease loss to follow-up by demonstrating to caregivers, health care providers, and other stakeholders the benefits strengthening the entire EID cascade.

Interventions discussed in this section are offered only as recent examples for the consideration of policy and program planners. Country- and local-level contexts should be carefully considered when selecting the intervention(s) most likely to produce desirable and sustainable outcomes.

3.2.1 General approaches

Strengthening referral mechanisms and linkages to care throughout the EID cascade is one approach that could increase ART initiation and improve overall retention. In a study from Mozambique, linkages

between maternal postpartum care and EID services were improved by 'enhanced EID referral' in which mothers, before being discharged, were directly accompanied by a nurse from the maternity ward to where EID services were offered, at which point they received counseling in private and a medical record was created for the infant (Ciampa et al. 2011). Mother-infant pairs who received the intervention had 3.4 higher odds of returning for EID follow-up than those who did not. Additionally, among all mother-infant pairs who ever returned for an EID visit during the study, intervention pairs returned a median time of 33 days after birth, compared to 56 days after birth for non-intervention pairs. Thus, the simple enhanced referral intervention, which was acceptable to facility staff and only cost an extra 5–10 minutes of their time, significantly increased the odds of EID follow-up overall and specifically during the recommended EID testing period (when supplementary at-birth testing is not available).

Non-health facility-based efforts to increase use of PMTCT and EID services also have potential for improving linkages to care and outcomes, as evidence from Nigeria demonstrates. Many HIV-related indicators in Nigeria were poor in 2014: less than 20 percent of pregnant women were tested for HIV, only 29 percent of HIV-positive pregnant women received ART, and rates of EID testing and ART receipt among children were even lower (Pharr et al. 2016). In this context, a working group in rural and overwhelmingly church-going Enugu State sought to evaluate a church congregation-based intervention aimed at reducing PMTCT barriers. Forty churches were randomized into 20 intervention churches and 20 control churches; all churches hosted baby showers for pregnant women, but the intervention group's showers included on-site health education and offered free lab testing, including HIV testing. In contrast, the control group's showers only referred women to the nearest health facility and encouraged pre- and postnatal care and HIV testing. Women from intervention and control groups were followed up 6–8 weeks after giving birth and linked to further care. In all, women from the intervention group were more likely to get an HIV test and to receive ART during pregnancy than those from the control group, and indicators for HIV-exposed infants (prophylaxis received, EID tested, and ART initiated) were better than national averages, though long delays in receiving EID results were also experienced. Since providing congregation-based health education information and integrated laboratory screenings for pregnant women instead of only providing referrals for services was acceptable to participants and increased participation along the PMTCT cascade, it is possible the approach could also be used to provide or strengthen EID and ART services in future programs (Pharr et al. 2016).

The use of peer educators (peer meaning people living with HIV), lay persons, and village health teams to conduct community-level outreach or one-on-one counseling with HIV-positive pregnant women is another intervention being used to disseminate PMTCT and EID information and link women to services. In Uganda, these approaches have been associated with increased proportions of mother-infant pairs attending six-week postnatal care visits and infants receiving EID tests by 14 weeks of age, compared to the previous year (Namukwaya et al. 2015). Following the example of programs in Malawi (Kim MH et al. 2012) and South Africa (Teasdale and Besser 2008), a study team trained outreach personnel to deliver counseling, home visits, and community visits on HIV and reproductive health topics to HIV-positive women recruited from antenatal care clinics at three urban hospitals in Kampala and one rural health center. Study participants received an average of 3.5 home visits: at enrollment, during pregnancy, two weeks after delivery, and at other points if they missed clinic visits. Among mother-baby pairs who continued study participation after delivery, attendance of a six-week postnatal visit (78.5 percent) and initiation of EID testing by 14 weeks of age (86.3 percent) were significantly higher across all study sites compared to percentages attending and testing in the year prior to the outreach intervention (37.1 percent and 53.6 percent). Researchers believed the use of peer educators, who conducted the majority of home visits, were a major factor in improving both indicators due to mother's increased comfort in discussing sensitive matters with educators also living with HIV (Namukwaya et al. 2015).

Malawi recently adopted a variety of facility- and community-based interventions focused on improving linkages to care for PMTCT and EID services, with promising results (Magongwa et al. 2018). The interventions start with the appointment of an EID focal person at a health facility, who participates in subsequent EID strengthening activities including registering HIV-exposed infants in the labor and delivery ward, immediately after birth, synchronizing ART visits for mother-infant pairs, flagging patient charts so mother-infant pairs are immediately identifiable, collecting a dried blood spot sample for EID at the six-week visit, employing "expert clients" to trace and refer mother-infant pairs who miss appointments, delivering information on PMTCT and EID to both health care providers and mother-infant pairs, and partnering with the group Riders for Health to improve timeliness and accountability of the EID sample transport system. Across the 95 health facilities where the interventions were deployed starting in 2016, the percentage of HIV-exposed infants receiving an EID test by two months of age increased from 38 in 2014/15 to 61 in 2016/17, and the average turnaround time for results decreased from 53 days to 23 days across the same period. Though a direct causal link cannot be drawn from the interventions to the observed outcomes, program implementers believed the interventions contributed to a structuring and prioritization of PMTCT and EID services and approaches that make adherence and retention in care easier for mother-infant pairs (Magongwa et al. 2018).

Research focusing on Mozambique's EID program sought to quantify the association between long turnaround times (from sample collection to result at health facility) and the probability of caregivers receiving the result (Deo et al. 2015). The study used routine data from before and after an intervention that equipped seven health facilities in Maputo with mobile-connected printers for receiving EID results electronically from the testing lab (as opposed to physically delivering results). Post intervention, the average turnaround time decreased from 68.1 to 41.1 days, and the average number of days from when results were available at facilities to when caregivers received them decreased from 56.7 to 20.6. Most results still took over 30 days to return to facilities (67 percent). Despite the improvements in turnaround time, fewer caregivers ever received results after the intervention (31 percent) than before (47 percent). Turnaround times and probabilities of collecting results varied widely across facilities, before and after intervention. Researchers found statistically significant associations between turnaround times greater than 30 days and reduced likelihood of result collection, and infant age and reduced likelihood of result collection (Deo et al. 2015). The absence of mechanisms for contacting caregivers to return when results were ready seemed to leave potential benefits of the intervention unrealized.

Though it may sound paradoxical, improving initiation and retention in care, result turnaround time, and scaling-up of services in general may also be achieved through consolidation. When Uganda faced the challenge of improving cost-effectiveness and efficiency of EID testing, the National EID Subcommittee proposed consolidating eight partner-run laboratories into one public laboratory for EID (Kiyaga et al. 2015). The subcommittee's plan better aligned the available capacity to run EID tests with actual number of patient samples requiring testing. This improved efficiency by reducing unused capacity and its associated overhead costs. It also improved EID program effectiveness by speeding up turnaround times (the central lab would not have to wait extended periods to gather enough samples for a 'batch' of tests) and thus clinical responses to results. The plan also included the creation of a hub-and-spoke model for sample transportation to the central lab, where each hub hospital was given a motorbike for collecting samples from surrounding health facilities and transporting them to the lab on a weekly basis (or more frequently).

Outcomes under Uganda's new central lab system were evaluated in 2012 and compared to the year prior, when the eight labs were last used. The evaluation found that recurrent costs of EID testing were about $17 lower per test at the central lab than at the eight labs, turnaround times (from sample collection to result returned to health facility) decreased from 49 days to 14 days, and percentages of infants receiving test results and initiating ART improved (Kiyaga et al. 2015). Building on these successes in 2013, the EID program added internet-connected GSM printers to hub facilities to instantly

transmit test results from the central lab, shaving additional days off result turnaround times. The central lab also began reporting real-time EID data to a web-based dashboard, a model the Ministry of Health plans to use for monitoring and evaluation of other priority programs.

Seeking to reduce EID result turnaround times and repeat health facility visits for caregivers, Zambia's Ministry of Health developed and piloted an SMS-based result reporting system at 10 health facilities in the Southern Province (Seidenberg et al. 2012). Prior to intervention, couriers delivered EID samples from health facilities to regional testing labs, then paper results back to health facilities, at which point staff attempted to contact caregivers to return or simply awaited the caregiver's next visit. The average Ministry of Health for EID results from sample collection to results reaching health facilities was 44.2 days, plus another 22.6 days for caregivers to return to facilities. For the pilot, designated health facility staff were trained to receive test results from the regional lab via SMS, then contact caregivers to return the facility for results and counseling. The SMS approach saw results returned to facilities an average of 26.7 days after sample collection, and caregivers receiving results after 8.3 additional days. In response to the success of the pilot, the Government of Zambia initiated national scale-up of the SMS results delivery system (Seidenberg et al. 2012).

Kenya has also deployed technology-based approaches to improving EID result turnaround times, ART initiation, and retention in care. Following a small but successful two hospital pilot, the KEMRI and other partners launched a 10-hospital pilot of the web-based (and mobile-friendly) HIV Infant Tracking System (Finocchario-Kessler et al. 2015). The system sends alerts to relevant health facility and lab staff to notify them of important EID events for patients, such as when they should collect a dried blood spot sample for testing, when the test results are ready, when to initiate retests, and when patients have missed visits and should be traced. It also contacts caregivers (or designated community health workers) via SMS, notifying them when to return to a health facility. After system implementation, each indicator was substantially better than the national average: the average turnaround time (from sample collection to caregivers receiving results) across pilot hospitals was 3.3 weeks, 90.7 percent of eligible infants initiated ART, and retention in care for nine-month retesting of HIV-exposed infants was 86.7 percent. All pilot hospitals adopted or intended to adopt the HIV Infant Tracking System for regular use after the pilot ended, and its effectiveness was expected to rise as cell phone technology and coverage improved in Kenya (Finocchario-Kessler et al. 2015).

3.2.2 Point-of-care testing

POC testing has been deployed as a new approach to address many of the challenges of EID. The main benefit of POC testing is that it can provide results to caregivers and initiate an appropriate clinical response within a single visit, eliminating the challenges of waiting days, weeks, or months for results, traveling for multiple follow-up visits, and the costs and risks of transporting samples and results (Diallo et al. 2017). POC testing assays including the Xpert HIV-1 Qual Assay and the Alere q HIV-1 Detect have been prequalified by the WHO and found comparable to lab-based assays for providing accurate results, while also requiring minimal training and hands-on time to use in low-resource primary health settings (Diallo et al. 2017; Jani et al. 2014).

The body of literature evaluating POC testing for EID is young, but early studies have shown encouraging results. Along with the PMTCT/EID interventions discussed earlier (Magongwa et al. 2018), Malawi began piloting POC testing in 2015 to evaluate potential impacts on treatment initiation rates and turnaround times (Mwenda et al. 2018). Patient data from before and after POC testing implementation was compared at seven health facilities; all 'before' patients had dried blood spot samples collected and transported for lab-based testing, in line with the standard of care practice, and all 'after' patients had whole blood samples drawn and tested immediately using the Alere q platform. Of the 789 patients who received POC testing, 785 received results the same day, 29 of the 45 found HIV

positive initiated ART the same day they received results, and 41 of the 45 initiated ART during the study period. By comparison, among 963 patients who received lab-based testing, 575 had still not received results within 60 days of sample collection, 7 of the 31 found HIV positive initiated ART the same day they received results, and 16 of the 31 initiated ART during the study period. In facilitating a higher proportion of infants initiating ART and doing so, in most cases, with no delay, POC testing for EID stands to be an important tool for achieving the 90-90-90 (and 95-95-95) targets in Malawi.

In a trial in Mozambique, POC testing was found to have significant turnaround time and related advantages over lab-based testing (Jani et al. 2018). Despite being older at the time of sample collection, infants using POC testing received results at a median age of 41 days, after a turnaround time of zero days. By comparison, infants using lab-based testing received results at 172 days of age, after a 125 day turnaround time. Among infants who were tested with POC technology, 98 percent received results in the same day, 66 percent with positive results initiated ART the same day, and nearly 90 percent with positive results had initiated ART within 60 days of sample collection. Proportions of infants initiating ART and remaining in care after 90 days of follow-up were significantly higher with POC testing than with lab-based testing. POC testing in this context provided results quickly, decreasing the opportunities for loss to follow-up, and enabling faster access to treatment.

As with all new technologies, challenges and limitations to effectiveness exist for POC platforms. As previously noted, Alere and Xpert assays are WHO prequalified and evaluated as having high sensitivity and specificity for whole blood samples (WHO 2017), but small sample volumes and higher limits of detection than lab-based assays may increase the risk of false negative results when maternal and infant prophylaxis are in use (Hsiao et al. 2016). Invalid test results due to machine or operator errors are another concern, despite platform designs emphasizing ease of use and minimal training requirements. In an evaluation of the Alere assay, 6 percent of samples had initial testing errors and required retesting to be resolved (Hsiao et al. 2016). In low-resource settings, the time and resource costs of retesting could pose real challenges to the added value of POC testing. These challenges are noted not to say that POC innovations should not be pursued, but rather that routine quality control, user training, and monitoring and evaluation systems are all key components to consider when integrating POC testing to EID programs.

The demonstrated potential of POC testing to improve coverage, timeliness, and effectiveness of EID programs is great, but optimal and sustainable results will be most likely with strategic implementation tailored to country contexts. New guidelines and frameworks for strategic POC testing integration, specifically for EID, have been published in recent years (Diallo et al. 2017; UNICEF 2018), and updates will come as more evidence is generated.

3.2.3 Costs and cost-effectiveness of EID interventions

Data on the costs and cost-effectiveness of EID interventions are limited. Cost-effectiveness of different EID testing strategies is influenced by other factors like PMTCT program effectiveness and attrition rates, complicating evaluation. Costs of EID testing have been explored in detail in the costing study report. Recent examples of programmatic costs and cost-effectiveness evaluations are described here for illustrative purposes.

The consolidation of eight EID testing laboratories in Uganda into one centralized laboratory reduced recurrent costs by $17 per test at the same time it sped up turnaround times and improved initiation and retention in care (Kiayaga et al. 2015). Savings came from the reduced consumables, human resources, rent, and utility costs needed to operate one lab instead of eight. Under ideal circumstances, the costs saved through increased efficiency could be redirected toward improving quality and coverage of services, such as reaching the nearly 40 percent of patients who still never received results.

Based on a cost-effectiveness modeling study for South Africa, testing infants at six weeks alone is more cost-effective and produces better clinical health outcomes than testing once at birth (Francke et al. 2016). Testing at birth and at six weeks further improved clinical outcomes, but the cost-effectiveness of the double-testing approach is dependent on mother-to-child transmission risk and the survival benefit of earlier ART initiation. A related study examined the cost-effectiveness of confirmatory testing for positive results, again in the context of South Africa (Dunning et al. 2017). Cost-effectiveness of confirmatory testing relative to no confirmatory testing was dependent on mother-to-child transmission risks and other factors, but confirmatory testing was ultimately recommended for South Africa and similar contexts to avert false-positive diagnoses and the high costs of unnecessary initiations of lifelong ART.

3.3 Kenya Experiences

3.3.1 Background

Kenya's main EID testing program is operated by NASCOP through a network of six regional laboratories and two additional hospital laboratories in Nairobi. The labs processed nearly 118,000 EID samples sent from over 1,500 facilities in 2017 (NASCOP 2018). Samples are collected as dried blood spots in drug dispensaries, health centers, and hospitals, transported via motorcycle couriers to district or subdistrict hospitals, and then onward to the regional labs for testing. Results are relayed electronically from labs to the district/subdistrict hospitals, where they are printed and sent via couriers back to the points of origin. Patients are informed of HIV-negative results at their next facility visit and are called or otherwise traced to return for care immediately for HIV-positive results, when possible. POC testing supported by Unitaid and the Elizabeth Glaser Pediatric AIDS Foundation began in August 2017 and has provided nearly 5,700 EID tests as of August 2018. (EGPAF 2018).

Under Kenya's 2016 guidelines, which align with WHO recommendations, all infants born to known or suspected HIV-positive mothers should be initiated on ARV prophylaxis and have a blood sample collected for EID testing at birth or as soon thereafter as possible, within two weeks (also referred to as very early infant diagnosis testing). Infants with positive first tests should be assumed HIV positive and started on ART as confirmatory testing is conducted, while infants with negative first tests should continue prophylaxis and be tested again at six weeks after birth. Confirmed HIV-positive infants should continue on the ART protocol, including viral load testing. HIV-negative infants should be retested with DNA/PCR (virological) tests at six and 12 months, and with HIV antibody tests at 18 months, and at six weeks after complete cessation of breastfeeding.

3.3.2 EID Testing Costs

Unit costs of different EID testing approaches estimated in our costing activity are shown in Table 1. KEMRI labs use two high-volume testing platforms, the Abbott m2000 RealTime and the Roche Cobas AmpliPrep - Cobas TaqMan, to conduct viral load and EID tests for their network of health facilities. Based on data provided by KEMRI and available from organizations engaged in POC testing, we also estimated unit costs for the Alere™ q and Cepheid GeneXpert IV platforms (EGPAF and UNITAID 2016; The Global Fund 2017). Costs for the lab-based approach include all costs incurred throughout the testing process, from sample collection to results received by patients, and are the average unit cost of samples from all facilities in the network. Costs for the POC platforms also include all costs throughout the process, with the assumptions that all testing is done at the true POC, each facility has one purchased platform with a five-year lifespan (Alere q or Xpert IV, whichever is most appropriate for

their weekly testing demand), the platforms are used at their maximum daily capacity, and testing is done by existing facility staff.

Table 1. Average Costs of EID Testing in Siaya County, 2016 (US$)

	Lab-based	Alere q	Xpert IV
Reagents	16.21	25.00	19.00
Supplies	2.83	1.19	2.17
Equipment	0.59	3.73	1.51
Human resources	1.88	1.21	1.56
Quality assurance	1.14	1.59	1.25
Training	1.29	0.29	0.35
Transportation	0.72	n/a	n/a
Non-salary recurrent	0.39	0.32	0.32
Total unit cost	25.05	33.37	23.29

Reagent costs, which dominate the total unit costs of each testing approach, are also the largest source of variation. The variation in equipment costs is noteworthy; costs are low for lab-based testing thanks to reagent rental schemes, where the testing platform is provided at no upfront cost in exchange for the lab agreeing to procure a negotiated quantity of tests at a negotiated rate over the course of the rental, whereas POC platforms must be purchased. Supply, human resource, and training costs are higher for lab-based testing as there are many more personnel and processes involved than for POC testing. Quality assurance costs for the POC platforms are calculated as 5 percent of the pre-quality assurance total unit cost, based on the proportional cost of quality assurance for lab-based testing; the process for POC quality assurance was undetermined at the time of writing but could take the forms of repeat POC testing, sending samples to the lab for verification, etc.

By assuming all POC platforms would be used to their full capacity, the unit costs in Table X represent something of a best-case scenario. In reality, our data on 2016 levels of demand for EID testing indicated that the busiest facility in our sample, a county referral hospital, had just 142 tests that year. The average annual number of EID tests at a sampled facility was 46.4, and the weekly average was 0.9 tests. With weekly testing capacities of 40 for the Alere q and 100 for the Xpert IV, 0.9 tests per week would mean lots of downtime, which would translate into much higher per test costs of equipment and training, even if longer lifespans were assumed for both. If the platforms were also used for viral load testing (pending approval of a viral load assay for the Alere q), a scenario we explored in the costing report, the impacts of low testing demand on unit costs would be lessened, but average costs would still be higher than in the full capacity utilization scenario, and in excess of $100 at some facilities.

3.3.3 EID Result Turnaround Times

Findings from our turnaround time data analysis are shown in Table 2. Facilities previously visited for the costing study were selected on the basis of having enough viral load and EID patients in 2016 for sampling purposes. Records for infants with EID testing in 2016 were sampled from each month, skipping months with no tests and repeating the process until 20 records were selected. In total, 300 records were gathered (one was later discarded as a duplicate) and after data cleaning, 288 could be used to calculate key turnaround time indicators. Most patient records were useable after follow-up and data cleaning, but missing data for some fields was common. Reasons for exclusion were key missing or

out of sequence dates, and follow-up testing instead of initial testing (n=2). Four samples were rejected at hubs or the lab, one patient was lost to follow-up, and one patient died before receiving test results.

Table 2. EID Turnaround Time Findings from Siaya County, 2016

Indicator	n
Facilities sampled	15
Patient records collected	299
Records with calculable turnaround times	288
Indicator	**Average**
Age in days at sample collection	69.8
Days from sample collection to result dispatch	22.3
Days from sample collection result available	33.8
Days from result available to result received	10.1
Days from sample collection to result received	42.6
Age in days at result received	112.8

Average age at sample collection was nearly 10 weeks, despite guidelines calling for sample collection at birth or within two weeks, in addition to six-week testing. Nine patients had samples collected within two weeks of birth, all occurring in the second half of the year. The average number of days from sample collection to result dispatch was similar to the official NASCOP turnaround time (calculated for the same phases) for Siaya County in 2016, 16 days. Results were available for patients at their original facility an average 33.8 days after sample collection, and all patients returned to receive them an average of 10.1 days later. Notably, HIV-negative patients returned for results 10.6 days after they were ready, while HIV-positive patients returned after 5.3 days, a statistically significant difference ($p<0.02$, two sample t-test). All infants identified as HIV positive (n=18) had initiated ART, typically the same day but in some cases after several weeks delay. The proportion of infants testing HIV positive was slightly higher in our sample (6.1 percent) than in Siaya County as a whole (5.3 percent) in 2016. The average age at which patients received initial EID results was 112.8 days.

NASCOP data indicate that the number of days from sample collection to testing to result dispatch have declined in Siaya County and nationally since 2016. The number of counties with collection-dispatch turnaround times of 20 or more days decline from 13 in 2016 to two in 2017, while the number of counties with turnaround times of 10 days or less increased from three to 18. Improvements were mainly in western Kenya, where the HIV is highly concentrated and the overwhelming majority of EID testing occurs (NACC 2016). Longer turnaround times were more common and persistent over time in eastern counties, several of which had fewer than 200 tests per year (NASCOP 2018). Turnaround time data on the last legs of the EID testing process, result delivery from hubs to points of collection and finally to patients, is not reported by NASCOP.

3.3.4 Other NASCOP Data Observations

NASCOP's dashboards for viral load and EID testing contain a wealth of information on numbers of tests, positivity rates, clinical outcomes, lab performance, turnaround time, partner-supported facilities, and more, from the national level down to individual facility levels, for some indicators. Data are updated in real time and new functions for visualizing data are frequently added. While it is beyond the scope of this report to use the dashboard and underlying database to analyze EID outcomes as has been

done for viral load testing (Mwau et al. 2018), several indicators are worth highlighting ahead of broader discussion on EID program scale-up. All indicators featured in Table 3 are from 2017, so data from the last complete year can be considered.

Table 3. Key Indicators from the NASCOP EID Dashboard, 2017

EID testing by type and age		
	Total	**HIV-positive**
Unique infants tested	89,365	2,828 (3.2%)
Initial EID tests:	75,133	2,815 (3.7%)
Infants age < 2 months tested	36,141	784 (2.2%)
Infants age 2-12 months tested	32,360	1,514 (4.6%)
Infants age 12-24 months tested	3,980	344 (8.6%)
Follow-up visit tests	33,339	463 (1.4%)
Confirmatory tests	1,576	590 (37.4%)
EID outcomes by mother's PMTCT regimen		
	Total	**HIV-positive**
Highly Active ART (standard)	46,990	1,524 (3.2%)
None	1,825	361 (19.8%)
EID outcomes by infant prophylaxis regimen		
	Total	**HIV-positive**
Nevirapine - 6 weeks + maternal ART or not breastfeeding (standard)	17,865	556 (3.1%)
None	5,341	580 (10.9%)

Data reported by NASCOP as of September 2018

Nearly 28 percent of infants diagnosed HIV positive in 2017 were identified by a sample collected within the first two months of life, highlighting the importance of initiating testing without delay. Beyond the value of enabling faster treatment initiation for HIV-positive patients, earlier testing provides points of engagement between caregivers and health care providers, which may be helpful in preventing later infections, a possible explanation for the lower rate of infections detected by follow-up testing. Interestingly, confirmatory EID and viral load testing, which is initiated when a false positive is suspected following a positive initial test, revealed nearly two-thirds of such cases were indeed false positives; relative to the costs, monetary and otherwise, of lifetime ART, the costs of repeat and confirmatory testing are trivial.

Reporting on EID outcomes by maternal PMTCT and infant prophylaxis regimens reveals the lowest hanging fruit for preventing new infections – HIV-positive pregnant women who received no treatment before and after birth. Many factors can lead to this, and the consequences are dire with nearly one in five infants born under such circumstances testing HIV positive. Infants who themselves received no prophylactic treatment after birth were similarly exposed to increased risk of infection, with nearly 11 percent testing positive. Infections were far less likely under the recommended PMTCT and infant prophylaxis regimens shown in the table, as well as under several over treatment approaches disaggregated by NASCOP.

4. DISCUSSION

Effective EID programs are essential to ensuring that HIV-positive infants receive lifesaving care and that HIV-exposed infants do not later seroconvert. Building such programs is a complex undertaking, comprising challenges of logistics, human resources, human nature, intersections with other health sector programs, and, of course, limited resources. For these reasons, the authors emphasize that there are no one-size-fits-all solutions to establishing or strengthening EID programs that can solve all the challenges all systems face, plus the unique challenges or priorities that may exist in particular countries. The preceding reviews and the following discussion are intended only to offer perspective on a range of challenges faced and solutions deployed by EID programs and supporting partners across sub-Saharan Africa, for the consideration of those tasked with building better EID programs.

It bears repeating that EID testing is but one component in the universe of care and treatment for people living with HIV. Improving PMTCT measures including maternal HIV diagnosis and ART initiation during pregnancy, use of infant prophylaxes after birth, and educational counseling for caregivers are the best approaches for preventing vertical transmission. Based on our literature review and experiences in Kenya, there is substantial room for improving coverage of these approaches in much of sub-Saharan Africa. Vertical transmission will still occur even under optimal PMTCT practices and thus improved prevention cannot replace the need for EID testing, but addressing such low-hanging fruit as patients receiving no preventative care will go a long way towards reducing new cases, improving equity of care, and freeing up resources to improve EID testing and treatment initiation.

Our literature review identified loss to follow-up, delays in turnaround times, and low ART initiation rates as some of the main challenges EID programs face in sub-Saharan Africa. We explored a number of approaches countries have used to address these challenges and found varying degrees of success, across countries and challenges. It is clear from logic as well as the evidence that these challenges are interrelated and interventions targeted at one may well have spillover benefits for the others. Accordingly, program managers, policymakers, and others should take care to assess and prioritize the full range of challenges their systems face so that interventions with the most potential benefits can be deployed first. The consolidation of eight regional labs into one central lab in Uganda is a good example of one (large) intervention improving turnaround times, likelihood of result receipt and ART initiation, and feasibility of program monitoring and evaluation, while also reducing testing costs (Kiyaga et al. 2015).

All health programs face the challenge of loss to follow-up, but the stakes are particularly high for patients needing EID testing. Left untreated, mortality and morbidity rates for HIV-positive infants rise quickly in the first weeks and months of life, and remain high thereafter. Extensive research has been done on factors that keep mother-infant pairs in care or drive them from it, including costs, geography, sociocultural factors, stigma, information availability, provider behavior. Fortunately, simple and low-cost interventions appear effective for improving retention in care, such as enhanced EID referral in Mozambique (Ciampa et al. 2011), community-based outreach and testing in Nigeria (Pharr et al. 2016), and peer educators/expert patients in Uganda and Malawi (Namukwaya et al. 2015; Magongwa et al. 2018). Technology-based communication interventions also saw increased result receipt and long-term retention in care in Kenya (Finocchario-Kessler et al. 2015). As mobile phone networks reach even the remotest parts of Africa, m-health approaches have potential to dramatically decrease loss to follow-up for all types of patients, though privacy and equity issues will need to be carefully managed (Seidenberg

et al. 2012). By facilitating same-day testing, result delivery, and treatment initiation as early as the day of birth, POC testing could also virtually eliminate loss to follow-up before testing and result receipt.

The time-sensitive nature of EID testing lies at the core of the delayed turnaround time challenge. Thanks to PMTCT efforts, the majority of infants will (accurately) test HIV-negative and, apart from the not-insignificant burden of uncertainty, will not suffer adverse clinical effects whether they receive their EID results immediately or after a three-month delay. This is not to minimize the desirability and benefits of timely testing and receiving a negative diagnosis – easing of the aforementioned uncertainty burden, delivery of counseling on remaining HIV-negative, improved retention in care for routine reasons and follow-up testing – but the major benefits of quick turnaround times are for HIV-positive infants in need of ART initiation. Supporting the notion that turnaround time, loss to follow-up, and low ART initiation are closely linked, research from Mozambique found that turnaround times greater than 30 days from sample collection to result availability at the POC were significantly associated with reduced caregiver likelihood to ever return for results (Deo et al. 2015).

Like loss to follow-up, turnaround time delays can occur at various points in the EID testing cycle. Kenya, Malawi, and Uganda used motorbike couriers to reduce delays between sample collection and sample arrival at a lab for testing, and Uganda also consolidated its eight labs into one to reduce test processing delays (Finocchario-Kessler et al. 2015; Magongwa et al. 2018; Kiyaga et al. 2015). Dispatch of test results from labs back to health facilities was sped up in Kenya, Mozambique, Uganda, and Zambia through technologies including internet-connected printers, a web-based platform, and SMS messaging to trained facility staff (Deo et al. 2015; Seidenberg et al. 2015). Kenya and Zambia also used SMS to inform caregivers when they could (and urgently should, in the case of positive results) come to facilities for their results. More traditional communications approaches, delivered in-person by expert patients who traced mother-infant pairs after missed appointments, were part of a package of interventions that saw turnaround times decrease in Malawi. POC testing, under most envisioned deployment scenarios, should reduce turnaround times to the span of a single facility visit.

The purpose of EID testing is to facilitate action: continued preventive care for HIV-negative infants for as long as they remain exposed, and initiation of life-saving ART for HIV-positive infants. Failure to initiate ART for HIV-positive infants undermines EID programming and diminishes the value of testing patients and delivering timely results. Loss to follow-up is a major source of ART initiation failure, as patients who never know their status cannot possibly act on it, but there are other factors that can lead to initiation failure, hence why we identify it as a distinct challenge. Denial of test results or their importance, whether due to inadequate information, sociocultural reasons, or other factors is a caregiver-side challenge that can be addressed through counseling. Community groups, peer educators, expert patients, and health providers are all sources of counseling that have been used to promote initiation and retention in care for infants (Kim MH et al. 2012; Pharr et al. 2016; Magongwa et al. 2018; Namukwaya et al. 2015; Teasdale and Besser 2008) Facility-level conditions including provider behavior, disjointed treatment programs, and inadequate referral mechanisms can also contribute to diagnosis results not being acted on. Identification of an EID focal person at health facilities in Malawi helped emphasize the importance of EID activities for all staff and stressed accountability for improving outcomes (Magongwa et al. 2018). In the recent past, before Treat All and Option B+, even ART guidelines were among the barriers to treatment initiation, but today the guidance is as clear as possible: all people diagnosed with HIV should initiate ART as soon as possible.

By empowering health providers to test and treat infants within a single facility visit, POC platforms have the potential to solve many of EID's major challenges. Same-day results, rather than turnaround times of weeks and months, eliminates multiple opportunities for loss to follow-up, and promotes immediate initiation of ART (Magongwa et al. 2018; Jani et al. 2018). Highly accurate but easy-to-use assays reduce dependence on highly skilled lab personnel who may be in short supply. Bringing testing capabilities

closer to rural and other hard-to-reach populations, whether through permanent platform deployment in clinics and health posts or directly to communities on outreach days, can help solve last-mile challenges and other issues of equity in care. Yet, for all its promise, POC testing also has limitations that must be noted.

Although lab-based and POC tests answer the same fundamental question – is HIV present in a given sample – other differences between the two approaches are so great that they can hardly be considered to serve the same function. Whereas a POC platform in a clinic, rural or urban, can provide nearly instant EID testing for patients in its catchment area, a few lab-based platforms in Kampala can provide relatively timely EID testing for all of Uganda (with the help of other testing-network infrastructure and logistics). A day without a patient seeking an EID test is a day of lost platform value-per-test for the clinic, while the lab-based platforms in Kampala receive a daily stream of samples and always operate near maximum capacity. In short, POC testing, strategically deployed, can be a precise tool for addressing EID bottlenecks and challenges faced in a given facility or region, but cannot at current prices be a replacement for high-capacity lab-based testing networks, especially in settings with limited resources. Assays for POC platforms to perform other tests, like viral load monitoring or tuberculosis detection, may help decrease downtime and otherwise share platform costs across program budgets, but high equipment and reagent costs will likely keep POC testing more expensive than lab-based testing for the near future.

For both its opportunities and limitations, it is worth remembering that POC-based EID testing is still very new and likely to improve with time. Current deployments are typically for Ministry of Health pilot programs or are operated/supported by non-government organizations like UNICEF and the Elizabeth Glaser Pediatric AIDS Foundation and thus operating more in parallel to national EID programs than as parts of them. Fortunately, new guidelines produced by UNICEF and partners provide highly detailed recommendations for deploying POC testing specifically in the context of scaling up national health system capabilities and expanding access to EID (UNICEF 2018). The guidelines represent the new gold-standard on POC integration and are likely to improve as more evidence is generated.

Lessons from Kenya and final considerations

Kenya's approach to EID testing is not without its challenges but still represents an aspirational model for countries developing their own capacities. The network of regional labs provides over 100,000 initial and follow-up tests for infants across the country and has demonstrated year-on-year improvements in coverage and turnaround time. NASCOP's EID dashboard and the underlying database are powerful tools for program managers, researchers, and casual observers alike to explore EID outcomes at the national, county, and even subcounty levels. Our costing study found EID costs per test are lower than in past years and recent costs from other sub-Saharan African nations, and our examination of facility EID registers found generally good data quality. While the year-after-year presence of several thousand HIV-positive pregnant women receiving no ART and a few thousand HIV-exposed infants receiving no prophylaxis is troubling and appears to be resulting in a preventable excess of vertical transmission, inclusion of these indicators on the EID dashboard's front page suggests the problem not unknown, and solutions are hopefully in the works. In terms of POC testing, the presence of an Elizabeth Glaser Pediatric AIDS Foundation-supported pilot program in Homa Bay County should be an excellent source of knowledge in the years ahead on costs, effectiveness, and how best to use POC testing to complement a well-functioning lab-based network.

There are no easy answers for how best to solve the complex challenges inherent in providing EID tests for millions of HIV-exposed infants in the first weeks of life. Guidelines based on the best available global evidence are a useful starting point, but all countries face unique national and subnational issues that will require a locally adapted blend of approaches to solve. This document explored a range of approaches,

large and small, technological and interpersonal, long- and short-term, deployed across sub-Saharan Africa in the past decade to improve the coverage and quality of EID programs. Our findings demonstrate that the interconnected challenges of loss to follow-up, delayed result turnaround times, and initiation of ART for HIV-positive infants can be mitigated in wide variety of ways, and therefore countries should feel empowered to experiment with approaches best suited to their priorities and resources. Where lab-based networks are already well established, prioritizing adherence to testing and treatment guidelines for current patients while conducting outreach to draw in underserved populations likely makes more sense than deploying new technologies. Conversely, in countries without robust networks, or regions wholly disconnected from them, POC and near-POC technologies may be good short-term solutions while labs and their supporting infrastructure are developed. Whatever approaches countries choose, monitoring and evaluation components such as the data dashboards used in Kenya, Malawi, and elsewhere should be included to promote accountability, transparency, and the sharing of best practices between countries, development partners, and other organizations working toward the global goal of ending the AIDS epidemic by 2030.

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