Early infant diagnosis of HIV infection in low-income and middle-income countries: does one size fit all?

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Despite expansion of services for prevention of mother-to-child transmission of HIV (PMTCT), about 700 infants acquire HIV every day. Early initiation of antiretroviral therapy for HIV-infected infants reduces mortality but requires diagnosis by virological testing, which is complex, expensive, and inaccessible in many settings. Little cost-effectiveness evidence exists about different strategies to deliver early infant diagnosis services. Cost-effectiveness will vary depending on entry points for testing, underlying prevalences of HIV, PMTCT coverage, treatment availability, programme attrition, and other factors. Appropriate policy responses are therefore context-specific. In most cases, early infant diagnosis should be concentrated at entry points where underlying infant HIV prevalence is highest (eg, malnutrition wards). This strategy contrasts with the tendency at present to test mainly within PMTCT programmes. If testing is undertaken in PMTCT programmes with high coverage, addition of a virological test at birth might have advantages, including greater predictive value, earlier diagnosis, and better infant follow-up. National programme managers should recognise the opportunity costs of the limited resources available, acknowledge the changing scenario of PMTCT scale-up, use implementation of provider-initiated testing and counselling, and tailor early infant diagnosis programmes to maximise health gains for children.

Introduction

More than 200 000 infants acquired HIV infection worldwide in 2012. Most of these children live in sub-Saharan Africa, where—in the absence of diagnosis and early treatment—50% of HIV-infected children die by age 2 years. The South African CHER trial showed that mortality was reduced four-fold when antiretroviral therapy was started for asymptomatic babies with HIV aged younger than 12 weeks compared with waiting until immunological or clinical disease progression. As a result, WHO guidelines were revised in 2008 to recommend immediate initiation of antiretroviral therapy during infancy. This recommendation was subsequently extended to all children with HIV aged younger than 2 years and most recently to children younger than 5 years, with the goal of reducing barriers to treatment initiation for children with the highest risk of death. However, implementation of early treatment requires early infant diagnosis, which is complex, expensive, and inaccessible in many settings.

In adults and older children, HIV is diagnosed with inexpensive HIV antibody tests. However, in younger children, these tests are ineffective because of the presence of indistinguishable maternal anti-HIV antibodies, which usually persist 10–12 months after birth, but have been reported up to age 18 months or longer. Thus, virological assays—especially HIV nucleic acid amplification tests—are the gold standard for early diagnosis of infants because they detect viral nucleic acids. However, these assays use specialised equipment, need trained technicians, and are roughly ten-times more expensive than antibody tests. Furthermore, testing is only one step along a pathway (figure 1) that leads to treatment initiation and retention in care. Loss to follow-up can occur at any stage, from collection of initial results, to confirmatory testing and, importantly, referral for assessment, treatment initiation, and maintenance of treatment.

Of 22 priority countries included in the WHO/UNAIDS global plan, only South Africa, Swaziland, Namibia, and Zambia had more than 50% coverage for early infant diagnosis of HIV in 2012, while five countries (Angola, Chad, Democratic Republic of Congo, Malawi, and Nigeria) reported coverage below 6%. Despite expansion of early infant diagnosis, coverage in low-income and middle-income countries remains low and has primarily targeted infants in prevention of mother-to-child transmission of HIV (PMTCT) programmes, in which HIV-positive mothers are identified during pregnancy. Other approaches are needed to maximise the benefits of scale-up of early infant diagnosis within available budgets to reach infants born to both known and previously undiagnosed HIV-infected women. Cost-effectiveness analysis can inform how limited resources can best be used, including which subgroups to prioritise.

In this Personal View, we discuss issues that national policy makers in low-income and middle-income countries—particularly in sub-Saharan Africa—could consider when deciding how to implement early infant diagnosis in the specific contexts of their own health systems.

Challenges of rollout of early infant diagnosis

Reviews of national early infant diagnosis services have tried to identify bottlenecks and understand programme trends (panel). Across both high-prevalence and low-prevalence countries with rapidly expanding early infant diagnosis services, challenges include late testing and identification of HIV-exposed infants, lack of integration of early infant diagnosis within child health services, delayed return of results, loss to follow-up before receipt of results, and unavailable or delayed treatment for infected infants.

Programme attrition is a major challenge in many settings. Results of a study of 11 sites in Cameroon showed that only 32% of infants with a positive PCR result
Drugs were provided during pregnancy for the prevention of new HIV infections among children to 65% (57–70%) in north Africa (less than 20%). Of the 21 sub-Saharan African countries prioritised by the global plan, antiretroviral coverage is much lower in Asia and the Pacific and the Middle East and the Caribbean (more than 90%), whereas coverage is higher in eastern and central Europe and the Middle East and North Africa (less than 20%).

Figure 1: The early infant diagnosis pathway with potential barriers

Adapted from Prendergast and colleagues. PMTCT coverage is highest in eastern and central Europe and the Caribbean (more than 90%), whereas coverage is much lower in Asia and the Pacific and the Middle East and North Africa (less than 20%). Of the 21 sub-Saharan African countries prioritised by the global plan, antiretroviral drugs were provided during pregnancy for the prevention of new HIV infections among children to 65% (57–70%) of pregnant women with HIV. PMTCT—prevention of mother-to-child transmission of HIV.

More encouraging data have been reported from Botswana (where 81% of infants exposed to HIV completed the early infant diagnosis cascade) and from Cameroon (where 84% of infants exposed to HIV completed the cascade before age 7 months). However, these findings might not be generalisable to all settings because intensive tracking mechanisms were adopted to improve rates of return for test results, leading to high retention in the early infant diagnosis cascade. In this context, the ongoing shift towards recommending that all HIV-positive pregnant and breastfeeding women start antiretroviral therapy (so-called option B’), irrespective of their own health, including life-long treatment (option B+), and the accompanying decentralisation of antiretroviral treatment to make this possible, might be a new way to integrate early infant diagnosis within a family-centred care approach, in which infants would ideally receive treatment at the same clinics as their mothers.

Outside PMTCT settings, provider-initiated testing and counselling (PITC), including ascertainment of HIV exposure using HIV-antibody tests of the mother and baby followed by early infant diagnosis, will be a crucial means of identifying HIV-infected infants born to previously undiagnosed mothers. Results of a recent study in Malawi show that uptake of early infant diagnosis was higher in children presenting for routine vaccination at age 6 weeks than in older children attending clinics, but that prevalence of both HIV-exposure and HIV-infection was lower. PITC will probably become even more important as effective PMTCT is scaled up, thus reducing the proportion of HIV-infected infants identified through PMTCT. Notable entry points for PITC include facilities caring for sick children, particularly malnutrition units where HIV prevalence can be especially high, testing after diagnosis of family members, and testing at maternal and child health service points.

PITC outside PMTCT settings has several benefits. First, it can identify HIV-infected mothers not reached by PMTCT programmes who are in need of treatment for their own health. Second, HIV-exposed and uninfected children can benefit from PMTCT interventions during breastfeeding. Third, it provides definitive diagnosis of HIV infection for infants presenting with symptoms consistent with HIV and for asymptomatic children presenting for routine vaccination, thus enabling treatment to be started early. These alternative entry points are especially important to prioritise in countries with high HIV prevalence. In all settings, effective local referral for antiretroviral therapy is essential to ensure benefits from early infant diagnosis. PITC and early infant diagnosis should be integrated as part of efforts to decentralise paediatric treatment programmes, and to increase the number of children taking antiretroviral therapy, thereby reducing early mortality and improving retention in care.

Testing algorithms and entry paths

WHO 2010 guidance to improve uptake of early infant diagnosis in low-income and middle-income countries recommends that infants born to HIV-infected mothers have a virological test—a nucleic acid amplification test or p24 antigen test from a liquid or dried blood spot sample. Although the guidance emphasises the need to avoid unnecessary treatment of uninfected infants because of treatment costs and difficulties ascertaining HIV status later, when anti-HIV antibodies might wane after early antiretroviral therapy, the consequences of missing HIV infection are arguably more serious in view of the high early mortality of HIV-infected infants. PITC and early infant diagnosis should be integrated as part of efforts to decentralise paediatric treatment programmes, and to increase the number of children taking antiretroviral therapy, thereby reducing early mortality and improving retention in care.
Data from South Africa suggest that advantages might be gained at PMTCT sites by shifting the timing of virological testing from 4–6 weeks to birth. Most infants infected perinatally, despite PMTCT interventions, acquire infection in utero and, although early infant diagnosis might be less sensitive at birth compared with at 4–6 weeks, this approach might improve retention and enable treatment to be started before mortality peaks at around 3 months. However, numbers of infected infants are likely to be very small. An additional advantage of testing closer to birth is a potential reduction in the number of false-negative results for infants exposed to effective PMTCT regimens (eg, extended infant nevirapine or maternal antiretroviral therapy during breastfeeding). However, insufficient evidence exists to assess the real performance of early infant diagnosis alongside new PMTCT regimens; WHO is in the process of obtaining additional evidence to revise current recommendations and advise on optimum testing strategies and careful consideration should be given to this issue when trying to maximise timely diagnosis of HIV-infected infants. Lastly, there is increasing interest in initiating definitive treatment in infected newborn babies very soon after birth to avoid seeding of viral reservoirs. This factor is postulated to be the mechanism underlying the recent case of functional cure of an infant reservoir. This factor is postulated to be the mechanism underlying the recent case of functional cure of an infant reservoir. Thus, increasingly, in countries with high HIV prevalence, early infant diagnosis is an important consideration because of the wide variability in prevalence between settings. A well-functioning PMTCT programme with good uptake and provision of maternal treatment would be expected to result in an infant HIV prevalence of around 2–3%, particularly if the B+ strategy is successfully implemented. However, at this prevalence, unless PMTCT coverage is very high (>95%), most HIV-infected infants will be those identified outside of PMTCT services—born to mothers with unknown HIV infection and exposure status and probably presenting only when symptoms develop. Thus, increasingly, in countries with high HIV prevalence, early infant diagnosis testing would diagnose more HIV infections when implemented in health-care settings in which PITC is provided followed by early diagnosis of symptomatic infants, rather than if those early infant diagnosis tests were provided within effective PMTCT programmes (eg, figure 2).

Some investigators argue that early infant diagnosis should be provided as a priority in PMTCT programmes—despite low HIV prevalence among infants in regions with effective PMTCT services—to promote better continuum of care, to monitor the effectiveness of PMTCT interventions, and to help HIV-infected women to get information about early infant diagnosis. However, the question remains: will prioritising early infant diagnosis at PMTCT sites, with the current timing of testing, maximise health gains for children with HIV—especially if, in the event of shortages, it is done at the expense of early infant diagnosis being available at other entry points with higher HIV prevalence? Differences in the socioeconomic profiles between mothers receiving

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**Panel: Case studies of implementation of early infant diagnosis**

**Malawi**

Early infant diagnosis started in 2007 and national guidelines recommend ascertainment of HIV exposure status for any child younger than 2 years who visits a health facility. Antiretroviral therapy is started in infants younger than 12 months with positive DNA PCR (without any confirmatory virological testing), children aged 12–24 months with positive serology, and sick children younger than 12 months, in whom treatment is stopped only if DNA PCR at 24 months (or at the end of breastfeeding) is negative for HIV. In 2011, Malawi adopted prevention of mother-to-child transmission of HIV (PMTCT) option B+. In the first quarter of 2013, only 1792 (24%) of 7468 HIV-exposed infants aged younger than 2 months had received a DNA PCR result, with 55 (3%) confirmed as HIV-positive. Expenditure on effective PMTCT is believed to reap greater health gains from reduced HIV transmission than is expenditure on early infant diagnosis, which requires lifelong treatment of HIV-infected infants who have substantial morbidity and mortality if not diagnosed and started on treatment early.

**Uganda**

Uganda’s early infant diagnosis programme has been rapidly scaled-up since 2007 and entry points for early infant diagnosis have been established. Data from four facilities showed a 50% increase 5 months after implementation in the number of HIV-exposed infants tested each month, a 13% increase in the proportion receiving results, and younger age at infant diagnosis. Additionally, more children (up to 56% taking antiretroviral therapy in one paediatric treatment facility) were identified through entry points other than PMTCT and linkage to antiretroviral treatment for infected infants also increased. However, challenges include shortage of human resources in non-PMTCT settings, where health-care workers have to prioritise urgent interventions over HIV testing. Priority has been given to entry points with highest HIV prevalence, recognising that more HIV-infected infants can be identified there, although this approach has had to be balanced against greater health system constraints in non-PMTCT settings.

**Thailand**

Since 2007, early infant diagnosis has been provided to all infants born to HIV-infected mothers. At the 16 reference centres, median time from blood spot sample collection to receipt at the referral laboratory is 5 days, and results are reported back to the hospital within 14 days for 89% of samples. Testing is done at 2 months and confirmatory testing is requested as soon as possible after a positive first result and at 4 months if the first test is negative. The cost of early infant diagnosis is estimated at US$20 per test, including costs of infrastructure, human resources, reagents, dried blood spot, and quality assurance. In Thai mothers who do not breastfeed, this strategy combined with immediate antiretroviral treatment for HIV-infected infants is highly cost-effective (incremental cost-effectiveness ratio US$1646 per life-year gained), compared with serology or clinical diagnosis and delayed initiation of treatment based on clinical or immune criteria. Although early infant diagnosis within PMTCT programmes seems to be cost-effective in Thailand, this might not be the case in other health-care systems with greater resource constraints.
PMTCT=prevention of mother-to-child transmission of HIV. ART=antiretroviral therapy.

Figure 2: Results when early infant diagnosis is applied in settings with different HIV prevalences

<table>
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<th>2%</th>
<th>5%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>50%</th>
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<tbody>
<tr>
<td>Loss to follow-up</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
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<td>500</td>
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<td>50</td>
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<td>1667</td>
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Estimates of costs per HIV-infected child identified, according to paediatric HIV prevalence and loss to follow-up. Assumptions include: use of a single test, a cost per test of $25, and 100% sensitivity and specificity. Calculated by: test cost × (1 / [prevalence × (1–loss to follow-up)]). Values are illustrative, so should not be referred to for other purposes.

Table: Costs per case identified and accessing treatment (US$), by prevalence and loss to follow-up

and not receiving PMTCT might also justify concentration of early infant diagnosis at specific sites after PITC.46,47

Decentralisation of early infant diagnosis testing to primary health clinics and maternal and child health facilities might offer an effective, equitable, and feasible approach to expanding access to early infant diagnosis, particularly when integrated with infant immunisation services.26,48 This strategy has been made possible by the introduction of virological testing using dried blood spots, which not only simplifies collection, storage, and transportation but is also much cheaper than traditional testing.49 Point-of-care virological testing will probably further enable decentralisation and improve retention in care, maximising the proportion of infants who receive results and are promptly assessed for treatment.45 However, although several point-of-care tests are in development, none have been launched. Field testing is ongoing for nucleic acid amplification testing and one ultrasensitive antigen p24 assay (Alere Q, Liat Analyser, Samba EID, Lynx HIV p24 Antigen). Furthermore, this strategy will be effective only if treatment initiation can be synchronised with infant diagnostic testing and both occur at lower-level health centres, following task-shifting from higher-level facilities.46

Seeking value from early infant diagnosis: what now?

The CHER trial1 clearly showed the health benefits of early initiation of treatment for HIV-infected infants. An accompanying economic analysis reported that the costs of antiretroviral therapy associated with early (mean age 10 weeks) versus deferred (mean age 27 weeks) treatment initiation were more than offset by lower costs of inpatient episodes.6 However, these analyses did not evaluate costs and cost-effectiveness of screening strategies. Whether the results can be generalised to other low-income and middle-income settings, where costs and frequency of infant stays might be lower, is unclear.

A few studies have estimated per-patient costs for early infant diagnosis in sub-Saharan Africa.17 In addition to costs of test kits, other expenses include personnel, supplies, and equipment, resulting in estimated costs per test of around US$24 in Uganda48 and $20 in Botswana.21 Further costs, not included in these estimates, include transporting specimens and results, laboratory overheads, training requirements, quality control and assurance processes, and variation in healthcare delivery systems.17 To determine the overall cost-effectiveness of a particular early infant diagnosis approach, it is necessary to know the lifetime costs and health consequences associated with all testing outcomes.

A study in Thailand49 assessed the cost-effectiveness of early infant diagnosis with immediate antiretroviral therapy compared with serology or clinical diagnosis and initiation of treatment based on immune or clinical criteria. Early infant diagnosis and immediate treatment in children younger than 24 months was cost effective for Thailand, costing US$1646 per life-year saved. The study participants were non-breastfeeding women in a population with estimated PMTCT coverage of more than 90%, an overall mother-to-child transmission rate of 3–9%, and 68% coverage of early infant diagnosis.46

To date, no cost-effectiveness studies have compared outcomes after early infant diagnosis at different entry points. Without these data, it is at least partly informative to examine the costs of identifying true positives based on HIV prevalence and loss to follow-up. The costs per person of accessing early treatment can vary by prevalence and loss to follow-up (table). For instance, in a setting with loss to follow-up of 10% and HIV prevalence of 2% (as may be expected in a well-functioning PMTCT programme)5 identification of each positive case costs $1389, assuming that a single $25 test has 100% sensitivity and specificity. However, in a setting with loss to follow-up of 50% and HIV prevalence of 30% (as may be expected in some paediatric malnutrition units) identification only costs $167 per patient. All else being equal, the costs of identification are more likely driven by prevalence (which
is likely to be higher in inpatient wards or malnutrition units than by loss to follow-up (which might be lower in PMTCT programmes). However, because prevalence varies between settings, a global estimate of the cost-effectiveness of early infant diagnosis will probably have little relevance for decision making in individual countries.

The key task for national policy makers and international partners is to determine how best to use available resources for early infant diagnosis to generate the greatest health gain in their countries. Cost-effectiveness analyses should account for specific contexts and local constraints. Some countries might be able to undertake such analyses, recognising their constraints, but in other countries, with more limited capacity, a more basic and exploratory process of health technology assessment is probably more feasible. In such cases, decision makers should identify the main drivers of cost-effectiveness to determine the most appropriate use of resources in that setting.

Decision makers must consider several issues when deciding how best to invest in early infant diagnosis. To assess how different approaches to delivery of early infant diagnosis might lead to health gains for children requires knowledge of the health outcomes of true positive, false positive, true negative, and false negative diagnoses and for non-recipients of early infant diagnosis. Based on this knowledge, decision makers then need to decide which test to use, what ages and entry points to target, and which algorithms to adopt. The opportunity costs of committing resources to a particular early infant diagnosis approach—defined as the health gains that could be realised by using these resources in other ways—should be considered.

Policy makers can maximise paediatric health by ensuring that the health gains from their chosen means of delivery exceed the health gains of other possible alternatives (ie, exceed their opportunity costs). This strategy will probably involve prioritisation of early infant diagnosis for settings of highest HIV prevalence, such as paediatric wards and malnutrition units. Provision of early infant diagnosis in settings with low prevalence (eg, those with effective PMTCT programmes) risks diversion of resources from settings where more HIV-infected infants can be identified from a given number of tests. These decisions are very context-specific and therefore need to be made by relevant local and national authorities.

Conclusions

Expansion of access to early infant diagnosis is increasingly recognised as a key means to scale up HIV prevention, treatment, and care for infants and children. However, efforts to expand testing and treatment for all are increasingly being challenged by the financial reality of limited and stagnating budgets as global economic pressures continue. National policy makers adopting or adapting global recommendations should therefore consider at which entry points early infant diagnosis should be prioritised and which testing algorithms should be used. A central concern should be how to optimise the outcomes of infants over the long-term. Because of the variation between settings, generalised estimates of the cost-effectiveness of early infant diagnosis have little use. Some countries might be able to undertake robust analyses accounting for the budgetary and health system constraints that they face, or could be informed by analyses from other countries with similar circumstances. National policy makers should recognise the opportunity costs of the limited resources available, acknowledge the changing scenario of PMTCT scale-up, ensure increased implementation of PITC, address gaps in access to early infant diagnosis, and tailor infant diagnosis programmes to maximise health gains in children. Innovative and effective approaches to HIV testing in infants and children in low-income and middle-income countries are urgently needed and the upcoming revision of current WHO recommendations for infant testing will be crucial to provide guidance for national adaptation of the testing algorithm.

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