Clinical impact and cost-effectiveness of early infant HIV diagnosis in South Africa: Test timing and frequency

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ABSTRACT

Background: Early infant HIV diagnosis (EID) and antiretroviral therapy dramatically reduce mortality. EID is recommended at six weeks of age, but many infant infections are missed.

Design/Methods: We simulated four EID strategies for HIV-exposed infants in South Africa: no EID (diagnosis only after illness), testing once (birth alone; 6 weeks alone) and twice (birth and 6 weeks). We calculated incremental cost-effectiveness ratios (ICERs) using discounted costs and life expectancies for all HIV-exposed (infected and uninfected) infants.

Results: In the base case (guideline-concordant care), no EID produced a life expectancy of 21.1y (HIV-infected) and 61.1y (HIV-exposed); lifetime cost averaged $1,430/HIV-exposed infant. The birth and 6 weeks strategy maximized life expectancy (HIV-infected: 26.5y; HIV-exposed: 61.4y), costing $1,840/infant tested. The ICER of 6 weeks alone vs. no EID was $1,250/year of life saved (YLS, 19% of South Africa’s per-capita GDP); birth and 6 weeks vs. 6 weeks alone was $2,900/YLS (45% of GDP). Increasing result-return and linkage to ART with 6 weeks alone improved survival more than adding a second test.

Conclusions: EID at birth and 6 weeks improves outcomes and is cost-effective, compared to 6 weeks alone. If scale-up costs are comparable, programs should add birth testing after strengthening 6-week testing programs.
INTRODUCTION

More than 1.5 million HIV-infected women become pregnant worldwide each year, resulting in over 150,000 infant HIV infections (1). Without antiretroviral therapy (ART), mortality among HIV-infected children reaches 50-65% by age 2 years, peaking in the first 2-3 months of life (2, 3). While 76% of these deaths can be averted by prompt ART initiation, this requires accurate early infant HIV diagnosis (EID) (4). The World Health Organization (WHO) recommends EID testing at 6 weeks of age for all HIV-exposed infants; however, only 50% were tested in 2014 (5-7). Because maternal anti-HIV antibodies are detectable in HIV-exposed infants’ sera, EID requires a costlier nucleic acid amplification test (NAT) (5, 8). In addition, many infants are lost at each step of the EID testing-to-treatment cascade: presentation to healthcare facilities for EID, offer and acceptance of testing, specimen transport and laboratory processing, result-return to caregivers, linkage to HIV care, and ART initiation (5, 8-11). Even in well-functioning EID programs, late diagnosis causes infants to delay ART initiation until well after the peak of HIV-related mortality (3).

Changes to current 6-week EID testing have been proposed, based on the fact that infants who are infected in utero have detectable virus at birth, but infants infected during delivery (intrapartum) or through breastfeeding (postpartum) have detectable virus only several weeks post-infection (8, 9, 12, 13). Infant antiretroviral prophylaxis - usually offered for 6 weeks after birth - could plausibly reduce NAT sensitivity at 6 weeks, although data remain equivocal (9, 14). Lilian and colleagues suggest that testing at birth, when most infants are in healthcare facilities, or 10 weeks, after infant prophylaxis has ended, may identify more HIV-infected children than testing once at 6 weeks (9, 15). Testing twice, at birth and at 6 or 10 weeks, could detect and treat intrauterine infections promptly at birth and intrapartum/early postpartum infections occurring before the second test. Optimal timing of EID depends primarily on three factors: the number of children who have become infected and have assay-detectable virus at each time.
point, the number presenting to care at each time point, and the number who will experience mortality before testing occurs. These factors are difficult to study in clinical trials, because substantial unobserved morbidity and mortality occur among children not in care. We used a model of infant HIV disease to examine the clinical benefits and cost-effectiveness of current and proposed EID strategies in South Africa, the country with the highest burden of HIV disease in the world, to inform EID recommendations in the 2015 WHO Consolidated HIV Testing Guidelines.

METHODS

Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-Pediatric model to evaluate four EID strategies for South African infants born to HIV-infected mothers: no EID (comparator); testing once at birth alone or 6 weeks alone; and testing twice at birth and 6 weeks. Model outcomes included short- and long-term survival, HIV-related healthcare costs, and life expectancy. To reflect outcomes and resource requirements for an entire HIV program, we projected results separately for HIV-infected infants and for a “birth cohort” of HIV-exposed infants (including both HIV-infected and HIV-uninfected children). Using birth cohort outcomes, discounted at 3%/year, we calculated an incremental cost-effectiveness ratio (ICER) for each strategy compared to the next less expensive alternative: difference in lifetime costs divided by difference in years of life saved (YLS). We considered interventions with ICERs <50% of South Africa’s per-capita gross domestic product (GDP; 0.5x $6,500 = $3,250) to be “cost-effective,” based on emerging literature; we also examined thresholds of 100% and 300% of GDP (16-19). A strategy with higher lifetime costs and lower life expectancy than a competing strategy is considered “strongly dominated;” when comparing ≥3 strategies, if a strategy has a higher ICER than another strategy with a higher cost, the first strategy is “weakly dominated” (Table 2, footnote). To understand the possible outcomes if guidelines were fully implemented in clinical practice, the base case simulated guideline-concordant care: 100% presentation for EID, result-return (proportion receiving result), linkage to care, and ART for surviving HIV-infected infants. In sensitivity analyses, we varied
uptake at each step in this cascade (0-100%), 10-week testing in place of 6-week testing, and other key model input data and assumptions. In scenario analyses, we examined selected clinical impacts of implementing *birth and 6 weeks* testing.

**CEPAC-Pediatric model**

The CEPAC-Pediatric model is a microsimulation model of pediatric HIV disease (Supplemental Information; http://www.massgeneral.org/mpec), expanded to incorporate infant HIV transmission and EID testing. Validation and calibration of model-projected OIs and survival for treated and untreated infants have been previously described (20, 21). Infants enter the model at birth, and are simulated until death. Maternal CD4 count and availability of medications for prevention of mother-to-child HIV transmission (PMTCT) determine the transmission risk during three time periods: intrauterine (one-time risk), intrapartum (one-time risk), and postpartum (monthly risk until breastfeeding cessation; we exclude non-perinatal HIV acquisition). All patients face age-stratified monthly risks of non-HIV-related mortality; after HIV infection, patients face additional age- and CD4-stratified risks of opportunistic infections (OI), OI-related mortality, and non-OI-related mortality.

Planned EID testing can occur at any age from 0-24 months. NAT sensitivity varies by type of infection (intrauterine, intrapartum, postpartum) and time since infection, to reflect the viremia necessary to be detectable. Undiagnosed HIV-infected children who develop an OI at any age also present to care and receive HIV testing. We simulated two available lifetime ART regimens with associated probabilities of HIV viral suppression and increases in CD4% (before age 5) or absolute CD4 (after age 5); the Supplemental Information describes ART failure and switching. Children engaged in care may also become lost to follow-up.
Modeled population

EID is currently recommended for infants known to be HIV-exposed (22); we therefore simulated infants born to women who were identified as HIV-infected during antenatal care. Based on current WHO and South African guidelines and data, we assumed that 90% of women received ART during pregnancy and breastfeeding (WHO "Option B/B+”), with a mean breastfeeding duration of 12 months (Table 1) (1, 23).

Modeled EID strategies

In the no EID strategy, an infant HIV infection was diagnosed upon presenting to care with a WHO 3/4 OI (Supplemental Figure A). In the EID strategies (birth alone, 6 weeks alone, birth and 6 weeks), we simulated a scheduled EID test at the specified age. In the base case, any positive NAT was followed by linkage to HIV care and a second, confirmatory NAT. We assumed ART was initiated for all children in HIV care, per WHO guidelines, with ART discontinuation if the confirmatory NAT was negative (the Supplemental Information describes care after false-positive results) (5). For infants who missed a scheduled test (e.g., sensitivity analyses with testing rates <100%), and for infants infected after 6 or 10 weeks of age, HIV was diagnosed only after an OI. We also examined 10-week testing and use of post-weaning "final status" tests, which are currently recommended but rarely completed (Supplemental Information) (22, 24).

Input data

Cohort characteristics, MTCT risks, disease progression, and ART outcomes were from African trials and cohort studies (Table 1; Supplemental Table A) (25-29). NAT sensitivity (base case: 100% >1 month after infection), specificity (98.8%), and costs ($25) were from WHO systematic reviews, published data, and expert opinion, and were varied widely in sensitivity analyses (9, 30). The model incorporates reduced mortality and OI risks for patients on ART, independent of CD4 and viral suppression (28). In the base case, we used values for these "ART-associated CD4-independent risk reductions" from our
previously published calibration analyses (21); we varied these widely in sensitivity analyses (Supplemental Information).

To examine the resources required for an HIV program, we included costs related to EID (all infants) and HIV care (HIV-infected infants). We used South African data on OI care costs for children aged <5 years (31). For OI care among older children and routine care at all ages, we multiplied South African adult resource utilization (outpatient visits, inpatient days, and laboratory testing) by South African unit costs (32-34). ART costs were from published price lists, with WHO weight-based dosing (35, 36). Our modeled NAT costs included assays, reagents, and staff time for specimen processing and result-return; we assumed healthcare infrastructure existed to provide birth testing (e.g., in labor and delivery wards or Bacillus Calmette-Guérin (BCG) vaccination clinics) and 6-week testing (e.g. vaccination or PMTCT clinics).

**Sensitivity analyses**

In the base case, we simulated guideline-concordant care: 100% probabilities of presentation for EID testing, result-return, and linkage to care and ART after diagnosis, with result-return (turnaround) time of 1 month (first EID test (37)). In univariate sensitivity analyses, we varied each of these probabilities and times, reflecting patient/caregiver-level behavior and setting-specific availability of ART and HIV care (ranges in Table 1). We also varied PMTCT availability in pregnancy and breastfeeding (with consequent reductions in MTCT risk); breastfeeding prevalence and duration; NAT specificity; NAT sensitivity (overall and as a function of age and PMTCT exposure); OI and mortality risks; ART-associated CD4-independent reductions in OI and mortality risk; loss to follow-up and virologic failure rates after ART initiation (applied lifelong); and costs of NATs, HIV care, and ART. In multivariate sensitivity analyses, we varied the most influential of these parameters simultaneously.
We also simulated strategies of EID testing at 10 weeks alone and birth and 10 weeks. These analyses quantified the additional early postpartum infections identified with 10-week versus 6-week testing, balancing this benefit against the risk that intrauterine-infected or intrapartum-infected infants would die before 10-week testing and subsequent ART initiation. Because of concern that NATs may have lower sensitivity during or immediately after infant antiretroviral prophylaxis, we also compared 10-week strategies to 6-week strategies with reductions in NAT sensitivity when used at 6 weeks of age (9, 38).

**Clinical scenario analyses**

We examined two scenarios to estimate the clinical impact of adding birth testing to existing 6-week programs, based on UNAIDS data (1). In Scenario A, given a partially-implemented 6 weeks alone program with 50% presentation for testing and 50% result-return, we compared: 1) adding a birth testing program (birth and 6 weeks with 50% testing and 50% result-return at both ages) to 2) improving testing and result-return within the existing 6 weeks alone program. In Scenario B, we addressed concerns that negative EID results at birth (excluding only intrauterine infection) may lead caregivers to forgo 6-week testing needed to identify intrapartum and early postpartum infection (39). We examined birth and 6 weeks with reduced testing in the 6-week component and identified the degree of attrition between birth and 6 weeks that would offset the benefits of adding birth testing to existing 6-week programs. Because neither the relative nor absolute costs of scaling-up birth and 6-week programs have been reported, we excluded costs from Scenarios A and B.

**RESULTS**

*Base case results: clinical outcomes*

Among the birth cohort, we projected a total MTCT risk of 4.9%: 1.8% intrauterine HIV infection, 1.2% intrapartum infection, 1.9% postpartum infection, and 95.1% HIV-exposed/uninfected, similar to South
African national estimates (40), Table 2). The no EID strategy (ART only for those surviving and presenting with an OI) led to the lowest projected survival for HIV-infected infants: 1-year survival 64.6%; life expectancy 21.1 years. In the base case (100% testing, result-return, and linkage), survival substantially increased with any EID program. Of the testing-once strategies, survival for HIV-infected infants was lower with birth alone (1-year survival 72.0%, life expectancy 24.4 years) than with 6 weeks alone (1-year survival 74.9%, life expectancy 25.9 years), due to the proportion of infants surviving with detectable virus at each age (Supplemental Figure B). Testing twice further increased survival: birth and 6 weeks led to 1-year survival of 76.6% and life expectancy of 26.5 years. The impact of any EID strategy for the entire birth cohort (HIV-exposed/uninfected and HIV-infected infants) was modest: 1-year survival ranged from 92.7-93.3% and life expectancy from 61.1-61.4 years (Table 2).

Base case results: costs and cost-effectiveness

No EID yielded the lowest projected HIV-related healthcare costs for the birth cohort; 1-year costs were $50/HIV-exposed infant, and lifetime undiscounted costs were $1,430/HIV-exposed infant (Figure 1, Table 2). With both testing-once strategies, 1-year birth cohort costs were similar ($70/infant), although lifetime costs varied more widely (birth alone: $1,670/infant; 6 weeks alone: $1,770/infant). With birth and 6 weeks, 1-year cost was $100/infant and lifetime cost was $1,840/infant. EID program costs ranged from $30 (testing once) to $55 (testing twice), representing 43-55% of 1-year costs and 2-3% of lifetime costs (Figure 1). In cost-effectiveness analyses, birth alone was weakly dominated (Table 2). The ICER of 6 weeks alone compared to no EID was $1,250/YLS (19% of South Africa's per-capita GDP), and the ICER of birth and 6 weeks vs. 6 weeks alone was $2,900/YLS (45% of GDP).

Sensitivity analyses: testing once

Among testing-once strategies, birth alone remained dominated and the ICER of 6 weeks alone vs. no EID remained <50% of GDP through wide variations in most parameters, if varied equally in all
strategies. There were two exceptions: if result-return rates were <10% or linkage to HIV care and ART was <10%, the ICER of 6 weeks alone vs. no EID exceeded 50% of GDP.

Sensitivity analyses: testing twice

The ICER of birth and 6 weeks compared to 6 weeks alone remained <50% of GDP despite wide variations in presentation for EID testing, use of confirmatory NATs, PMTCT coverage, and post-weaning testing. The ICER of birth and 6 weeks compared to 6 weeks exceeded 50% of GDP, and therefore 6 weeks alone would be preferred by this economic criterion, if the ART-associated CD4-independent reductions in mortality and OI risk were <78%, NAT specificity was <98% or sensitivity was <30%, linkage to ART was <15%, result-return was <16%, PMTCT coverage was ≥97%, the cost of adding a birth testing program to an existing 6-week testing program was >$6/infant, NAT costs exceeded $31, mean result-return time exceeded 3 months, probability of late virologic failure was >4.6%/month, OI risks were reduced by 20%, or clinical care costs were >1.3x base case values (Figure 2). In multivariate sensitivity analyses, birth and 6 weeks was more expensive but less effective than 6 weeks alone if the benefit of ART was further reduced (OI risks doubled, combined with ART-associated CD4-independent reductions in OI and mortality risk <10%), or if linkage to ART and retention in care were both extremely low (linkage <10%, combined with loss to follow-up >2.0%/month).

Sensitivity analyses: 10-week testing strategies

Among HIV-infected infants, clinical outcomes were modestly worse if testing-once occurred at 10 weeks alone rather than at 6 weeks alone (1-year survival 72.9 vs. 74.9%, life expectancy 25.3 vs. 25.9 years) but similar if testing-twice occurred at birth and 10 weeks or birth and 6 weeks (1-year survival 75.9 vs. 76.6%, life expectancy 26.3 vs. 26.5 years; Table 2, Supplemental Table C). Mortality among intrauterine-infected and intrapartum-infected infants before 10-week EID and ART initiation outweighed the survival benefit for the small additional number of postpartum-infected infants identified between 6
and 10 weeks of age (Supplemental Figure B). However, if NAT sensitivity was <60% at 6 weeks of age and unaffected at 10 weeks of age, 10 weeks alone was clinically superior to 6 weeks alone. Similarly, if NAT sensitivity was <80% at 6 weeks and unaffected at 10 weeks, birth and 10 weeks was clinically superior to birth and 6 weeks. Economically, 10 weeks alone was dominated (Supplemental Table C); differences between the two testing-twice strategies were small.

**Clinical scenario analyses**

In Scenario A, clinical outcomes improved more by scaling up partially implemented 6 weeks alone programs than by adding birth testing at current uptake levels (Figure 3). Given a 6 weeks alone program with 50% testing/50% result-return (Figure 3: bar I, 1-year survival 63.4%), adding birth testing with 50% testing/50% result-return improved survival minimally (bar II, 64.4%). In contrast, improving 6 weeks alone testing and result-return to 75% (bar III, 68.1%) or 100% (bar V, 74.9%) led to greater survival gains. In Scenario B, attrition between the two scheduled testing times markedly reduced the effectiveness of the birth and 6 weeks program. One-year survival among HIV-infected infants was worse with birth and 6 weeks than 6 weeks alone when >37% of patients receiving a negative birth test result failed to present for scheduled 6-week testing.

**DISCUSSION**

We simulated early infant HIV diagnosis (EID) strategies for HIV-exposed infants in South Africa, with three primary findings. First, testing once in the first months of life, regardless of age at testing, markedly improves survival among HIV-infected infants compared to no EID. Among the testing-once strategies, 6 weeks alone is clinically and economically superior to birth alone. Six-week EID programs have been reported as cost-effective among formula-fed infants in Thailand; our study confirms the cost-effectiveness of current EID recommendations for breastfeeding infants in South Africa (41, 42). Although low rates of result-return and linkage to HIV care attenuate the cost-effectiveness of EID
programs, 6-week testing remains cost-effective unless attrition rates are extremely high (≤10% of HIV-infected infants linking to care and ART).

Second, a guideline-concordant program offering EID twice at birth and 6 weeks will further improve survival and be cost-effective in South Africa, compared to a 6 weeks alone program, under most scenarios (Figure 2). The cost-effectiveness of testing twice depends on MTCT risk and on the degree to which ART initiation in the first months of life reduces HIV-related mortality (Figure 2); few data are available about the latter (3, 4). To ensure the clinical benefits of adding birth testing to 6-week programs, avoiding attrition between the birth and 6-week encounters is critical. Care providers must also emphasize that negative birth results indicate only that infants were not infected in utero; testing at later ages is needed to identify intrapartum and postpartum infections. If >37% of infants receiving a negative birth-test result fail to present for 6-week tests, as seen in Cape Town (39), the survival benefits of adding birth testing to a fully-implemented 6-week program are lost. Additionally, for existing 6-week programs, clinical outcomes are improved to a much greater degree by maximizing 6-week uptake than by adding birth testing at low uptake levels (Figure 3).

Third, the benefit of testing twice remains substantial regardless of whether the second test is offered at 6 or 10 weeks. Although 10 weeks alone is inferior to 6 weeks alone, the decision between birth and 6 weeks and birth and 10 weeks can be made based on programmatic and feasibility considerations, including current immunization and PMTCT follow-up visits, which usually occur at 6 weeks (5, 9, 11). However, birth and 10 weeks becomes superior to birth and 6 weeks if antiretrovirals for PMTCT reduce NAT sensitivity at 6 weeks of age to <80%. The few available reports have estimated 6-week sensitivities of 75-100% with antiretroviral exposure (9, 14). Further investigation of the impact of antiretrovirals on assay sensitivity will be critical.
There are several limitations in our model-based analysis. Important developments in medication availability, clinical care, and healthcare costs will undoubtedly occur over infants’ lifetimes, and long-term model-based projections for children are uncertain. We addressed this uncertainty by calibrating the model to ensure that results matched current survival, MTCT risk, and OI data (20, 21, 40), and then varying factors likely to change over time, such as OI outcomes, ART availability, and costs. Except where noted, these sensitivity analyses did not change our policy conclusions; they also suggest that while economic results are specific to South Africa, clinical results may be generalizable to many settings. Next, we were not able to fully assess economic trade-offs of scaling up an existing 6-week program compared to adding birth testing. We find that if adding birth testing to 6-week testing costs ≥$6/infant tested, *birth and 6 weeks* will no longer be cost-effective compared to *6 weeks alone* at the 50% GDP threshold. Little is known about the resources required to implement or expand EID programs. A South African pilot birth testing program was costly (six full-time staff identified and tested HIV-exposed infants, returned results, and initiated ART; Karl Technau, personal communication). It is plausible that scale-up of 6-week programs might be costlier (e.g., developing systems to trace HIV-exposed infants not presenting for care), but there are no data on these costs. In the absence of available scale-up costs, we focused our scenario analyses on clinical outcomes. Finally, this work addresses infants known to be HIV-exposed. In many settings, maternal HIV status may not be known or adequately documented on infant health cards, or maternal infection may occur after antenatal HIV testing (1). Strategies to detect HIV exposure are likely to improve infant health in high-HIV prevalence settings (43).

In summary, we find that current EID recommendations to test once at *6 weeks alone* markedly improve infant outcomes and are of good value in South Africa compared to *no EID*. Testing twice, at *birth and 6 weeks*, will further improve outcomes and be cost-effective when uptake is high. If scale-up costs are comparable, policymakers should add birth testing after optimizing 6-week EID programs, alongside careful attention to retaining infants with negative birth test results in care.
DISCLOSURES

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the World Health Organization.

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FIGURE LEGENDS

Figure 1. One-year and lifetime per-patient healthcare costs: EID strategies for HIV-exposed infants in South Africa

Panel A. One-year costs. One-year total HIV care costs per HIV-exposed infant tested range from $50 for no EID to $100 for birth and 6 weeks testing. Costs of the EID program itself, including costs of assays, personnel, specimen handling, and result-return, are shown in black, and range from $30 (testing once) to $55 (testing twice). These costs exclude "implementation costs" associated with adding a new program if none existed previously.

Panel B. Total and component lifetime costs. Panel B shows the components of lifetime total costs per HIV-exposed infant tested. Routine HIV care, CD4 and HIV viral load monitoring, OIs, and end-of-life care, and ART comprise the majority of lifetime costs. EID program costs are shown in black and comprise 2-3% of lifetime costs.

EID: early infant diagnosis; USD: US dollar; wk: week; ART: antiretroviral therapy; OI: opportunistic infection

Figure 2. Tornado diagram: key parameters that change the cost-effectiveness of EID at birth and 6 weeks compared to 6 weeks alone.

Key parameters varied in model sensitivity analyses are shown on the left. Values in parentheses indicate the range examined (from the value leading to the lowest ICER to the value leading to the highest ICER), with base-case values after the semicolon. ICERs for the comparison of birth and 6 weeks vs. birth alone are shown on the horizontal axis, in 2013 USD/YLS. The range of ICER for each varied parameter is indicated by the blue horizontal bars. Longer bars indicate parameters to which the model results were more sensitive. The solid, red vertical line indicates the ICER for birth and 6 weeks vs. birth alone using all base-case parameters: $2,900/YLS. The dotted black vertical line indicates 50% of South Africa's per-capita GDP (0.5x $6,500 = $3,250), the dashed black vertical line indicates 100% of GDP ($6,500), and
the solid black vertical line indicates 300% of GDP ($19,500). The value for each parameter at which the ICER crosses the 50% GDP threshold is listed within each horizontal bar. This figure provides a framework for when decisions are made on cost-effectiveness grounds – the value within the horizontal bar indicates when one would favor 6 weeks alone over birth and 6 weeks by this criterion. Bars extending to the far-right axis indicate scenarios in which birth and 6 weeks results in an ICER of >$20,000/YLS in comparison to 6 weeks alone, or becomes strongly dominated by 6 weeks alone (more expensive and less effective).

ART: antiretroviral therapy; GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; USD: United States dollar; YLS: year of life saved; NAT: total nucleic acid; OI: opportunistic infection; mth: month

Figure 3. Scaling up 6-week EID programs or adding birth testing: Scenario A

We projected the impact of scaling up existing 6 weeks alone EID programs and of adding birth testing to existing 6 weeks alone programs. For a 6 weeks alone program with 50% testing and 50% result-return, one-year survival among HIV-infected infants is projected at 63.4% (bar I). Adding birth testing to this program, also with 50% testing and 50% result-return, would improve outcomes minimally (to 64.4%, bar II). In contrast, scaling up the 6 weeks alone program with 75% testing and 75% result-return (bar III, one-year survival 68.1%) or closer to 100% testing and 100% result-return (bar V, one-year survival 74.9%) would improve outcomes to a much larger degree. Five-year and lifetime outcomes followed similar trends.
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### Table 1. Selected data parameters for CEPAC-Pediatric model analysis of early infant HIV diagnosis (EID) testing in South Africa

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<th>Cohort characteristics</th>
<th>Value (range for sensitivity analyses)</th>
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<td>Age, months (SD)</td>
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<td>Percent male infants</td>
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<td>Mothers with CD4 ≤350 cells/µL before ART</td>
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<td>Breastfeeding (proportion of all infants)(^a)</td>
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<td><em>Intrauterine (IU)/intrapartum (IP)—one-time risk</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On ART (60% IU transmission; 40% IP transmission)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Not on ART (38% IU transmission; 62% IP transmission)</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postpartum (PP)—monthly risks during breastfeeding</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>On ART</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Not on ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Mixed or complementary feeding</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>Probability maternal status known in pregnancy</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Probability mother on ART in pregnancy and breastfeeding</td>
<td>90 (40-100)</td>
<td>(3)</td>
</tr>
<tr>
<td>Monthly maternal mortality risk</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EID cascade parameters</th>
<th>Guideline-concordant</th>
<th>Range examined</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of presenting to a testing visit (%)</td>
<td>100</td>
<td>0-100</td>
<td></td>
</tr>
<tr>
<td>Probability of being offered and accepting test (%)</td>
<td>100</td>
<td>0-100</td>
<td></td>
</tr>
<tr>
<td>Probability of receiving test results (%)</td>
<td>100</td>
<td>0-100</td>
<td></td>
</tr>
<tr>
<td>Delay between primary test and result receipt (SD)</td>
<td>1 month (0 months)</td>
<td>0-5 months</td>
<td>Scenario-specific assumptions</td>
</tr>
<tr>
<td>Delay between confirmatory test and result receipt (SD)</td>
<td>0 months (1 month)</td>
<td>0-3 months</td>
<td></td>
</tr>
<tr>
<td>Probability of linking to care/ART after diagnosis (%)</td>
<td>100</td>
<td>0-100</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nucleic Acid Test (NAT) assay characteristics</th>
<th>Base case value (%)</th>
<th>Range examined (%)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity for IU infection (by age)</td>
<td>100 (all ages)</td>
<td>0-100 (all ages)</td>
<td>(4)</td>
</tr>
<tr>
<td>Sensitivity for IP infection (by age)</td>
<td>Month 1: 0</td>
<td>Month 1: 0</td>
<td>(4)</td>
</tr>
<tr>
<td>Sensitivity for PP infection (by time since infection)</td>
<td>Later months: 100</td>
<td>Later months: 90-100</td>
<td>(4)</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.8 (all ages)</td>
<td>85-100 (all ages)</td>
<td>(4)</td>
</tr>
</tbody>
</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>ART outcomes</th>
<th>Value (%)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r/ABC/3TC (1st-line ART)</td>
<td>[91]</td>
<td>(5, 6)</td>
</tr>
<tr>
<td>(EFV or NVP)/AZT/3TC (2nd-line ART)</td>
<td>[75]</td>
<td></td>
</tr>
<tr>
<td>ART efficacy: HIV RNA &lt;400c/mL at 24 weeks on ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ages 0-59 months</td>
<td>[91]</td>
<td>(5, 6)</td>
</tr>
<tr>
<td>Ages 60+ months</td>
<td>[75]</td>
<td></td>
</tr>
<tr>
<td>ART-associated CD4-independent risk reductions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk reduction in opportunistic infection (age 0-13)</td>
<td>[85]</td>
<td>(8)</td>
</tr>
<tr>
<td>Risk reduction in opportunistic infection (age 13+)</td>
<td>[32]</td>
<td>(9)</td>
</tr>
<tr>
<td>Risk reduction in mortality (age 0-13)</td>
<td>[90]</td>
<td>(8)</td>
</tr>
<tr>
<td>Risk reduction in mortality (age 13+, range by CD4)</td>
<td>[55-96]</td>
<td>(9)</td>
</tr>
</tbody>
</table>

Costs

<table>
<thead>
<tr>
<th>Costs</th>
<th>Value (USD)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic infection care (per event, range by age, CD4%/CD4, type of event)</td>
<td>[260-2,175]</td>
<td>(10-14)</td>
</tr>
<tr>
<td>ART (per month, range by regimen, dose/age)</td>
<td>[7-40]</td>
<td>(12, 13)</td>
</tr>
<tr>
<td>NAT assay&lt;sup&gt;d&lt;/sup&gt;</td>
<td>25 (sensitivity analysis: 5-75)</td>
<td>Assumption</td>
</tr>
<tr>
<td>NAT result-return for negative tests + indicated counselling</td>
<td>1.83</td>
<td>Assumption (nurse time x salary) (15)</td>
</tr>
<tr>
<td>NAT result-return for positive tests + indicated counselling</td>
<td>3.05</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SD: standard deviation; IU: intrauterine; IP: intrapartum; PP: postpartum; WHO: World Health Organization; TB: tuberculosis; OI: opportunistic infection; MTCT: mother-to-child transmission; ART: antiretroviral therapy; EID: early infant diagnosis; NAT: nucleic acid test; USD: United States dollar

<sup>a</sup> Exclusive breastfeeding (first 6 months of life) in 55%; mixed breastfeeding (first 6 months of life) in 25%; replacement feeding from birth in 20%. After 6 months of age, all infants still breastfeeding are assumed to receive complementary feeding (breast milk and other liquids/solids).

<sup>b</sup> PMTCT coverage was based on UNAIDS reports: >95% HIV testing in antenatal care; >95% ART use after positive HIV test (0.95*0.95=0.90). PMTCT coverage scenarios of 100% lead to projected intrauterine/intrapartum MTCT risks of 1.0%, reflecting, for example, a population of women who are on ART throughout most of pregnancy with excellent medication adherence.

<sup>c</sup> Costs were in 2013 USD, from the healthcare system perspective.

<sup>d</sup> NAT costs include assays, reagents, and personnel time for counseling, blood draws, specimen transport and processing, and quality control.
REFERENCES

Table 2. Base-case model results: Early infant HIV diagnosis (EID) testing in South Africa

## I. Clinical and economic projections

### MTCT outcomes

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected infants</th>
<th>Birth cohort</th>
<th>Lifetime costs (2013 USD, per person)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9% of entire birth cohort:</td>
<td>4.9% HIV-infected; 1.8% IU, 1.2% IP, 1.9% PP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Economic and clinical outcomes

<table>
<thead>
<tr>
<th>EID strategy</th>
<th>One-year survival (%)</th>
<th>Life expectancy (years, undiscounted)</th>
<th>One-year survival (%)</th>
<th>Life expectancy (years, undiscounted)</th>
<th>Birth cohort (undiscounted)</th>
<th>HIV-infected infants (undiscounted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No EID</td>
<td>64.6</td>
<td>21.1</td>
<td>92.7</td>
<td>61.1</td>
<td>$1,430</td>
<td>$29,100</td>
</tr>
<tr>
<td>Birth alone</td>
<td>72.0</td>
<td>24.4</td>
<td>93.1</td>
<td>61.3</td>
<td>$1,670</td>
<td>$33,520</td>
</tr>
<tr>
<td>6 weeks alone</td>
<td>74.9</td>
<td>25.9</td>
<td>93.2</td>
<td>61.4</td>
<td>$1,770</td>
<td>$35,470</td>
</tr>
<tr>
<td>Birth and 6 weeks</td>
<td>76.6</td>
<td>26.5</td>
<td>93.3</td>
<td>61.4</td>
<td>$1,840</td>
<td>$36,300</td>
</tr>
</tbody>
</table>

## II. Incremental cost-effectiveness ratios (ICERs) for select EID strategies

<table>
<thead>
<tr>
<th>EID strategy</th>
<th>Birth cohort life expectancy (years, discounted)</th>
<th>Birth cohort lifetime costs (USD per person, discounted)</th>
<th>Incremental cost-effectiveness ratio ($/YLS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No EID</td>
<td>25.7</td>
<td>$660</td>
<td>Comparator</td>
</tr>
<tr>
<td>Birth alone</td>
<td>25.8</td>
<td>$780</td>
<td>Dominateda</td>
</tr>
<tr>
<td>6 weeks alone</td>
<td>25.8</td>
<td>$820</td>
<td>$1,250</td>
</tr>
<tr>
<td>Birth and 6 weeks</td>
<td>25.8</td>
<td>$870</td>
<td>$2,900</td>
</tr>
</tbody>
</table>

## III. Sensitivity analyses: Selected results for 10-week EID strategies (complete results in Appendix)

<table>
<thead>
<tr>
<th>EID strategy</th>
<th>HIV-infected infants</th>
<th>Birth cohort</th>
<th>Lifetime costs (2013 USD, per person)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One-year survival (%)</td>
<td>Life expectancy (years, undiscounted)</td>
<td>One-year survival (%)</td>
</tr>
<tr>
<td>10 weeks alone</td>
<td>72.9</td>
<td>25.3</td>
<td>93.1</td>
</tr>
<tr>
<td>Birth and 10 weeks</td>
<td>75.9</td>
<td>26.3</td>
<td>93.3</td>
</tr>
</tbody>
</table>

Abbreviations: IU: intrauterine infection; IP: intrapartum infection; PP: postpartum infection; EID: early infant diagnosis; ART: antiretroviral therapy; USD: United States dollar; YLS: year of life saved.

a. Dominated: A strategy that has higher lifetime costs and lower life expectancy than a competing strategy is said to be “strongly dominated,” in which case no ICER is calculated. When comparing three or more strategies, if a strategy has a higher ICER than a competing strategy with a higher lifetime cost (as is the case here), then the strategy is said to be “weakly dominated,” reflecting a less efficient use of healthcare resources than a linear combination of other strategies, and the ICERs of all strategies are recalculated with that strategy omitted (66). ICERs are calculated from unrounded model output, and are then rounded to the nearest $50.
**A**

One year costs per infant (USD)

- **No EID**: $50 (43%)
- **Birth**: $70 (43%)
- **6 wk**: $70 (43%)
- **Birth + 6wk**: $100 (55%)

*Excludes implementation costs

**B**

Lifetime costs per infant (USD)

- **No EID**: $1,430
- **Birth**: $1,670
- **6 wk**: $1,770
- **Birth + 6wk**: $1,840

- **EID costs***
- **Monitoring**
- **ART**
- **Routine care**
- **OI and death**

*Excludes implementation costs
ART-associated CD4-independent
Reduction in OI and mortality risk (90-0%; 85/90%)
Specificity of NAT assay (100-85%; 98.8%)
Sensitivity of NAT assay (100-0%; 100%)
Probability of linkage to ART after
HIV diagnosis (100-0%; 100%)
Probability of test result return (100-0%; 100%)
PMTCT coverage (0-100%; 90%)
Cost per infant of adding birth testing to an existing 6-week program ($0-$300; $0)
Cost of NAT assay ($5-$75; $25)
Result-return time (0-5 mths ± 1 mth; 1 mth ± 0 mths)
Probability (monthly) of virologic failure after initial suppression (0.5-5.0%; 0.9%)
Risk of OIs (2.0-0.5x base case values)
Cost of clinical care (0.5-2.0x base case values)
HIV-Infected Infants: One Year Survival (%)

- I: 63.4% Present, 50% Result-Return
- II: 64.4% Present, 50% Result-Return
- III: 68.1% Present, 75% Result-Return
- IV: 70.4% Present, 75% Result-Return
- V: 74.9% Present, 100% Result-Return
- VI: 76.6% Present, 100% Result-Return