Clinical effect and cost-effectiveness of incorporation of point-of-care assays into early infant HIV diagnosis programmes in Zimbabwe: a modelling study

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Summary

Background New point-of-care (POC) assays for early infant HIV diagnosis are costlier than conventional total nucleic acid assays, but could increase access to testing, shorten time to results, and expedite initiation of antiretroviral therapy. We aimed to assess the clinical benefits and cost-effectiveness of incorporating these POC assays into early infant diagnosis programmes in Zimbabwe.

Methods We used the Cost Effectiveness of Preventing AIDS Complications (CEPAC)—Pediatric model to examine the clinical benefits, costs, and cost-effectiveness of replacing conventional assays for early infant HIV diagnosis with POC assays at age 6 weeks in Zimbabwe. We simulated two strategies for early infant HIV diagnosis: conventional and POC. Modelled assays differed in sensitivity; specificity; time to, and probability of, return of results; and cost. Model outcomes included survival, life expectancy, and mean lifetime per-person treatment cost, which were reported separately for all HIV-exposed infants and all infants with HIV. We calculated incremental cost-effectiveness ratios with discounted (3% per year) costs and life expectancy from a health-care system perspective for all HIV-exposed infants. We judged incremental cost-effectiveness ratios of $1010 (Zimbabwe’s annual gross domestic product per person) or less per year of life saved to be cost-effective.

Findings When conventional assays were used for early infant diagnosis, projected undiscounted life expectancy was 22.7 years for infants with HIV and 62.5 years for all HIV-exposed infants, at a cost of $610 per HIV-exposed infant. Use of POC assays for early infant HIV diagnosis improved projected undiscounted life expectancy to 25.5 years among infants with HIV and 66.1 years among HIV-exposed infants at a cost of $690 per HIV-exposed infant. At age 12 weeks, survival among all infants with HIV was 76.1% with the conventional testing strategy and 83.5% with the POC testing strategy. The incremental cost-effectiveness ratio of POC assays versus conventional assays for early infant diagnosis was $680 per year of life saved. When conventional assay characteristics remained constant, this ratio remained under the cost-effectiveness threshold as long as the specificity and sensitivity of the POC assay were greater than 92% and 65%, respectively. Our results were robust to plausible variations in POC assay cost, the probability of ART initiation, and probability of return of the results of POC testing.

Interpretation Compared with conventional assays, POC assays for early infant HIV diagnosis in Zimbabwe will improve survival, extend life expectancy, and be cost-effective for HIV-exposed infants.

Funding Elizabeth Glaser Pediatric AIDS Foundation, US National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and Unitaid.

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Introduction

Each year, nearly 1.4 million children are born to HIV-infected mothers worldwide.1 Although 76% of pregnant women living with HIV now have access to antiretroviral therapy (ART) to prevent transmission to their infants, 160,000 children acquired HIV in 2016.12 Without treatment, half of all children born with HIV die in early infancy. Although WHO recommends early infant HIV diagnosis testing at age 6 weeks for all HIV-exposed infants, less than 50% of these infants undergo such testing.3 A primary reason for this gap is that virological assays (ie, PCR-based assays) are needed to diagnose HIV in infants, and this advanced technology is often available only at central laboratories. The logistic difficulties of transporting samples to these laboratories and returning results to health facilities often leave caregivers waiting several months for the results of early infant diagnosis tests.12 Nearly half of infants tested never receive their results, and only 50–80% of those who test positive and receive results are eventually linked to care and ART.12

New point-of-care (POC) early infant HIV testing technologies are now available.4 If strategically integrated...
Research in context

Evidence before this study
Although WHO recommends HIV testing at age 6 weeks for all HIV-exposed infants, less than 50% of these infants worldwide have access to early infant HIV testing. New point-of-care (POC) assays for early infant HIV diagnosis arecostlier than conventional total nucleic acid assays, but might increase access to diagnostic results, shorten time to return of results, and expedite initiation of antiretroviral therapy. Although trials and implementation studies have shown operational improvements in, and clinical benefits of, POC testing, the cost-effectiveness of these novel assays compared with conventional assays remains largely unknown. We searched PubMed by combining the search terms “point-of-care” and “early infant HIV diagnosis” with health economic terms (“cost-effectiveness”, “cost benefit”, and “ICER”) for studies published in English from inception up to Sept 25, 2018. We did not identify any studies in which the cost-effectiveness of POC and conventional early infant HIV testing were compared.

Added value of this study
We report the first cost-effectiveness modelling study informed by real-world data from a large-scale implementation initiative into national early infant diagnosis networks, these POC assays could both increase the number of HIV-exposed infants who are diagnosed and substantially reduce waiting times for results and time to initiation of ART, thereby decreasing infant mortality. POC assays are simpler and faster than laboratory-based assays, and do not require extensive training or complex infrastructure. However, the clinical effect and cost-effectiveness of these novel POC assays for early infant HIV diagnosis are largely unknown. An early infant HIV diagnosis initiative, launched by Unitaid and the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), has expanded access to POC testing in nine African countries.7 We used a validated computer model of paediatric HIV disease, populated with programme assessment data from Zimbabwe, to examine the clinical benefits and cost-effectiveness of POC assays for early infant HIV diagnosis in Zimbabwe.

Methods
Study design and overview
We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)—Pediatric model to assess the clinical effects, costs, and cost-effectiveness of integration of POC assays into early infant HIV diagnosis programmes in Zimbabwe.8 9 10 We modelled a population of infants born to HIV-infected mothers presenting to early infant HIV testing at age 6 weeks, and simulated two testing strategies for early infant HIV diagnosis: conventional assays and POC assays. Model outcomes included short-term and long-term survival, HIV-related health-care costs, and life expectancy. To reflect outcomes and resource requirements for an entire HIV programme, we projected results for the full cohort of HIV-exposed infants (including infants with and without HIV). We also assessed clinical outcomes for HIV-infected infants specifically. Using HIV-exposed outcomes, discounted at 3% per year, we calculated the incremental cost-effectiveness ratio for the POC strategy compared with the conventional strategy in 2016 US$ per year of life saved. This ratio is a useful metric for programme planners because it is comparable across many health programmes.11 On the basis of emerging literature, we defined an incremental cost-effectiveness ratio of less than Zimbabwe’s 2016 annual gross domestic product (GDP) per person (ie, $1010) as cost-effective.12 In one-way and multi-way sensitivity analyses, we varied key model input data and assumptions, including parameters associated with diagnosis, ART initiation, assay characteristics, and costs for both the conventional and POC strategies. Although the base-case analysis focused on the Unitaid and the EGPAF project, we included all available relevant data for the range of assessed sensitivity analyses (appendix p 13).

Model description
The CEPAC—Pediatric model is a validated individual-level, state-transition model of paediatric HIV disease, which has been expanded to incorporate perinatal HIV transmission and early infant HIV diagnosis.8 10 Infants enter the model at birth and are simulated until death. Maternal CD4 cell count and ART availability determine the risk of mother-to-child HIV transmission during three periods: the intrauterine period (a one-time risk), the intrapartum period (a one-time risk), and the post-partum period...
(a monthly risk until breastfeeding cessation, which excludes acquisition of HIV outside mother-to-child transmission). All infants face age-stratified monthly risks of non-HIV related mortality, and those with HIV face additional age-stratified and CD4-stratified risks of opportunistic infections, mortality related to opportunistic infections, and mortality unrelated to opportunistic infections. Planned early infant HIV diagnosis can occur at any time from age 0 months to 24 months.

After HIV infection is confirmed, children have a probability of initiating ART. Once on ART, children have an initial probability of early virological suppression, and children with early virological suppression have a monthly risk of treatment failure. Although HIV viral load is suppressed by effective ART, CD4% (or total CD4 cell count) increases, leading to reduced risk of opportunistic infection and mortality. Children engaged in care can also be lost to follow-up and then subsequently return to care.

Modelled population and early infant diagnosis strategies

Because early infant HIV testing is recommended only for infants known to be exposed to HIV, we simulated a population of infants born to women who were identified as HIV infected during antenatal care. On the basis of WHO recommendations and Zimbabwe national guidelines and data, we simulated that 93% of women who were identified as living with HIV during pregnancy received ART during pregnancy and breastfeeding (WHO option B+). Women who breastfed (80% of the population) did so for a mean duration of 18 months (SD 2).

We focused our analysis on early infant HIV diagnosis at age 6 weeks to remain consistent with the Unitaid and EGPAF pilot project and the structure of most programmes for early infant HIV diagnosis in sub-Saharan Africa. For conventional and POC assays, we assigned different diagnostic characteristics (sensitivity and specificity), costs, and early infant HIV diagnosis cascade characteristics (ie, probability of return of results, time to return of results, and ART initiation rate). In the base case, any positive conventional or POC result was followed by a second, confirmatory assay of the same type and the opportunity for ART initiation if the infant was successfully linked to care. We varied the probability of ART initiation between the conventional and POC strategies on the basis of pre-pilot and post-pilot study data from the Unitaid and EGPAF project.

For those who began treatment, ART was stopped if the confirmatory assay and a third conventional assay (all sent before ART initiation) were negative. For infants missed by early infant HIV testing or who were infected after age 6 weeks, HIV infection was assumed to be diagnosed at presentation to care later with a WHO stage 3 or 4 opportunistic infection or at an 18-month clinic visit.

<table>
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<th>Data sources</th>
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We derived the risk of mother-to-child HIV transmission from clinical trials and cohort studies in Africa. Mortality data for HIV-exposed but uninfected infants were from pooled UNAIDS analyses. Because detailed clinical data about HIV progression in infants taking ART and those not taking ART were unavailable for Zimbabwe, we used clinical data inputs calibrated to other southern populations.
Table 1: Selected input parameters for a model-based analysis of point-of-care EID versus conventional EID in Zimbabwe

<table>
<thead>
<tr>
<th>Value</th>
<th>Data sources*</th>
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| HIV care per month (range by age, CD4%, and CD4 cell count) | $3275–3369 Mabugu (2012)
| CD4 test                   | $479 Global Fund (2017) |
| ART regimen per month (range by regimen, dose, and age and weight of infant) | $850–4400 Doherty et al (2014),Clinton Health Access Initiative (2016) |
| Conventional assay         | $2418 (1.4% error rate) Global Fund (2017) |
| Point-of-care assay        | $2761 (6% error rate) Hsiao et al (2016) |

Data are mean (SD), %, or cost in 2016 US$. ART=antiretroviral therapy. EID=early infant diagnosis. Global Fund=Global Fund to Fight AIDS, Tuberculosis and Malaria. *Here we cite previous Cost Effectiveness of Preventing AIDS Complications papers in which the same primary data sources were used; full primary data sources are listed in the appendix (p 13). Errors during point-of-care testing (eg, because of platform malfunctions, human error) lead to an inconclusive test result and repeat testing, but do not affect return of results.

Table 2: Economic and clinical outcomes for a model-based analysis of point-of-care early infant diagnosis vs conventional early infant diagnosis in Zimbabwe

<table>
<thead>
<tr>
<th>Infants with HIV</th>
<th>HIV-exposed infants</th>
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<tr>
<td>1-year survival</td>
<td>Life expectancy (undiscounted)</td>
</tr>
<tr>
<td></td>
<td>69.0%</td>
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<tr>
<td></td>
<td>78.0%</td>
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Scenario and sensitivity analyses

In one-way sensitivity analyses, we varied the probability of return of results, the time to return of results, and the likelihood of ART initiation to reflect setting-specific availability of paediatric ART services and patient-level and caregiver-level behaviour. We also assessed conventional and POC assay characteristics with wide ranges of sensitivity, specificity, and assay costs. Additionally, we varied parameters that apply equally to both strategies, including the risks of mother-to-child HIV transmission for women taking and not taking ART, duration of breastfeeding, and coverage of antiretroviral drugs for prevention of mother-to-child transmission. In multi-way sensitivity analyses, we simultaneously varied clinically relevant parameters that have prompted the most concern about successful field implementation of POC assays for early infant HIV diagnosis (ie, probability of, and time to, return of results with conventional assays and sensitivity of POC assays). Data from other countries in the Unitaid and EGPAF project informed plausible parameter ranges for all sensitivity analyses.

In four scenario analyses, we examined optimistic, intermediate, and pessimistic conditions of uptake along the early infant HIV diagnosis cascade for both the conventional and POC strategies; a prioritised POC testing strategy in which infants of women with HIV who did not receive ART during pregnancy received POC testing whereas all others were tested by conventional means;
poorer ART outcomes after POC testing; and poorer ART outcomes after both POC and conventional testing (appendix p 10).

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
In the base-case analysis, we projected a total mother-to-child transmission risk of 5.2% for the entire HIV-exposed cohort (1.4% of infants acquired HIV in utero, 1.0% acquired HIV in the intrapartum period, and 2.8% acquired HIV postpartum). Thus, 94.8% of HIV-exposed infants were not infected. The clinical effect of POC testing for the entire HIV-exposed cohort was small, with the proportion of infants surviving to 1 year increasing from 93.1% with conventional testing to 93.4% with POC testing, and projected undiscounted life expectancy increasing from 62.5 years with conventional testing to 62.6 years with POC testing (table 2). For infants with HIV, the proportion of infants surviving to 1 year was 78.0% with POC testing and 69.0% with conventional testing, and undiscounted life expectancy was 25.5 years with POC testing and 22.7 years with conventional testing (table 2). At age 12 weeks, survival among all infants with HIV was 76.1% with the conventional testing strategy and 83.5% with the POC testing strategy; survival with conventional testing varied by time to return of results (figure 1).

Conventional testing was associated with lower projected HIV-related health-care costs than POC testing in the HIV-exposed cohort (lifetime cost per HIV-exposed infant S610 vs S690; table 2). Lifetime costs in the HIV-infected cohort were also higher with POC testing than with conventional testing (S13460 vs S11830), reflecting improved access to ART and longer survival while receiving care and ART (table 2).

In HIV-exposed infants, the incremental cost-effectiveness ratio of POC testing compared with conventional testing was S680 per year of life saved (roughly 67% of Zimbabwe’s annual GDP per person; table 3). In sensitivity analysis, the incremental cost-effectiveness ratio of POC testing compared with conventional testing exceeded S1010 per year of life saved if HIV-related health-care costs doubled across both strategies or if ART costs tripled across both strategies (figure 2). The cost-effectiveness of POC testing remained robust (ie, incremental cost-effectiveness ratio <S1010 per year of life saved) throughout plausible variations in parameters such as assay sensitivity, specificity, and cost, and variations along the POC cascade (figure 2). When ranged to extreme values, POC early infant HIV testing was no longer cost-effective if the assay cost exceeded S60, if less than 50% of infants undergoing testing received test results, if assay sensitivity was less than 65%, if assay specificity was less than 92%, or if less than 45% of infants initiated ART after receiving positive results. By contrast, the incremental cost-effectiveness ratio of POC testing compared with conventional testing remained less than S1010 per year of life saved despite plausible variations in parameters applied to both strategies (breastfeeding duration and practices, coverage of antiretroviral drugs for prevention of mother-to-child HIV transmission, presentation for early infant HIV testing [50–100%], and conventional assay sensitivity [70–100%], specificity [90–100%], and cost [$1–10]). Longer time to, and lower probability of, return of results with conventional testing did not change policy conclusions (appendix p 23).

In multi-way sensitivity analysis, even if the probability of the return of results of conventional testing was 90% (compared with 80% in the base-case scenario), POC tests with sensitivity of greater than 65% retained cost-effective in the HIV-exposed cohort (figure 3A). Furthermore, based on the lowest PCR-based POC sensitivity point estimate

![Figure 1: Early survival of infants with HIV diagnosed by conventional or POC testing at age 6 weeks in Zimbabwe](image)

Table 3: Cost-effectiveness outcomes for a model-based analysis of point-of-care early infant diagnosis vs conventional early infant diagnosis in Zimbabwe

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<tr>
<td>Conventional early infant diagnosis</td>
<td>25.7 years</td>
<td>$370</td>
<td>Comparator</td>
</tr>
<tr>
<td>Point-of-care early infant diagnosis</td>
<td>25.8 years</td>
<td>$420</td>
<td>$680</td>
</tr>
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ART costs (3x; 0.5x–3x)

POC assay cost ($2.60–5.00)

POC assay return of results (99.5%; 100–70%)

POC assay sensitivity (96.0%; 95.1–97.5%)

POC assay specificity (100%; 98.8–100%)

ART initiation after POC assay (98.5%; 100–70%)

HIV-related health-care costs (1x; 0.5x–3x)

Figure 2: Tornado diagram of key parameters and thresholds that affect the cost-effectiveness of POC early infant HIV diagnosis compared with conventional early infant HIV diagnosis

Parameters were varied in one-way model sensitivity analyses. Values in parentheses show the base-case values and the range examined (from the value leading to the lowest ICER to that leading to the highest ICER). The range of ICERs for each varied parameter is shown by the blue horizontal bars; longer bars show parameters to which model results were more sensitive. The darker vertical line shows the ICER for all base-case parameters (i.e., $680 per year of life saved), whereas the lighter vertical line shows Zimbabwe’s 2016 annual gross domestic product per person (i.e., $1010), which is the cost-effectiveness threshold. POC=point-of-care. ICER=incremental cost-effectiveness ratio. ART=antiretroviral therapy.

reported in published work (93·3%).20 POC testing remained cost-effective even if the probability of return of results of conventional testing improved to 100%. If time to return of conventional testing results was shortened to 1 month, POC testing remained cost-effective as long as the sensitivity of the POC assay exceeded 75% (figure 3B).

In a modelled scenario, POC testing led to greater life expectancy than conventional testing under each of the optimistic, intermediate, and pessimistic conditions of uptake along the early infant diagnosis cascade (appendix p 24). POC testing was also cost-effective compared with conventional testing in seven of nine combinations of conditions (table 4). POC testing remained cost-effective in the three other scenarios modelled (appendix p 24).

Discussion

In this model-based analysis, incorporation of POC assays into early infant diagnosis programmes at age 6 weeks in Zimbabwe substantially improved survival and life expectancy among HIV-infected infants, and was cost-effective for all HIV-exposed infants, compared with conventional testing. Our work had four main findings.

First, the operational characteristics of POC testing—i.e., improved time to return of results, increased likelihood of return of results, and increased initiation of ART—resulted in substantially improved short-term survival for HIV-infected infants compared with conventional testing. This benefit extended to long-term survival, with an increase in projected life expectancy of 2.8 years among HIV-infected infants who underwent POC testing compared with those who underwent conventional testing.4 POC testing was more costly than conventional testing (lifetime costs were $80 more per HIV-exposed infant), because of the greater numbers of children in care and on ART, and the longer life expectancies during which care and ART costs were accrued. Despite these slightly higher costs, POC early infant HIV testing was a cost-effective intervention by international standards for Zimbabwe, with an incremental cost-effectiveness ratio of $680 per year of life saved, well below the country’s annual GDP per person.

Second, a key driver of the benefit of POC early infant HIV testing is reduced time to return of results, which can be as high as 3 or 4 months in conventional early infant HIV testing settings.7 Reduced time to return of results increased the proportion of infants who received results and were linked to HIV care, and substantially decreased mortality in the early months of life. In settings with longer delays in time to return of results for conventional testing, POC testing was associated with an even greater reduction in early mortality. Although trials and implementation studies of the clinical effects of POC testing for early infant HIV diagnosis have not yet generated data for long-term survival outcomes, the association between shorter time to return of results with POC testing and increased ART initiation remains consistent across studies throughout sub-Saharan Africa.5–26

In our model-based analysis with a time to return of results of 1 month with conventional testing—a threshold that has been difficult to reach in most settings—POC testing was associated with decreased mortality even at lower-than-reported probabilities of return of results and ART initiation.7 This finding suggests that timely return of test results is one of the predominant mechanisms by which early infant HIV diagnosis programmes avert early infant mortality.

Third, there have been concerns that POC assays have low sensitivity compared with conventional assays.1 Assignment of the lowest reported values for the sensitivity of PCR-based POC assays did not change our model-projected policy conclusions. Although reductions in POC assay sensitivity lead to smaller increases in false negative results and missed diagnoses, these outcomes should be balanced against the missed diagnoses due to suboptimal return of results of conventional testing. In our analysis, large improvements in both the probability of, and the time to, return of results of conventional assays were needed to offset the slightly lower sensitivity of the POC assay. A systematic review of POC CD4 cell count measurement in Africa had similar findings: improvements in retention of patients along the testing and treatment cascade for POC CD4 cell count measurements outweighed the superior sample processing, quality control, and technical characteristics of laboratory-based CD4 cell count measurement.27 In our analysis, the POC assay for early infant HIV diagnosis needs to have a sensitivity of less than 65% to make conventional testing the preferred strategy, whereas reported sensitivities for PCR-based POC assays such as RDs miPima (Abbott, Lake Forest, IL, USA) and GeneXpert (Cepheid, Sunnyvale, CA, USA) range from 93·3% to 98·5%.28,29
Fourth, POC testing for early infant HIV diagnosis remained cost-effective under a range of assumptions, despite plausible variations in breastfeeding practices, coverage of antiretroviral drugs for prevention of mother-to-child transmission of HIV, and improvements in the conventional testing cascade. These findings are consistent with those of studies of the cost-effectiveness of other POC technologies, such as POC CD4 cell count measurement and viral load assays. However, if the total cost of ownership of POC testing increased from the base-case value of $28 per test to $60 per test, POC testing was no longer the preferred strategy. Total cost of ownership reflects potential fluctuations in throughput or increased service and maintenance costs that could be associated with service delivery in rural or low-serviced settings. A cost of $60 per test has been reported for RDx mPima when throughput is reduced to less than 0.5 tests per day. Mean daily use of POC machines for early infant HIV testing in the Unitaid and EGPAF project in Zimbabwe is 1.51 tests per day. Only 5% of sites for POC testing in Zimbabwe do fewer than 0.5 tests per day. However, this threshold might not be relevant for other countries. Our analysis assumes replacement of available conventional testing with POC testing, but we do not examine the most efficient placement of a limited number of POC testing machines. There are probably several ways to implement POC early infant HIV testing that do not require one machine at every site. In Zimbabwe, the Unitaid and EGPAF project has successfully implemented a hub-and-spoke model, in which samples are sent from spoke sites to central hub sites with POC machines for processing. Additionally, if POC machines could be used for additional purposes, such as tuberculosis diagnosis or monitoring of viral loads, that would lead to substantial changes in use, costs, and clinical benefit.

Our analysis has several limitations. Although modelling is a useful tool for projection of future outcomes in the absence of long-term empirical data, changes in treatment availability, clinical care, and health-care costs are likely to occur over infants’ lifetimes, and long-term model-based projections for children are uncertain. We addressed this uncertainty by calibrating our model to ensure that results matched data for survival, risk of mother-to-child HIV transmission, and opportunistic infections and then varying factors and policies likely to change over time, such as coverage of antiretroviral drugs for prevention of mother-to-child transmission, ART availability, frequency of monitoring of CD4 cell counts and viral loads, and costs. Except when noted, plausible changes in these parameters did not change our policy conclusions. Our base-case analysis simulated a population of HIV-exposed infants undergoing early infant HIV testing (100% uptake) for both the POC and conventional strategies to describe the full potential of these programmes. Thus we have over-
estimated the clinical benefit of both modelled strategies, especially conventional testing, for which low uptake has been widely reported throughout sub-Saharan Africa.\(^6\) We addressed this issue through a scenario analysis, in which we assessed each strategy with the highest and lowest values reported in published literature for steps along the early infant HIV diagnosis cascade and for conventional and POC assay characteristics. Although the model included costing inputs for conventional and POC testing drawn from the Global Fund's total cost of ownership, these estimates do not include health worker costs and infrastructure upgrades that might be needed for centralised laboratories or health facilities. A detailed costing analysis of the POC early infant HIV diagnosis programme in Zimbabwe, which will add to the total cost of ownership estimates by refining logistics and training costs and including costs for site monitoring, quality assurance, and sample transport, is underway. Data for comprehensive costs of POC testing in other settings are also crucial. In the absence of such data, we have done extensive sensitivity analyses and identified cost thresholds above which POC testing would no longer be cost-effective.

Overall, our results were robust across a wide range of sensitivity and scenario analyses, suggesting that they might be largely generalisable to other sub-Saharan African countries, except those where early infant HIV testing is sparse. Ensuring the timely return of results of early infant HIV tests and increasing the proportion of infants who receive results are of crucial importance to prevent infant mortality in the early months of life. Policy makers should incorporate POC assays into early infant HIV diagnosis programmes to optimise outcomes along the care cascade and thereby improve clinical outcomes for infants undergoing HIV testing at 6 weeks of age.

**Contributors**
SCF led the design and execution of this model-based analysis, interpreted results, and led all writing and editing efforts. JC, ES, SM, and ET contributed to the initial conceptualisation of the analysis, and were responsible for procurement of data for relevant input parameters, and advised and consulted on the analysis plan, model inputs, and Article preparation. LD, RPW, CMD, and KAF provided substantive input into the modelling plan and interpretation of model-based results. ALC oversaw all stages of the analysis from inception through completion, provided feedback on all data, interpreted results, and handled Article preparation issues. All authors reviewed and approved the Article before submission.

**Declaration of interests**
RPW, CMD, KAF, and ALC have received funding to their institutions from the US National Institutes of Health. Additionally, CMD has received funding from the Harvard University Center for AIDS Research, and RPW has received funding from the Massachusetts General Hospital Steve and Deborah Gorlin Award. All other authors declare no competing interests. This work was funded under the terms of Cooperative Agreement UAI-AA-A-15-0070 to EPICUP (SG, BEN). This Comment was made possible by the generous support of the American people through USAID. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPPAR, USAID or the US Government.

**Acknowledgments**
This work was funded by Unitaid (EB21/R088), the Elizabeth Glaser Pediatric AIDS Foundation (R01TA), the Envision Kennedy Shriver National Institute of Child Health and Human Development (R01HD079214), the US National Institute of Allergy and Infectious Diseases (R01AI058716, R37AI093269, and T32AI007422), and the Steve and Deborah Gorlin MGH Research Scholar Award. The contents of this Article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health, the Elizabeth Glaser Pediatric AIDS Foundation, or Unitaid. We gratefully acknowledge our collaborators at the Elizabeth Glaser Pediatric AIDS Foundation and Unitaid for their insightful contributions to the analysis and their support in procurement and interpretation of relevant data from their large-scale POC early infant HIV testing initiative; all study participants and staff; and Nicole McCann for her assistance with preparation of the Article.

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