Clinical Consequences of Using an Indeterminate Range for Early Infant Diagnosis of HIV: A Decision Model

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Background: To minimize false-positive diagnoses of HIV in exposed infants, the World Health Organization recommends confirmatory testing for all infants initiating antiretroviral therapy (ART). In settings where confirmatory testing is not feasible or intermittently performed, clinical decisions may be aided by semi-quantitative cycle thresholds (Cts) that identify positive results most likely to be false-positive.

Methods: We developed a decision analysis model of HIV-exposed infants in sub-Saharan Africa to estimate the clinical consequences of deferring ART for infants with weakly positive (“indeterminate”) results. We assessed the degree to which “indeterminate” results may reduce the number of infants starting ART unnecessarily while missing a small number of HIV-infected infants. Our primary outcome was the ratio of averted unnecessary ART regimens to additional HIV-related deaths (due to false-negative diagnosis) at different Ct cutoffs.

Results: The clinical consequences of adopting an indeterminate range varied with the prevalence of HIV and Ct cutoff. Considering a Ct cutoff ≥33, adopting an indeterminate range could prevent a median of 1.4 infants from receiving ART unnecessarily (95% UR: 1.0–2.0) for each additional HIV-related death. This ratio could be improved by prioritizing infants with indeterminate results for confirmatory testing [median 8.8 (95% UR: 6.0–13.3)] and by adopting a higher cutoff [median 82.3 (95% UR: 49.0–155.8) with Ct ≥36].

Conclusions: When implemented in settings where confirmatory testing is not universal, the benefits of classifying weakly positive results as “indeterminate” may outweigh the risks. Accordingly, the World Health Organization has recommended Ct values ≥33 be considered indeterminate for infant HIV diagnosis.

Key Words: early diagnosis, clinical decision-making, cost-effectiveness, mathematical model, indeterminate result, false-positive

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INTRODUCTION

As programs to prevent mother-to-child transmission of HIV are scaled-up globally, the prevalence of HIV among exposed infants born to HIV-infected mothers will continue to decrease. However, with low levels of perinatal transmission and imperfect diagnostic tests, a substantial fraction of positive HIV test results may occur in infants who are truly uninfected, with the potential that many of these infants will receive long-term antiretroviral therapy (ART) as a result. The World Health Organization (WHO) recommends that positive HIV test results be confirmed by a second independent test on a new sample. However, in some high-burden settings, the proportion of infants receiving appropriate confirmatory testing is less than 20%, creating challenges for clinicians who must weigh the risks of false-positive diagnoses against the high mortality faced by infants with untreated HIV.

In settings where confirmatory testing is not routinely conducted, clinical decisions may be aided by additional semi-quantitative information which accompanies the results of positive nucleic acid amplification tests (NAATs) generally used for early infant diagnosis. This semi-quantitative result, reported as a cycle threshold (Ct), reflects the number of amplification cycles completed before the detection of viral nucleic acid: A low Ct indicates more rapid detection (corresponding to a higher viral load), and a high Ct indicates slower detection (corresponding to a lower viral load). Currently, manufacturers recommend that any HIV nucleic acid detected (regardless of the Ct value) may be interpreted as a qualitative “positive” result. However, classifying the weakest results (ie, highest Ct values) as “indeterminate” may allow programs to triage infants with such results for repeat or confirmatory testing before initiating ART.

The implications of incorporating these semi-quantitative results have not been fully explored. We
therefore constructed a decision analysis model to estimate the clinical consequences of adopting guidelines using an indeterminate range for early infant HIV diagnosis in settings of incomplete confirmatory testing of positive results. We present anticipated tradeoffs between false-positive diagnoses and potential missed cases at a variety of Ct values that may be used to define indeterminate results.

**METHODS**

**Population of Interest and Model Structure**

Our analysis traced the economic and clinical outcomes of a hypothetical population of 10,000 HIV-exposed infants in sub-Saharan Africa with an HIV prevalence of 2.5% among infants at the time of initial EID testing. In this population, we evaluated the performance of 2 diagnostic and treatment algorithms (Fig. 1): (1) standard of care (SoC) versus (2) the adoption of an Indeterminate Range, defined as a Ct value above a given threshold on NAAT testing for early infant HIV diagnosis.

In both algorithms, all HIV-exposed infants received an initial NAAT for HIV diagnosis within 6 weeks of birth. The sensitivity and specificity of this assay, coupled with the infant’s HIV status (Fig. 1A), determine the probability of a negative test result (defined as a result with no HIV nucleic acid detected and no Ct reported, depicted as the white area to the left in Fig. 1B). In the SoC algorithm, all detectable (nonnegative) results are classified as positive; in the Indeterminate Range scenario, nonnegative test results are classified as either positive (a Ct value lower than the selected Ct cutoff) or indeterminate (a Ct value higher than the selected Ct cutoff). For each possible Cutoff, the probabilities of positive versus indeterminate results for HIV-infected and HIV-uninfected infants (dark gray and light gray areas in Fig. 1B, respectively) are determined by empirical distributions of Ct values from a meta-analysis (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/B371 and Luo et al, “Use of an indeterminate range in HIV early infant diagnosis: a systematic review and meta-analysis” submitted with this manuscript).

The SoC diagnostic algorithm used for our analysis was adopted from contemporary WHO guidelines for early infant diagnosis of HIV (Fig. 1C). Under the SoC, infants with any initial nonnegative HIV test result (whether due to HIV infection or false-positive results) immediately receive ART and, according to WHO guidelines, should have a confirmatory test performed. However, in the SoC algorithm, a proportion of these infants do not receive confirmatory testing and thus are assumed to carry an HIV diagnosis (and ART recommendation) for life. The remaining infants have samples sent for confirmation, with confirmatory test results arriving after a protracted delay. While the length of these delays may vary across settings, we assume an average delay of 6 months, based on available data. The confirmatory test is assumed to be definitive, with ART interrupted after a negative result and continued after a positive result. Infants with an initial negative test are not treated or confirmed.

In the Indeterminate Range algorithm (Fig. 1D), positive results (Ct values lower than the selected cutoff) are treated the same as under the SoC. However, infants with indeterminate test results do not receive presumptive ART and only receive a lifelong HIV diagnosis and ART recommendation if a confirmatory test also returns a nonnegative result. Importantly, infants with indeterminate test results for whom confirmatory testing is not performed do not receive ART (highlighted in orange). We present results from 2 separate comparisons of the Indeterminate Range algorithm to the SoC. In the first, we assume that a given percentage of infants with nonnegative results (15% in the base case) will receive confirmatory testing, regardless of Ct value. However, this strategy may not be the most efficient use of limited confirmation capacity, as those infants with indeterminate results (high Ct values) are most likely to be falsely positive. In the second comparison, we assume that, in the Indeterminate Range scenario, all infants with indeterminate results will receive a confirmatory test, and we compare this to confirmatory testing of an equal number of randomly selected infants in the SoC (reflected in the use of dashed and solid lines in Fig. 1D).

In both scenarios, we assume for simplicity that HIV-infected infants who initially receive a false-negative diagnosis will obtain a correct diagnosis at the age of 2 years (due to, eg, serological testing at the conclusion of breastfeeding). We therefore assume that these infants experience a mortality risk associated with untreated HIV for 2 years. All HIV-infected infants (and HIV-uninfected infants with false-positive results) who survive to age 2 are assumed to have a lifelong indication for ART and to incur annual costs associated with HIV care throughout life (modeled as an average of 35 years longer for HIV-uninfected infants). Greater loss to follow-up before confirmatory testing is expected under the Indeterminate Range due to mortality among the additional missed HIV cases; therefore, we assume that such infants experience elevated mortality for 6 months to account for delays in treatment initiation. Further details on treatment and mortality may be found in the Supplementary Methods, Supplemental Digital Content, http://links.lww.com/QAI/B371.

**Clinical Outcomes and Cost-Effectiveness Outcomes**

To characterize the clinical and economic outcomes of a policy switch from SoC to implementation of an Indeterminate Range algorithm, we calculated the incremental number of infants unnecessarily put on treatment, missed cases, and HIV-related deaths in the Indeterminate Range scenario relative to SoC. Because the use of an Indeterminate Range often reduces the number of infants unnecessarily put on treatment compared with SoC, these are presented as negative—beneficial—values. Our primary outcomes of interest were the incremental number of HIV-uninfected infants unnecessarily receiving long-term ART (false-positives), the incremental number of HIV-related deaths, and the ratio of incremental unnecessary
FIGURE 1. Test results and treatment decisions for simulated HIV-exposed infants under standard of care and Indeterminate Range algorithms. A, Infants with HIV-infected mothers are assumed to have a given prevalence of HIV. The result of each infant’s initial test is determined by the infant’s HIV status, the sensitivity/specificity of the assay, and (in the Indeterminate Range scenario) the distribution of Ct values among nonnegative results. B, Decreasing Ct values (equivalent to increasing viral loads) are plotted from left to right. The red area represents negative results below the limit of detection of the assay. In the standard of care algorithm (C), any nonnegative result (blue area) receives presumptive ART unless (and until) a confirmatory test returns a negative result. In the Indeterminate Range algorithm (D), Ct values below the threshold (more rapid detection, blue) trigger presumptive treatment unless (and until) a confirmatory test returns a negative result, whereas Ct values above the threshold (slower detection, purple) do not receive ART unless a confirmatory test is performed which returns a nonnegative result. The key clinical difference between algorithms—care for infants with high Ct results who do not receive confirmatory testing—is outlined with a dotted box. In the scenario under which the indeterminate range is used to prioritize confirmatory testing, all indeterminate results receive confirmatory testing but no frankly positive results (low Ct) receive confirmatory testing (illustrated by solid paths).
ART courses to incremental HIV-related deaths in the Indeterminate Range scenario compared to the SoC. A higher ratio can be interpreted as more favorable for the Indeterminate Range scenario (preventing more unnecessary treatments for each additional death that occurs). This ratio is highest (most favorable to the Indeterminate Range) when the Ct cutoff is stringent (giving fewer indeterminate results) and the prevalence of HIV is low. As the aspirational value of an Indeterminate Range policy is to repurpose funding saved (by minimizing unnecessary ART) for more effective HIV prevention and control activities, our secondary outcomes of interest included the incremental cost-effectiveness ratio (ICER) measured as the incremental cost per disability-adjusted life year (DALY) averted (see the Supplementary Methods for further details, Supplemental Digital Content, http://links.lww.com/QAI/B371). Because the SoC is expected to have better health outcomes, but to be more expensive, ICERs are reported as the (negative) incremental cost of an Indeterminate Range policy over the (positive) additional DALYs compared with SoC. More negative (larger magnitude) ICERs can be interpreted as more favorable to an Indeterminate Range policy than less negative ICERs.

Model costs included testing, presumptive ART care, and life-long HIV care. Unit costs of testing were based on multi-country estimates assuming 80% instrument use (personal communication, “All-in Roche EID Cost” via the Clinton Health Access Initiative). Costs of ART care in the first 2 years of life were derived from estimates of the mean total cost per patient-year.21 After age 2, each surviving patient receiving ART inures an estimated (per patient) lifetime cost of HIV care beyond age 2.19 See Table S1, Supplemental Digital Content, http://links.lww.com/QAI/B371 for results from a wide range of lifetime costs.

In each scenario, DALYs are estimated to account for morbidity across the life course (described in the Supplementary Methods, Supplemental Digital Content, http://links.lww.com/QAI/B371). We considered a lifetime time horizon with costs and utilities discounted at 3% annually. Based on the life expectancy and disability weights in our model, the DALYs lost because of one HIV-related infant death are comparable to the DALYs lost because of 19.6 infants receiving ART unnecessarily (95% UR: 17.9–21.7). This threshold is highly dependent on life expectancies, economic discounting, and the subjective valuation of receiving ART unnecessarily. Any such threshold should be interpreted cautiously.

Sensitivity Analyses

For each scenario modeled, 10,000 sets of parameter values were created by probabilistically sampling from the parameter ranges defined in Table 1 (assuming uniform distributions unless noted), and outcomes were simulated for each parameter set. Outcome values are reported for the 50th, 2.5th, and 97.5th percentiles from these simulations.

Multivariable sensitivity analysis was performed using nonparametric partial rank correlation coefficients with respect to our primary outcome of interest and to our cost-effectiveness outcome (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/B371). Secondary one-

| TABLE 1. Model Parameters and Sensitivity Sampling Ranges |
|---------------------------------------------------------|
| Parameter | Median | Low* | High* | Reference |
| Assay characteristics | | | | |
| Sensitivity† | 99.2% | 98.93% | 99.36% | 11,29 |
| Specificity† | 99.86% | 99.81% | 99.89% | 30 |
| 2-year risk of mortality | | | | |
| Untreated HIV | 52% | 47% | 57% | 10,31 |
| Treated HIV | 7.6% | 6.9% | 8.3% | 32,33 |
| HIV-uninfected | 4.4% | 4.0% | 4.8% | 34 |
| 6-month mortality (untreated HIV) | 14% | 15% | 15% | 10,31 |
| Costs (2017 US dollars, USD) | | | | |
| HIV test | $23 | $21 | $25 | 21 |
| ART (per patient-year of treatment) | $317 | $286 | $346 | 21 |
| Lifetime HIV care from age 2 to death (per patient) | $9890 | $8970 | $10,840 | 19 |
| Disability weights (per discounted life-year) | | | | |
| On ART, HIV-infected | 0.08 | 0.07 | 0.09 | 35 |
| On ART unnecessarily, HIV-uninfected† | 0.05 | 0.05 | 0.06 | 35 |
| Untreated HIV | 0.58 | 0.53 | 0.64 | 35 |
| Life expectancy at age 2 (yrs) | | | | |
| HIV-Infected | 28 | 25 | 31 | 35 |
| Uninfected | 63 | 57 | 69 | 35 |
| Proportion of HIV-infected infants with initial NAAT results§ | | | | |
| Above Ct 30 | 24.3% | 21.9% | 26.5% | |
| Above Ct 31 | 18.5% | 15.7% | 21.5% | |
| Above Ct 32 | 12.8% | 10.5% | 15.5% | |
| Above Ct 33 | 8.4% | 6.7% | 10.5% | |
| Above Ct 34 | 3.9% | 3.0% | 5.0% | |
| Above Ct 35 | 1.9% | 1.4% | 2.4% | |
| Above Ct 36 | 0.5% | 0.4% | 0.6% | |
| Proportion of HIV-uninfected infants with initial NAAT results§ | | | | |
| Above Ct 30 | 98.2% | 98.0% | 98.3% | |
| Above Ct 31 | 98.2% | 98.0% | 98.3% | |
| Above Ct 32 | 97.1% | 96.9% | 97.3% | |
| Above Ct 33 | 93.2% | 92.7% | 93.7% | |
| Above Ct 34 | 88.5% | 87.8% | 89.3% | |
| Above Ct 35 | 68.2% | 66.1% | 70.4% | |
| Above Ct 36 | 36.9% | 32.9% | 41.0% | |

*Low/High refers to the minimum/maximum values of parameters sampled from uniform distributions and 2.5th/97.5th percentile values from continuous distributions.
†Sampled from a normal distribution on the odds scale for uncertainty analysis.
‡Estimated from worry and daily medication for a generic disease.
§Proportion refers to all nonnegative results (determined by sensitivity/speciﬁcity).
†§Proportion refers to all nonnegative results (determined by sensitivity/speciﬁcity). Sampled uniformly using nested conditional probabilities; see the Supplementary Methods for more information and the meta-analysis in submission with this manuscript.
||Personal communication, “All-in Roche EID Cost” via the Clinton Health Access Initiative.
ART, antiretroviral therapy; Ct, cycle threshold; NAAT, nucleic acid amplification testing.
way sensitivity analyses evaluated the impact of HIV prevalence (see Figure S3, Supplemental Digital Content, http://links.lww.com/QAI/B371) and the independent probability of confirmatory testing (see Figures S4 and S6, Supplemental Digital Content, http://links.lww.com/QAI/B371) on model outcomes.

RESULTS

Clinical Outcomes and Incremental Effectiveness

In our reference scenario, we estimated that, for every 10,000 HIV-exposed infants tested, 250 would be HIV-infected. Under the SoC, we projected that 2.3 (95% UR: 1.8–3.1) of these would test false-negative and 20.0 (95% UR: 18.2–21.9) would die within 2 years. Of the remaining 9750 HIV-uninfected infants, assuming that 15% of all initially nonnegative tests would receive confirmatory testing, 11.6 infants (95% UR: 9.3–15.4) would test false-positive and be placed on treatment unnecessarily under the SoC (Table 2). (For reference, the performance of the SoC with 100% confirmation is presented in Table S2, Supplemental Digital Content, http://links.lww.com/QAI/B371). Adopting an Indeterminate Range algorithm range defined by Ct ≥33 with 15% confirmatory testing resulted in an estimated median of 20.5 initially false-negative diagnoses (95% UR: 16.8–25.0), resulting in 28.1 (95% UR: 25.3–31.2) HIV-related deaths, while reducing the number of unnecessary tests to 0.8 (95% UR: 0.6–1.1). More limited (higher) Ct cutoff values resulted in fewer HIV-infected infants receiving false-negative diagnoses, but more infants receiving treatment unnecessarily (Table 2).

By contrast, if confirmatory testing were performed on all infants with indeterminate results defined by Ct ≥33, an estimated median of 0.9 HIV-uninfected infants would be placed on ART unnecessarily and 21.3 HIV-infected infants would die (Table 2). In the corresponding SoC algorithm with an equal number of confirmatory tests as the Ct ≥33 estimate, we estimate a median of 11.9 uninfected infants would be placed on ART unnecessarily, and 20.0 HIV-infected infants would die. In this scenario, therefore, adopting an Indeterminate Range defined by Ct ≥33 would avert 11.0 (95% UR: 8.8–14.3) unnecessary treatments while incurring 1.2 (95% UR: 0.9–1.7) additional deaths: a ratio of 8.8 unnecessary treatments averted for each excess (95% UR: 6.1–13.4).

Table 2 illustrates incremental clinical outcomes of adopting an Indeterminate Range algorithm, assuming that all infants with indeterminate results are prioritized for confirmatory testing (and compared against an SoC where the same number of confirmatory tests are performed), and Figure 3 illustrates the corresponding ratio of unnecessary treatments averted to excess deaths at different levels of HIV prevalence.

Table 2. Clinic Outcomes and Incremental Effectiveness of Indeterminate Range Algorithms

| Diagnostic Algorithm | Infants With Indeterminate Results* | Confirmatory Tests Performed* | HIV-Infected Infants Potentially Missed | HIV-Infected Uninfected Infants on ART | Total HIV-Related Deaths | Unnecessary ART Courses Averted† | Excess HIV-Related Deaths† |
|-----------------------|-----------------------------------|--------------------------------|----------------------------------------|----------------------------------------|--------------------------|---------------------------------|--------------------------|
| SoC                   | 15% confirmatory testing          | 0                              | 39.2 (38.8–39.9)                       | 2.3 (1.8–3.1)                          | 11.6 (9.3–15.4)          | 20 (18.2–21.9)                  | —                        |
| ≥36                   |                                   | 6.3 (5.1–8.1)                   | 39.2 (38.8–39.9)                       | 3.4 (2.8–4.2)                          | 7.3 (5.8–9.8)            | 20.5 (18.7–22.3)               | 4.3 (3.3–5.8)             | 0.5 (0.3–0.6) |
| ≥35                   |                                   | 14 (11.7–17.3)                  | 39.2 (38.8–39.9)                       | 6.4 (5.2–7.7)                          | 3.7 (2.9–5)              | 21.9 (19.9–23.8)               | 7.9 (6.3–10.5)            | 1.8 (1.3–2.4) |
| ≥34                   |                                   | 21.9 (18.5–26.5)                | 39.2 (38.8–39.9)                       | 10.8 (8.8–13.2)                        | 1.3 (1.1–1.8)            | 23.8 (21.6–26.1)               | 10.3 (8.2–13.6)           | 3.7 (2.8–4.9) |
| ≥33                   |                                   | 33.7 (28.5–40.1)                | 39.2 (38.8–39.9)                       | 20.5 (18.6–25)                         | 0.8 (0.6–1.1)            | 28.1 (25.3–31.2)               | 10.8 (8.7–14.3)           | 6.2 (6–10.4) |
| ≥32                   |                                   | 45.1 (38.6–52.8)                | 39.2 (38.8–39.9)                       | 30.0 (25.0–35.7)                       | 0.3 (0.3–0.5)            | 32.3 (29–36)                   | 11.3 (9–14.9)             | 12.2 (9.7–15.4) |
| ≥31                   |                                   | 59.4 (51.9–67.7)                | 39.2 (38.8–39.9)                       | 42.3 (36.3–48.8)                       | 0.2 (0.2–0.3)            | 37.7 (33.8–42.1)               | 11.4 (9.1–15.1)           | 17.7 (14.3–21.6) |
| ≥30                   |                                   | 73.8 (66.8–80.9)                | 39.2 (38.8–39.9)                       | 54.8 (49.7–59.7)                       | 0.2 (0.2–0.3)            | 43.2 (39.4–47.8)               | 11.4 (9.1–15.1)           | 23.1 (19.5–27.4) |

Indeterminate results prioritized* when DNA PCR>1000 copies/mL

In first analysis, 15% of all infants with an initial nonnegative result (positive and indeterminate) receive a confirmatory test, regardless of Ct value or testing algorithm. In the priority confirmation analysis, 100% of infants with initial indeterminate results (and no infants with positive results) receive a confirmatory test, compared to an SoC scenario where the same number of infants receive confirmatory testing.

†Incremental outcomes are calculated for the Indeterminate Range algorithm relative to the SoC in which the same numbers of confirmatory tests were performed. Results have been rounded for presentation. Difference/ratio results are calculated before rounding.

ART, antiretroviral therapy; SoC, standard of care.
Sensitivity Analyses and Cost-Effectiveness Analysis

The most important drivers of the ratio of unnecessary ART averted to excess HIV deaths, as assessed by partial rank correlation, were the prevalence of HIV (PRCC = 0.84) and the proportion of test results from HIV-infected infants falling above the Indeterminate Range cutoff (PRCC = 0.82). In addition, ICER values were strongly correlated with the assumed lifetime cost of HIV care and life-expectancy of HIV-infected infants (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/B371 for more details). For further results detailing the impact of HIV prevalence, see Figure S3, Supplemental Digital Content, http://links.lww.com/QAI/B371.

Implementing an Indeterminate Range as described in the 15% confirmatory testing analysis (Ct cutoff of $33, HIV prevalence 2.5%) would result in an estimated $201,700 (95% UR: $165,200–$249,800) in cumulative savings compared with SoC, and prioritizing indeterminate results for confirmatory testing would result in $128,200 (95% UR: $103,600–$164,400) in savings (Table 3). Most incremental costs resulted from long-term ART, whereas most incremental DALYs reflected HIV-related mortality (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/B371). Lowering lifetime costs of ART among HIV-uninfected patients (eg, allowing patients to be lost to care) reduced the incremental savings of the Indeterminate Range scenario, thereby moderately reducing its cost-effectiveness (see Figure S7, Supplemental Digital Content, http://links.lww.com/QAI/B371). Assuming 15% of nonnegative results receive confirmatory testing, the ICERs of the Indeterminate Range relative to SoC ranged from $929 (95% UR: $1102–$793) per DALY (Ct $30) to $17,508 (2.5th percentile: $179,316) per DALY (Ct $36; Table 3 and see Figure S8, Supplemental Digital Content, http://links.lww.com/QAI/B371 for further details). In the scenario where all infants with indeterminate results are prioritized for confirmatory testing, the ICERs of the Indeterminate Range ranged from $2050 (95% UR: $2894–$1568) per DALY (Ct $30) to $9451 (95% UR: $32,983–$5010) per DALY (Ct $33). At Ct cutoffs above 33, fewer results are classified as indeterminate (and those which are indeterminate have a higher probability of being HIV-uninfected). Therefore, as the cutoff increases, the relative cost-effectiveness of the SoC decreases (Table 3).

DISCUSSION

This simplified decision model illustrates the tradeoffs associated with using semi-quantitative HIV testing results to define an Indeterminate Range for early infant HIV diagnosis. Our results suggest that the use of an Indeterminate Range...
will modestly increase the number of false-negative diagnoses. However, thoughtful, setting-specific selection of the criteria used to define indeterminate results can provide substantial economic savings while minimizing harmful health outcomes. For example, if indeterminate results are used to prioritize infants for confirmatory testing, such a policy can prevent 82 infants from receiving unnecessary lifelong ART for every additional death due to missed HIV.

These savings, if effectively repurposed, could result in even greater health gains for infants and other people living with HIV. This analysis was presented at a WHO Expert Group meeting; the WHO subsequently released recommendations that NAAT results with an indeterminate classification (at a Ct value of 33 or greater) should be repeat-tested using the same sample before result dispatch.

It is important to contextualize our results given the WHO recommendations. Our analysis simulates confirmatory testing (of a second, independent sample), whereas WHO recommends repeat-testing (of the same sample). While WHO recommends repeat-testing before dispatch from the lab, thus avoiding the need for clinicians to interpret indeterminate results, our analysis assumes that clinical decisions are informed by Ct values (including indeterminate results) while awaiting confirmatory testing. We did not evaluate repeat testing in this analysis, as there are currently no available data on the distributions of repeat test results to inform our model. If repeat testing generates similar results to confirmatory testing, then our results will be conservatively biased (favoring SoC), as we incorporated a time delay between initial and confirmatory testing.
that should not occur with repeat testing. However, if
repeat tests are more closely correlated with initial results
than confirmatory tests, the benefits of performing repeat
testing after an indeterminate result may be less than
projected here. Future empirical work can help quantify
this correlation, enabling more robust modeling of the
consequences of repeat testing.

We also provide data on the clinical consequences of
adopting Ct cutoffs other than the currently recommended
≥33. These results suggest that higher (more limited) Ct
cutoffs (eg, ≥35 or ≥36) classify fewer infants as indeter-
minate and thus minimize the number of infants misclassified
as false-negative—but at the expense of relatively smaller
gains in false-positive diagnoses averted. By contrast, lower
(more inclusive) Ct cutoffs (eg, ≥30 or ≥31) maximize the
number of infants who are appropriately diagnosed as HIV-
negative, but accordingly misclassify more infants who are
truly HIV-infected as indeterminate. For programs where
positive, but accordingly misclassify more infants who are
appropriately diagnosed as HIV-
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appropriately diagnosed as HIV-

This analysis also helps to operationalize the use of
semi-quantitative Ct results of HIV testing in infants, the
value of which has been suggested in earlier work. A recent
systematic review of 32 studies across 8 countries found that
16.5% of nonnegative PCR results were indeterminate (Ct
≥33) (see Luo et al, submitted with this manuscript). The
South African National Health Laboratory Service (NHLS)
has similarly documented that indeterminate results have
accounted for an increasing fraction of all nonnegative test
results since 2015,\textsuperscript{26} and NHLS has provided formal
clinical guidelines for the management of indeterminate
results since 2015,\textsuperscript{26} recommending 1–3 additional confirmatory
NAAT and/or viral load tests for infants receiving an
indeterminate result. Our results illustrate the potential utility
of Indeterminate Range policies in settings where confirma-
tory testing is not routinely available (or available only after
long delays).

The projections presented here depend importantly on
estimates for several key parameters. The most influential
determinant of the tradeoffs of an Indeterminate Range policy
was the prevalence of HIV among HIV-exposed infants—
a value that will vary greatly across settings. In addition, our
results were dependent on the proportion of nonnegative
results among HIV-uninfected infants falling in the Indeter-
minate Range. Our estimates for this parameter were
inferred from available data (see Luo et al). Should these
values vary substantially across populations or diagnostic
instruments, the tradeoff values at specific Ct cutoffs will shift
accordingly. The incremental cost-effectiveness of adopting
an Indeterminate Range is strongly driven by the cost of HIV
care for false-positive patients. If these costs are lower than

\begin{table}
\centering
\caption{Incremental Cost-Effectiveness of Indeterminate Range Algorithms}
\begin{tabular}{|c|c|c|c|c|}
\hline
Diagnostic & Total Costs\textsuperscript{†} & Total DALYs & Incremental Cost\textsuperscript{‡} of & Incremental DALYs of & ICER\textsuperscript{†} (Incremental Cost per
Algorithm & & & Indeterminate Range\textsuperscript{§} & Indeterminate Range\textsuperscript{§} & DALY per DALY)\textsuperscript{§} \\
\hline
15% confirmatory & & & & & \\
testing\textsuperscript{*} & & & & & \\
SoC & $2786 (2553–3021) & 14,661 (13,196–16,167) & — & 2.4 (1.0 to 5.9) & $175,508 (17,916 to 164,736) \\
≥36 & $2736 (2509–2965) & 14,663 (13,199–16,168) & $49 (65 to 38) & 21 (12 to 33) & $4717 (959 to 2961) \\
≥35 & $2684 (2462–2907) & 14,683 (13,220–16,185) & $101 (130 to 81) & 54 (35 to 76) & $2719 (4420 to 1911) \\
≥34 & $2637 (2420–2856) & 14,716 (13,255–16,218) & $147 (186 to 120) & 132 (97 to 176) & $1525 (2076 to 1188) \\
≥33 & $2582 (2368–2799) & 14,795 (13,337–16,297) & $202 (250 to 165) & 208 (160 to 268) & $1218 (1558 to 990) \\
≥32 & $2528 (2319–2743) & 14,873 (13,409–16,371) & $255 (311 to 209) & 308 (246 to 383) & $1030 (1256 to 863) \\
≥31 & $2466 (2257–2678) & 14,972 (13,516–16,472) & $318 (383 to 264) & 409 (339 to 491) & $929 (1102 to 793) \\
≥30 & $2402 (2201–2611) & 15,074 (13,616–16,568) & $381 (450 to 321) & 147 (181 to 123) & $1568 (17,916 to 164,736) \\
Indeterminate results prioritized\textsuperscript{*} & & & & & \\
≥36 & $2754 (2526–2985) & 14,656 (13,192–16,162) & $48 (65 to 37) & 5.2 (7.8 to 3.4) & Dominated\textsuperscript{†} \\
≥35 & $2708 (2484–2933) & 14,655 (13,191–16,160) & $90 (119 to 71) & 6.1 (11 to 2.4) & Dominated\textsuperscript{†} \\
≥34 & $2675 (2455–2896) & 14,659 (13,196–16,162) & $118 (154 to 94) & 23 (9.1 to 3.6) & Dominated\textsuperscript{†} \\
≥33 & $2659 (2441–2879) & 14,675 (13,212–16,177) & $128 (164 to 104) & 34 (42 to 23) & $9451 (32,983 to 5010) \\
≥32 & $2644 (2427–2864) & 14,690 (13,230–16,192) & $137 (173 to 112) & 29 (17 to 42) & $4686 (8936 to 3025) \\
≥31 & $2631 (2415–2849) & 14,712 (13,250–16,212) & $143 (178 to 118) & 50 (36 to 66) & $2835 (4410 to 2034) \\
≥30 & $2618 (2403–2836) & 14,734 (13,273–16,234) & $147 (181 to 123) & 72 (36 to 90) & $2050 (2894 to 1568) \\
\hline
\end{tabular}
\textsuperscript{*In first analysis, 15% of all infants with an initial nonnegative result (positive and indeterminate) receive a confirmatory test, regardless of Ct value or testing algorithm. In the priority confirmation analysis, 100% of infants with initial indeterminate results (and no infants with positive results) receive a confirmatory test, compared to an SoC scenario where the same number of infants receive confirmatory testing. \\
\textsuperscript{†}ICERs are presented in 2017 USD (in thousands). Negative values indicate the Indeterminate Range scenario is less costly than SoC. \\
\textsuperscript{‡}Results have been rounded for presentation. Difference/ratio results are calculated before rounding. \\
\textsuperscript{§}Results are accounted for an increasing fraction of all nonnegative test results since 2015,\textsuperscript{26} and NHLS has provided formal clinical guidelines for the management of indeterminate results since 2015,\textsuperscript{26} recommending 1–3 additional confirmatory NAAT and/or viral load tests for infants receiving an indeterminate result. Our results illustrate the potential utility of Indeterminate Range policies in settings where confirmatory testing is not routinely available (or available only after long delays). \\
\textsuperscript{¶}Total costs and incremental costs are presented in 2017 USD (in thousands). Negative values indicate the Indeterminate Range scenario is less costly than SoC. \\
\textsuperscript{‡}ICERs are presented in 2017 USD per DALY. Dominated values indicate that the Indeterminate Range policy was both less expensive and more effective (fewer DALYs) than SoC. \\
\textsuperscript{¶}Results have been rounded for presentation. Difference/ratio results are calculated before rounding.
\end{table}
projected—for example, if treatment costs fall (see, Table S1, Supplemental Digital Content, http://links.lww.com/QAI/B371) or retention in care is poor (see Figure S7, Supplemental Digital Content, http://links.lww.com/QAI/B371)—then adopting an Indeterminate Range may be less cost-effective. Because such future costs are difficult to estimate with precision, our primary analysis focuses instead on the numbers of infants affected.

Necessarily, this model simplifies many complexities of EID testing. For example, our model does not consider transmission after initial testing; although such transmission is expected to be similar under SoC and an Indeterminate Range, the SoC will result in more falsely-positive infants. These infants may receive (unintended) preventive benefits from ART, which may improve the cost-effectiveness of the SoC; however, we also omit social effects (eg, stigmatization of false-positive diagnoses) unfavorable toward the SoC. Our model assumes that all surviving, false-negative HIV-infected infants begin ART by age 2; although this is optimistic, we also incorporate high counterbalancing 2-year mortality risks (up to 57%) for untreated HIV. Finally, we simulated a hypothetical sub-Saharan setting to illustrate the utility of an Indeterminate Range algorithm where confirmatory testing is not widely available. This abstracted context will not represent any specific EID setting (especially those outside of sub-Saharan Africa), although we evaluate a variety of scenarios of transmission and confirmatory testing in our sensitivity analyses.

In conclusion, this decision model illustrates the trade-offs associated with adopting an Indeterminate Range for early infant HIV diagnosis, showing how such an algorithm can help to derive maximum benefit from incomplete diagnostic information. We demonstrate that, although optimal clinical outcomes are obtained by ensuring confirmatory testing for all HIV-exposed infants with nonnegative results (an approached previously projected to be cost-saving in South Africa), prioritizing infants with indeterminate results (high Ct values) for confirmatory tests is likely to improve diagnosis and save costs when confirmatory testing is not universally conducted. Importantly, the desirability of such a policy may depend on several key factors including the prevalence of HIV, the economic and human costs of unnecessary ART, and the willingness to pay of individual programs and stakeholders. These findings align with current WHO recommendations to perform repeat-testing on all samples with an indeterminate value (at a Ct threshold of 33 or greater) and may inform future WHO guidance as the epidemiology and management of early infant HIV diagnosis continue to evolve.

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