

A Randomized Trial of Point-of-Care Early Infant Human Immunodeficiency Virus (HIV) Diagnosis in Zambia

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Background. Point-of-care (POC) early infant diagnosis (EID) provides same-day results and the potential for immediate initiation of antiretroviral therapy (ART).

Methods. We conducted a pragmatic trial at 6 public clinics in Zambia. HIV-exposed infants were individually randomized to either (1) POC EID (onsite testing with the Alere q HIV-1/2 Detect) or (2) enhanced standard of care (SOC) EID (off-site testing at a public laboratory). Infants with HIV were referred for ART and followed for 12 months. Our primary outcome was defined as alive, in care, and virally suppressed at 12 months.

Results. Between March 2016 and November 2018, we randomized 4000 HIV-exposed infants to POC ($n = 1989$) or SOC ($n = 2011$). All but 2 infants in the POC group received same-day results, while the median time to result in the SOC group was 27 (interquartile range: 22–30) days. Eighty-one (2%; 95% confidence interval [CI]: 1.6–2.5%) infants were diagnosed with HIV. Although ART initiation was high, there were 15 (19%) deaths, 15 (19%) follow-up losses, and 31 (38%) virologic failures. By 12 months, only 20 of 81 (25%; 95% CI: 15–34%) infants with HIV were alive, in care, and virally suppressed: 13 (30%; 16–43%) infants in the POC group vs 7 (19%; 6–32%) in the SOC group (RR: 1.56; .7–3.50).

Conclusions. POC EID eliminated diagnostic delays and accelerated ART initiation but did not translate into definitive improvement in 12-month outcomes. In settings where centralized EID is well functioning, POC EID is unlikely to improve pediatric HIV outcomes.

Clinical Trials Registration NCT01682810.

Keywords. early infant diagnosis of HIV; point-of-care diagnosis; prevention of mother-to-child HIV transmission; pediatric HIV; low- and middle-income country.

Each year, an estimated 1.3 million newborns are exposed to human immunodeficiency virus (HIV)-1 through gestation, childbirth, and breastfeeding [1]. A massive global effort has expanded prevention of mother-to-child transmission (PMTCT) services, with nearly 90% of pregnant women with HIV estimated to have received antiretroviral drugs in 2019 [2]. Despite these efforts, PMTCT sometimes fails [3]. The course of HIV infection in newborns is often aggressive [4], and immediate antiretroviral therapy (ART) confers significant survival benefit [5]. For this reason, early infant HIV diagnosis (EID) is critical to the global AIDS response [6].

A virologic test is required for definitive HIV diagnosis in newborns. This is achieved by polymerase chain reaction (PCR) testing for HIV DNA or RNA—a technology best suited to centralized laboratories. While the assay costs associated with centralized testing can be lowered through economies of scale [7], this logistically complex approach may also introduce diagnostic delays [8]. It is not uncommon for children to die or become lost to follow-up while awaiting EID test results in low-resource settings across Africa [9].

The development of several new point-of-care (POC) diagnostics [10, 11] offers a promising alternative to centralized EID. Point-of-care EID has been promoted by policy makers as a solution to the well-recognized challenges of centralized testing [3, 12]. Several field studies have confirmed the accuracy and feasibility of POC EID testing [13–17] and 2 recently completed cluster-randomized trials conducted in Kenya, Mozambique, and Zimbabwe confirm that POC EID improves proximate indicators such as time-to-EID result and time-to-ART initiation [18, 19].

We investigated whether POC EID technology would improve 12-month clinical outcomes for infants with HIV in urban

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Zambia. We hypothesized that a POC strategy (with same-day results) would improve ART initiation rates and overall engagement in care. Our study is unique in its individually randomized, pragmatic design and its use of a clinically important primary outcome: alive, in care, and virologically suppressed at 12 months.

METHODS

Trial Design and Interventions

We conducted an unmasked, individually randomized, pragmatic trial of POC EID versus enhanced standard of care (SOC) EID at 6 public-sector health centers in Lusaka, Zambia. Detailed study procedures have been outlined in a prior publication [20]. Briefly, we identified HIV-exposed infants when they returned for postnatal care. We offered enrollment to HIV-exposed infants who were between 4 and 12 weeks old and whose parent/guardian was willing and able to provide informed consent. We excluded infants with medical conditions requiring management at a referral facility. Beginning with Protocol version 5.0 (15 August 2016), we also excluded multiple births.

Infants assigned to POC EID received same-day testing with Alere q HIV-1/2 Detect—a qualitative nucleic acid amplification test for the detection of HIV-1 (groups M/N and O) and HIV-2 (Abbott Laboratories; Abbott Park, IL, USA). We collected whole blood by heel-stick and transferred 25 μ L into the assay cartridge. The specimen was run in real time according to the manufacturer's specifications [21]. Additional heel-stick samples were collected on 2 Whatman 903 cards (GE Healthcare Bio-Sciences Corporation, Piscataway, NJ, USA) and archived.

Infants assigned to enhanced SOC had a heel-stick blood specimen applied to 2 Whatman 903 cards. One card was sent to a public laboratory, where the Roche COBAS AmpliPrep/TaqMan HIV-1 Qualitative Test v2.0 (Roche Molecular Diagnostics, Pleasanton, CA, USA) was used. The other card was archived. These participants were then given an appointment to return 4 weeks later to receive their EID result. Study staff monitored the return of results from the public laboratory. If 3 weeks elapsed without return of a result, we used the archived specimen to perform EID on the COBAS platform in a research laboratory as part of the trial's "safety net."

Infants with negative EID results were exited from the study once their parent/guardian had been notified of the result. Infants with positive EID results were referred for immediate initiation of ART and had a blood sample sent for confirmation of infection (using the Roche COBAS Qualitative Test). When the initial and confirmatory test results were discordant ($n = 2$), we performed a third blood draw and used those results as a tiebreaker.

We scheduled study visits to correspond to clinic visits and saw trial participants with HIV at months 3, 6, and 12. The trial provided plasma HIV viral load testing (Roche COBAS

AmpliPrep/TaqMan HIV-1 Test v2.0; Roche Molecular Diagnostics, Pleasanton, CA, USA) for all participants with HIV at 6 and 12 months. When infants did not attend a study visit, we made up to 3 attempts to contact their parent/guardian through phone calls and home visits.

Zambian national guidelines prescribe lopinavir/ritonavir-based regimens as first-line therapy for newborns with HIV and allow ART to be started while awaiting confirmatory EID results. Routine care involves monthly visits for the first year of life with adherence assessment at each visit. Laboratory monitoring, including HIV viral load testing, is recommended 3 times during the first year [22].

Separation of Trial Procedures From Clinical Activities

All trial sites had established programs for PMTCT and HIV treatment. Our pragmatic design [23, 24] deliberately separated study procedures from clinical care with the following exceptions: our study nurses performed HIV pre- and post-test counseling, drew the diagnostic sample, and communicated EID test results to families; they also managed confirmatory EID testing. Our patient navigators accompanied the families of infants with positive EID results to the ART clinic.

For infants with HIV, we communicated 6- and 12-month viral load results to the HIV treatment program. If virologic failure was diagnosed, we immediately referred the family for adherence counseling and scheduled a repeat viral load test 4 weeks later. All care decisions were made by the ART clinic teams.

Outcome Measures

The trial's primary outcome was defined as being alive, in care, and virally suppressed (plasma viral load <200 copies/mL) at 12 months. In accordance with international clinical guidelines, we defined virologic failure as plasma viral load of 200 copies/mL or greater. The trial's secondary outcomes included (1) the proportion of children with HIV who started ART within 6 months and (2) the proportion of children starting ART who remained in care at 12 months.

We also compared the time between initial diagnostic blood draw and the HIV test result becoming available to the facility and, separately, to the participant's parent/guardian. In an analysis restricted to the enhanced SOC group, we measured time-to-result with and without the trial EID safety net.

Sample Size

As described previously [20], the effect size estimate was derived from a simulation that considered ART initiation, retention in care, survival, and viral suppression. We hypothesized that POC EID would improve ART initiation from 40% to 80% and improve viral suppression at 12 months from 80% to 90%. From an analysis of pediatric HIV outcomes at the same clinics [22], we also estimated that 22% of children would

become lost to follow-up and that 6% would die by 12 months. When these estimates were applied as conditional probabilities, we anticipated 23% programmatic success in the control group and 52% programmatic success in the intervention group.

Our original design assumed 3% of eligible children would be HIV positive. We thus planned to randomize 2876 HIV-exposed infants and follow 86 infants with HIV (80% power; 2-sided $\alpha = .05$). However, over the 30 months of enrollment, the mother-to-child transmission rate declined from 3% to 1% (Supplementary Figure S1a and S1b). As a result, we obtained supplemental funding and expanded the trial to 4000 HIV-exposed infants (Protocol version 6.0; 31 January 2018).

Randomization and Masking

Infants were allocated to either POC EID or enhanced SOC EID using a complete randomization approach with 1:1 probability [25]. We generated separate randomization assignments for each of the sites using draws from the Bernoulli distribution with $P = .5$ in the R software environment (<https://www.r-project.org/>). Sequentially numbered, opaque, sealed envelopes were created by staff not involved with participant enrollment [26]. At the time of randomization, study staff opened the next numbered envelope to reveal allocation. Masking of either participants or providers was not deemed feasible.

Statistical Analysis

Infant outcomes were analyzed according to their assigned HIV testing strategy, and HIV infection status was ascertained for all randomized participants. Infants with an initial HIV-positive test result and in whom, due to death or follow-up loss, we were unable to perform a confirmatory test result ($n = 4$) were considered HIV positive. Statistical analyses were conducted using a 2-sided .05 significance level.

We treated the primary outcome (alive, in care, virally suppressed at 12 months) as a binomial proportion and compared its frequency between the randomized study groups using an estimated risk ratio (RR) and risk difference (RD) with corresponding 95% Wald confidence intervals (CIs). There were no missing data for this endpoint. The proportion of infants with HIV who remained alive and in care at 12 months was compared between groups using the same analytic approach as the primary analysis. ART initiation at 6 months (180 days) was compared between study groups using an RR and RD based upon a binomial proportion analysis. Infants who were lost to follow-up or died before 180 days without starting ART were counted as having not started ART.

We used a Kaplan-Meier approach to estimate the per-group probability of (1) the EID test result becoming available to the

facility, (2) the EID test result being received by the participant's parent/guardian, and (3) among infants with HIV, the probability of ART initiation. The corresponding 95% CI for each Kaplan-Meier estimate was computed using Greenwood's variance and a log-log transformation. Time-to-ART initiation was compared between groups using a log-rank test. A Kaplan-Meier approach was used to censor (or exclude) follow-up loss and estimate the RR for 1-year mortality; the corresponding 95% CI was computed using Greenwood's variance estimates of risk and a log-transformation. Second-born twins ($n = 3$) enrolled prior to Protocol version 5.0 were excluded from these analyses.

Data and Safety Monitoring Board and Interim Analysis

We convened a Data and Safety Monitoring Board (DSMB) comprising African investigators who reviewed trial progress and safety outcomes. Interim effectiveness analyses were conducted when 12-month primary endpoint data were available for ~50% and 75% of HIV-positive participants. A total of 5 DSMB reviews took place, including 3 reviews of effectiveness data. A Haybittle-Peto alpha spending approach [27] was used for interim effectiveness analyses (ie, 99.9% CIs), thus leaving $\alpha = .05$ for the final analysis.

RESULTS

Between March 2016 and November 2018, we approached the parents/guardians of 4100 infants deemed potentially eligible for participation (Figure 1). Of these, 91 did not meet inclusion criteria and 9 declined participation. A total of 4000 HIV-exposed infants were randomized: 1989 to POC and 2011 to enhanced SOC. Participants were a median age of 6.4 weeks old (range: 4.0–12.0 weeks), most of the children ($n = 3830$; 96%) were born to mothers who had received antiretrovirals, and most ($n = 3895$; 97%) had received infant prophylaxis (Table 1).

With the exception of 2 participants, infants assigned to POC EID received a same-day result. In the enhanced SOC group, the median time to the facility receiving a test result was 27 days (interquartile range [IQR]: 22–30 days) and the median time to a parent/guardian receiving the result was 32 days (IQR: 28–39 days) (Figure 2A and 2B). The majority of infants randomized to enhanced SOC EID relied upon the trial's diagnostic safety net. At 60 days postrandomization, the facility had received only 835 of 2009 (41.6%; 95% CI: 39.4–43.8%) test results from the public laboratory. This proportion was increased to 2005 of 2009 (99.8%; 95% CI: 99.5–99.9%) through the trial's safety net (Table 2). At 90 days postrandomization, the parent/guardian of all infants allocated to POC EID had received their child's HIV test result (100%; 95% CI: 99.8–100%), compared to 1882 of 2009 (97.6%; 95% CI: 96.1–98.6%) allocated to enhanced SOC (Table 3).

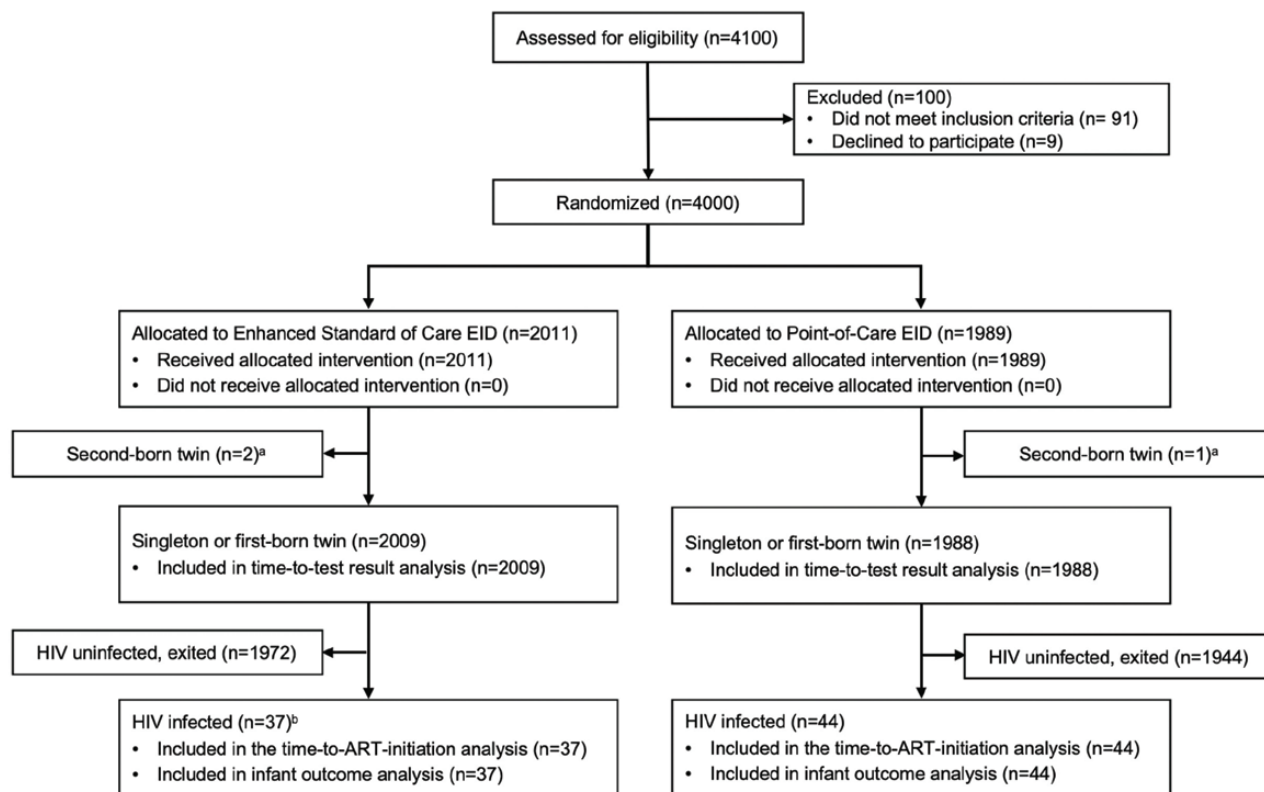


Figure 1. Participant flow diagram. ^aProtocol version 5.0 (15 August 2016) excluded twins and higher-order multiples; none of the 3 sets of twins randomized were HIV positive. ^bIncludes 2 infants who died and 2 infants who were lost to follow-up prior to confirmatory testing. Abbreviations: ART, antiretroviral therapy; EID, early infant diagnosis; HIV, human immunodeficiency virus.

A total of 81 infants (2.0%; 95% CI: 1.6–2.5%) were diagnosed with HIV (Supplementary Table 1), including 44 (2.2%) in the POC EID group and 37 (1.8%) in the enhanced SOC group (difference: .4%; 95% CI: –.5% to 1.2%). HIV status was confirmed with a second test in 77 infants, while 2 (both randomized to enhanced SOC) were lost to follow-up and 2 (both randomized to enhanced SOC) died prior to confirmatory testing. Antiretroviral therapy was successfully initiated within 180 days (Table 4) among 40 of 44 infants in the POC EID group (90.9%; 95% CI: 80.3–97.1%), compared to 30 of 37 infants in the enhanced SOC group (81.1%; 95% CI: 67.2–91.7%). Median time to ART initiation, was 0 days (IQR: 0–1.5 days) in the POC EID group, compared to 36 days (IQR: 28–47 days) in the enhanced SOC group (log-rank $P < .0001$; Figure 3).

Among the 81 infants with HIV, there were 15 deaths (19%), 15 follow-up losses (19%), and 31 virologic failures (38%) (Table 5). When follow-up losses were right-censored (or excluded), we observed lower mortality among infants randomized to POC EID compared with those randomized to enhanced SOC. However, our sample size was small, leading to imprecision in the strength of association (RR: .45; 95% CI: .17–1.18). This effect was muted when follow-up loss and death were combined. At 12 months, 51 infants with HIV (63%) were alive and in care: 30 of 44 (68%) in the POC EID group versus 21 of 37

(57%) infants in the enhanced SOC group (RR: 1.20; 95% CI: .85–1.70) (Figure 4, Table 5).

By 12 months, only 20 infants with HIV (25%; 95% CI: 16–34%) were alive, in care, and virally suppressed (Table 5). Considering this result by randomization group, 13 infants (30%; 95% CI: 16–43%) in the POC group versus 7 infants (19%; 95% CI: 6–32%) in the enhanced SOC group were alive, in care, and virally suppressed at 12 months (RR: 1.56; 95% CI: .7–3.50).

DISCUSSION

Prior studies have confirmed the accuracy and feasibility of POC EID testing [13–17], and 2 recent cluster-randomized trials have found POC EID to be highly beneficial in reducing time-to-EID result and time-to-ART initiation [18, 19]. However, randomized data on the clinical effectiveness of POC EID strategies are lacking. This pragmatic trial conducted in urban Zambia found that POC EID with the Alere q HIV-1/2 Detect assay improved the time-to-HIV diagnosis and time-to-ART initiation over an enhanced standard of care that bolstered offsite EID with a “safety net.” Despite these proximal indicators of EID success, POC EID did not translate into definitive clinical benefit. The trial’s primary endpoint (being alive, in care,

Table 1. Participant Characteristics at Randomization

	Enhanced SOC (n = 2011)	POC EID (n = 1989)
Infant sex, n (%)		
Male	1003 (50%)	1003 (50%)
Female	1008 (50%)	986 (50%)
Infant age, median (range), weeks		
	6.4 (4.0, 12.0)	6.4 (4.0, 12.0)
Gestational age at delivery, n (%)		
Term (≥ 37 weeks)	1904 (95%)	1865 (94%)
Preterm (< 37 weeks)	101 (5%)	123 (6%)
Missing or unknown	6 ($< 1\%$)	1 ($< 1\%$)
Birth weight, median (Q1, Q3), g		
	3000 (2700, 3300)	3000 (2700, 3300)
Birth weight < 2500 g, n (%)		
	218 (11%)	209 (11%)
Mode of delivery, n (%)		
Vaginal	1910 (95%)	1886 (95%)
Cesarean	97 (5%)	103 (5%)
Infant feeding at enrollment, n (%)		
Breast, exclusively	1901 (95%)	1854 (93%)
Formula	78 (4%)	95 (5%)
Mixed	32 (2%)	40 (2%)
Mother's age, median (Q1, Q3), years		
	29 (25, 34)	29 (25, 34)
Missing or unknown, n (%)	5 ($< 1\%$)	3 ($< 1\%$)
Father's age, median (Q1, Q3), years		
	35 (30, 40)	35 (30, 40)
Missing or unknown, n (%)	398 (20%)	375 (19%)
Mother's schooling, median (Q1, Q3), years		
	8 (6, 10)	9 (7, 11)
Missing or unknown, n (%)	27 (1%)	8 ($< 1\%$)
Father's schooling, median (Q1, Q3), years		
	12 (9, 12)	12 (9, 12)
Missing or unknown, n (%)	311 (15%)	294 (15%)
Mother's marital status, n (%)		
Married or cohabitating	1754 (87%)	1721 (87%)
Not married or cohabitating	254 (13%)	267 (13%)
Missing or unknown	3 ($< 1\%$)	1 ($< 1\%$)
Mother's parity, median (Q1, Q3)		
	3 (2, 4)	3 (2, 4)
Missing or unknown, n	3	3
Mother's living children, median (Q1, Q3)		
	3 (2, 4)	3 (2, 4)
Missing or unknown, n	3	3
Mother received ARVs for PMTCT, n (%)		
No	93 (5%)	76 (4%)
Yes ^a	1917 (95%)	1913 (96%)
Missing or unknown	1 ($< 1\%$)	0 (0%)
Infant received ARVs for PMTCT, n (%)		
No	58 (3%)	45 (2%)
Yes	1951 (97%)	1944 (98%)
Missing or unknown	2 ($< 1\%$)	0 (0%)

Abbreviations: ARV, antiretroviral; EID, early infant diagnosis; HIV, human immunodeficiency virus; PMTCT, prevention of mother-to-child HIV transmission; POC, point of care; Q, quartile; SOC, standard of care.

^aOne mother (whose infant tested HIV negative) received zidovudine monotherapy for PMTCT; all others received a 3-drug combination.

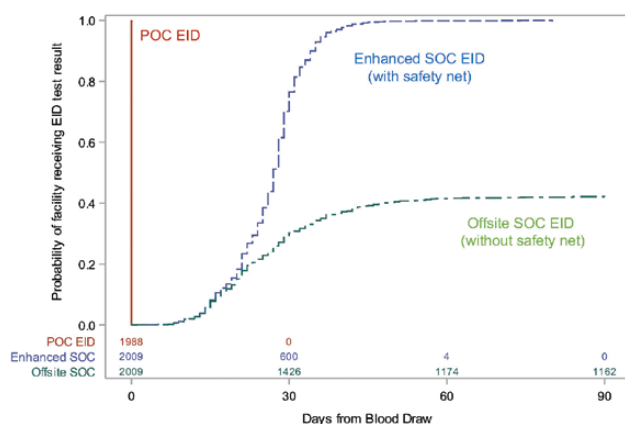
and virally suppressed at 12 months) was achieved in only one-quarter of participants. These findings suggest that, in settings where centralized EID is well functioning, POC EID is unlikely to improve long-term clinical outcomes among those who are HIV positive.

Our original sample size had to be expanded from 2876 to 4000 HIV-exposed infants over the course of the study, a testament to the success of the Lusaka District PMTCT program. Despite PMTCT program success, however, HIV treatment of newborns in our setting continues to be challenging. One-third of infants died or became lost to follow-up over the course

of the trial, similar to what we observed more than a decade ago in our initial study of infant treatment outcomes [22]. Additionally, among those participants who were retained at 12 months, fewer than half achieved viral suppression.

Much work is needed to strengthen support for adherence and disclosure in pediatric HIV care settings in Zambia. One practical way to support adherence would be through child-friendly ART formulations, making it easier to administer ART to very young children [28]. Our findings also highlight the need to improve retention in care. Attrition likely results from multilevel barriers to HIV care. Greater investment to fully

A: Time to facility receiving EID test result^a



B: Time to parent or guardian receiving EID test result

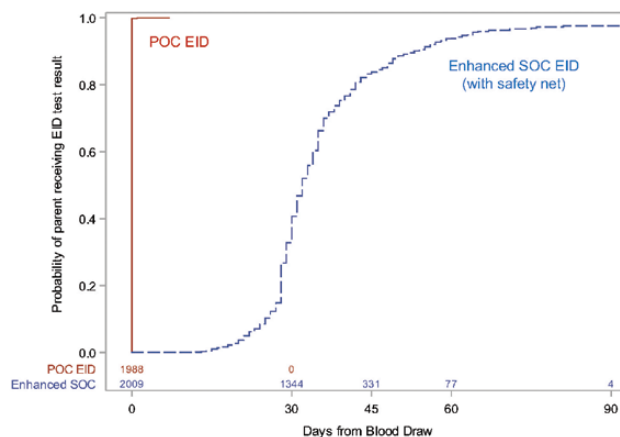


Figure 2. Time to result by randomization group. ^aThe enhanced SOC (blue line) and offsite SOC without safety net (green line) represent time-to-result for the same infants (those randomized to enhanced SOC). Follow-up time for the offsite SOC without safety net (green line) was censored at 90 days after the initial blood draw. Abbreviations: EID, early infant diagnosis; POC, point of care; SOC, standard of care.

Table 2. Probability of Facility Receiving EID Test Result

	Total Infants	Within 30 Days		Within 60 Days	
		Received Result	Estimate (95% CI) ^a	Received Result	Estimate (95% CI) ^a
SOC (without safety net) ^b	2009	607	30.2% (28.3%, 32.3%)	835	41.6% (39.4%, 43.8%)
Enhanced SOC	2009	1536	76.5% (74.6%, 78.3%)	2005	99.8% (99.5%, 99.9%)
POC EID ^c	1988	1988	100.0% (99.8%, 100.0%)	1988	100.0% (99.8%, 100.0%)

Abbreviations: CI, confidence interval; EID, early infant diagnosis; POC, point of care; SOC, standard of care.

^aKaplan-Meier estimate with corresponding 95% CI computed using Greenwood's variance and a log-log transformation.

^bSOC without safety net is presented for illustrative purposes to demonstrate expected time-to-result in the absence of the safety net provided by the trial. This group contains the same infants as the enhanced SOC group.

^cExact Clopper-Pearson 95% CIs are reported because all infants in the POC EID group received an EID test result.

Table 3. Probability of Parent or Guardian Being Informed of EID Test Result

	Total Infants	Within 45 Days		Within 90 Days	
		Received Result	Estimate (95% CI) ^a	Received Result	Estimate (95% CI) ^a
Enhanced SOC	2009	1676	83.8% (82.1%, 85.3%)	1882	97.6% (96.1%, 98.6%)
POC EID ^b	1988	1988	100.0% (99.8%, 100.0%)	1988	100.0% (99.8%, 100.0%)

Abbreviations: CI, confidence interval; EID, early infant diagnosis; POC, point of care; SOC, standard of care.

^aKaplan-Meier estimate with corresponding 95% CI computed using Greenwood's variance and a log-log transformation.

^bExact Clopper-Pearson 95% CIs are reported because all parents/guardians in the POC EID group were informed of the EID test result.

Table 4. Probability of Starting Antiretroviral Therapy Among Infants With HIV

	Total Infants	Within 30 days		Within 60 days		Within 180 days ^b	
		Initiated ART	Estimate (95% CI) ^a	Initiated ART	Estimate (95% CI) ^a	Initiated ART	Estimate (95% CI) ^a
Enhanced SOC EID	37	13	35.1% (22.1%, 52.7%)	29	78.4% (64.2%, 89.8%)	30	81.1% (67.2%, 91.7%)
POC EID	44	39	88.6% (77.4%, 95.8%)	39	88.6% (77.4%, 95.8%)	40	90.9% (80.3%, 97.1%)

Abbreviations: ART, antiretroviral therapy; EID, early infant diagnosis; HIV, human immunodeficiency virus; POC, point of care; SOC, standard of care.

^aKaplan-Meier estimate with corresponding CI computed using Greenwood's variance estimate and the log-log transformation. Infants who died or were lost to follow-up were categorized as not having started ART. No infants were right-censored, in which case the Kaplan-Meier approach is equivalent to an empirical distribution function.

^bPlanned secondary endpoint at 180 days.

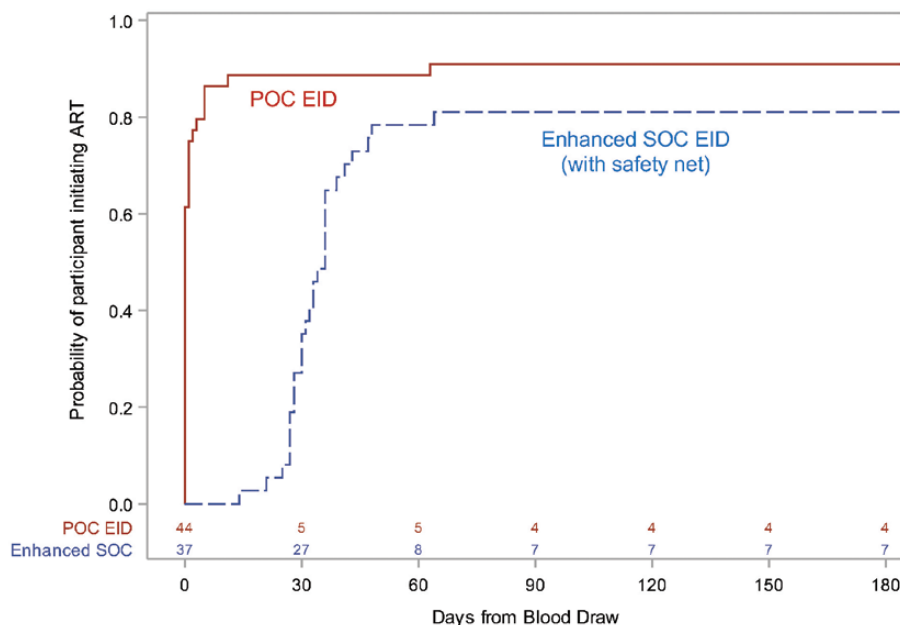


Figure 3. Time-to-ART initiation among infants with HIV. Infants who died or were lost to follow-up remained in the denominator for this analysis. The numbers below the cumulative probability curves represent the number of infants at risk (ie, those infants with HIV who had not yet initiated ART). Abbreviations: ART, antiretroviral therapy; EID, early infant diagnosis; HIV, human immunodeficiency virus; POC, point of care; SOC, standard of care.

understand and address these barriers in the clinical, pharmacy, and laboratory systems is urgently needed. Innovative interventions that address stigma should also be prioritized, as stigma continues to be a key driver of HIV treatment outcomes [29].

Strengths of this study include its randomized, pragmatic design and its clinical effectiveness endpoint. In addition to reporting proximal outcomes (time-to-HIV diagnosis and time-to-ART initiation), we also report a composite primary outcome (alive, in care, and virally suppressed) that can inform local and regional policy.

We also note several important limitations. Although we enrolled a large number of HIV-exposed infants in this study, the majority were not infected at the 6-week EID visit. Our primary analysis depended upon the outcomes of a subgroup of children with HIV (n = 81). Thus, our power to detect modest differences in the 12-month outcomes between the 2

EID strategies was limited by lower-than-expected numbers of HIV infections. Additionally, we did not collect qualitative data as part of this trial, limiting our insight into barriers to treatment and adherence. We were also unable to assess either the potential contribution of drug resistance to poor outcomes in infants with HIV or to follow uninfected infants to determine the risk of adverse clinical and developmental outcomes.

We were compelled by the principle of equipoise to provide a safety net to ensure that all infants enrolled in our trial received an EID result within 4 weeks. As a result, we could not directly compare the clinical effectiveness of POC EID with the extant SOC EID program in Lusaka. As most infants relied on the trial's safety, our findings suggest that focused investment to improve existing centralized systems may yield similar programmatic benefit as POC EID. Hybrid implementation models [30] in which POC platforms are used to expand EID access

Table 5. Probability of Death, Follow-up Loss, and Failure to Achieve Viral Suppression Among Infants With HIV

Status	Total, n (%)	Enhanced SOC EID, n (%)	POC EID, n (%)	PValue ^a	Risk Difference (95% CI)	Risk Ratio (95% CI)
HIV positive at enrollment	81	37	44	–	–	–
Known to have died	15 (18.5%)	10 (27.0%)	5 (11.4%)	–	–	–
Lost to follow-up	15 (18.5%)	6 (16.2%)	9 (20.5%)	–	–	–
Alive and in care at month 12	51 (63.0%)	21 (56.8%)	30 (68.2%)	.2888	11.4% (–9.7%, 32.5%)	1.20 (.85, 1.70)
HIV RNA <200 copies/mL at month 12 ^b	20 (39.2%)	7 (33.3%)	13 (43.3%)	.4716	10.0% (–16.9%, 36.9%)	1.30 (.63, 2.70)
Alive, in care, suppressed at month 12 ^c	20 (24.7%)	7 (18.9%)	13 (29.5%)	.2692	10.6% (–7.8%, 29.1%)	1.56 (.70, 3.50)

Abbreviations: EID, early infant diagnosis; HIV, human immunodeficiency virus; POC, point of care; SOC, standard of care.

^aChi-square tests of proportion.

^bDenominator for virologic suppression is those alive and in care at 12 months.

^cPrimary endpoint.

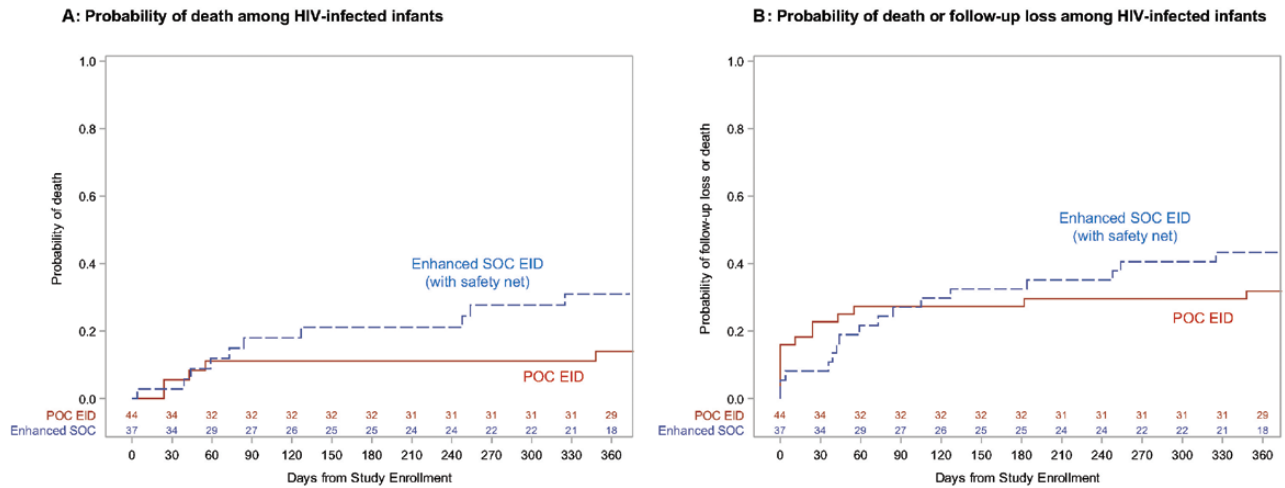


Figure 4. Probability of death and follow-up loss among infants with HIV. The numbers below the cumulative probability curves represent the number of infants at risk. In panel A, follow-up is right-censored at the last study-related contact for each infant; and in panel B, follow-up loss is counted as an event. Abbreviations: EID, early infant diagnosis; HIV, human immunodeficiency virus; POC, point of care; SOC, standard of care.

in hard-to-reach areas while simultaneously strengthening existing centralized EID systems should also be evaluated.

In conclusion, POC EID is accurate, feasible, and improves proximate indicators such as time-to-ART initiation by providing same-day HIV test results. However, in settings where centralized EID is well functioning, POC EID is unlikely to improve pediatric HIV outcomes. Zambia is among only 5 Joint United Nations Program on HIV and AIDS (UNAIDS) focus countries to have achieved 95% coverage of PMTCT services [3], yet much work is needed to ensure that those infants who do become infected with HIV remain healthy and achieve viral suppression. As policy makers decide whether POC technologies are appropriate for implementation in specific settings, they should carefully weigh the costs and benefits of these new technologies against a commensurate investment in improving pediatric HIV care and treatment outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. C. J. C. and J. S. A. S. conceived and designed the trial and drafted the manuscript and coordinated edits. C. J. C., C. E. F., M. L., F. M., R. L., E. M., and H. M. participated in participant recruitment and data collection. K. R. M., P. T. S., and A. G. A. analyzed the data. All authors provided critical input during development of the manuscript.

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Ethics statement. Ethical approval for the trial was granted by the University of Zambia Biomedical Research Ethics Committee (BREC Ref:

010-02-13), the Zambian Ministry of Health, and the University of North Carolina at Chapel Hill Institutional Review Board (IRB Number: 12-1346). Participation in the trial was voluntary. Trained study personnel approached parents/guardians of potential participants, described the study, and obtained written informed consent prior to study enrollment.

Prior presentation. The primary results of this trial were presented at the 2020 Conference on Retroviruses and Opportunistic Infections (CROI), Boston, Massachusetts; 11 March 2020; Oral Abstract #133.

Data sharing. A de-identified copy of the dataset underpinning these analyses will be made available in the public domain prior to publication.

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