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Klinikum der Ludwig-Maximilians-Universität München

Costs and cost-effectiveness of neonatal HIV early infant diagnosis (EID) versus standard of care EID in Mozambique and Tanzania

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.)
an der Medizinischen Fakultät
der Ludwig-Maximilians-Universität München

vorgelegt von
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aus
Roseville / USA

Jahr
2024

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

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Tag der mündlichen Prüfung: 06.12.2024

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Abstract

Introduction: Prompt and affordable access to early infant diagnosis (EID) for HIV is critical, especially for neonates acquiring HIV during gestation for whom mortality in the first months of life is high without treatment. Late diagnosis causes delays in access to lifesaving antiretroviral treatment. Point-of-care (PoC) testing at birth offers an opportunity for same-day treatment initiation at the earliest time possible. However, accurate cost data is needed for planning scale-up and assessing sustainability of EID programs.

Methods: We estimated the health system cost of birth plus 4–6-week testing (very early infant diagnosis; VEID) compared to standard of care (SoC) HIV testing at 4-6 weeks only, both with immediate linkage to treatment. This cost and cost-effectiveness study was nested within the cluster-randomized LIFE study conducted at 28 primary health facilities and evaluated costs of using the Abbott mPIMA™ in Mozambique and Cepheid GeneXpert® in Tanzania for HIV testing. We report empirical costs in the LIFE study and additionally simulate integrated and EID program costs scaled to routine demand for EID.

Results: The estimated cost per test in the LIFE study was $39.12 (95% CI: $37.69, $39.99) for VEID versus $40.57 ($40.57, $42.84) for SoC in Mozambique and $36.23 ($34.99, $38.40) for VEID versus $43.88 ($41.12, $45.21) for SoC in Tanzania. Estimated cost per HIV-exposed infant tested and initiated on ART were $85.44 ($84.17, $87.64) for VEID versus $37.05 ($36.47, $38.51) for SoC in Mozambique and $68.34 ($67.15, $71.99) for VEID versus $37.38 ($35.31, $38.82) for SoC in Tanzania. Neonates tested at birth started ART at median 0.86 weeks of age compared to 4.71 weeks of age receiving SoC procedures ($p<0.0001$). Scaling costs to current routine demand for EID reduced the test cost by up to 28% in Mozambique and up to 14% in Tanzania. Utilization of PoC platforms varied across time and health facility, with many sites exhibiting potential to increase efficiency and reduce equipment costs by increasing utilization.

Conclusion: Birth testing is more expensive but results in more frequent and significantly earlier ART initiation. When considering placement of limited PoC analyzers and scale-up of EID programs, alternative solutions that increase efficiency of PoC analyzers such as multiplexing for cost-sharing across programs or increasing access to PoC testing through hub-and-spoke service delivery should be explored.

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ABC	Abacavir
ART	Antiretroviral treatment
AZT	Zidovudine
BCA	Bias-adjusted and accelerated
CCR	Child at risk clinic
CHAI	Clinton Health Access Initiative
CI	Confidence interval
CRT	Cluster-randomized trial
DBS	Dried blood spot
EID	Early infant (HIV) diagnosis
GDP	Gross domestic product
HIV	Human immunodeficiency virus
ICER	Incremental cost effectiveness ratio
ISO	International Organization for Standardization
LPV/r	Lopinavir/ritonavir
MoH	Ministry of Health
NAT	Nucleic acid testing
NVP	Nevirapine
PCR	Polymerase chain reaction
PoC	Point-of-care
PMTCT	Prevention of mother-to-child (HIV) transmission
RCH	Reproductive and child health
SoC	Standard of care
TB	Tuberculosis
VEID	Very early infant (HIV) diagnosis
VT	Vertical transmission
US$	United States dollar
WHO	World Health Organization
3TC	Lamivudine

1. Introduction

1.1 HIV burden affecting infants and children

The need for scalable and cost-effective human immunodeficiency virus (HIV) prevention, detection, and care in children remains high with roughly 1.3 million mothers living with HIV giving birth each year globally[1]. Despite notable increases in access to prevention of mother-to-child transmission (PMTCT) health services, including widespread coverage of lifelong ART for pregnant women living with HIV (known as Option B+), progress towards eliminating new HIV infections among children has stalled. In 2022, an estimated 1.5 million children aged 0-14 years were living with HIV and 130,000 newly acquired HIV, the majority through vertical transmission during gestation, birth, or breastfeeding. Of these new infections, over 90% occurred in the African region, with approximately 58,000 (45%) in eastern and southern Africa, the region historically most impacted by HIV.

Particularly for infants acquiring HIV during gestation and birth, HIV disease progresses rapidly. Without access to treatment, roughly a third of HIV-positive infants die in the first year of life and half before two years of age[2]. A peak of mortality occurs around 2-3 months of age[3]. In 2022, roughly 84,000 children living with HIV died, 35,000 (42%) in eastern and southern Africa[1]. Early access to antiretroviral treatment (ART) can reduce mortality substantially, with the greatest benefit seen in the first six months of life[4, 5].

Timely identification of HIV-positive infants is critical to the pediatric HIV response, with late diagnosis and poor linkage to care leading to delays in access to lifesaving ART. The World Health Organization (WHO) recommends that all infants born to mothers living with HIV receive an early infant diagnosis (EID) test in the first two months of life with immediate initiation of ART for positive infants[6]. However, in 2022, only 68% of HIV-exposed infants were tested in the first two months of life, and only 64% of children aged 0-14 years living with HIV in eastern and southern Africa were on treatment[1] (**Figure 1**).

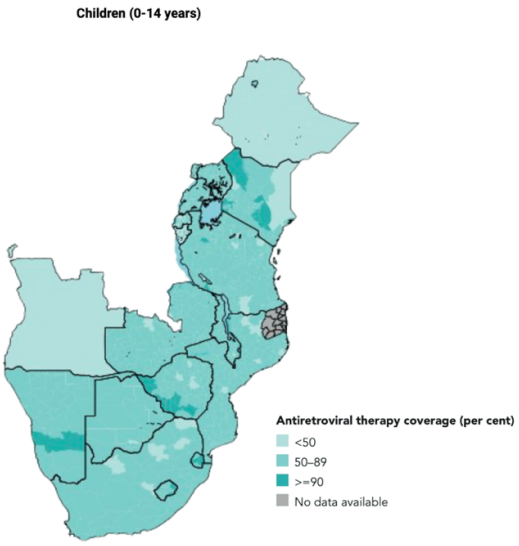

Figure 1: Antiretroviral treatment coverage among children (0-14 years), subnational levels, eastern and southern Africa, 2022. Source: UNAIDS epidemiological estimates, 2023.

1.2 Early infant HIV diagnosis and linkage to treatment

Due to the persistent presence of maternal antibodies during early life, diagnosis of HIV in infants requires a virologic test using nucleic acid testing (NAT) technologies. WHO guidelines recommend NAT for all infants at risk of acquiring HIV at 4-6 weeks and nine months of age and a non-virologic test (i.e., HIV antibody) at 18 months of age or three months after the cessation of breastfeeding, whichever is later[6]. The guidelines also recommend that all HIV-exposed infants receive post-natal HIV prophylactic treatment, either nevirapine (NVP) for six weeks after birth or NVP for 6-12 weeks plus zidovudine (AZT) for six weeks after birth (enhanced post-natal prophylaxis). Positive HIV test results should be confirmed with a second NAT, but ART should be initiated immediately upon a first positive result while awaiting confirmatory results. Recommended ART regimens prior to 2022 included AZT, lamivudine (3TC), and NVP syrups and abacavir (ABC)/3TC dispersible tables plus lopinavir/ritonavir (LPV/r) granules once the infant reached four weeks of age and weighed at least 3kg. LPV/r granules have since been replaced by dolutegravir dispersible tablets for infants at least four weeks of age and 3kg as the recommended first treatment option[7, 8].

Conventional EID program structures typically centralize NAT in referral laboratories, which requires specialized equipment and personnel as well as coordination across multiple sections of the health system. Bottlenecks enroute to appropriate treatment can arise from a lack of supplies or trained staff at the health facility, the need for sample transport across sometimes long distances, a lack of testing reagents or qualified personnel at the central laboratory, inadequate communication of results back to health facilities, delays or gaps in communication of results to the caregiver, and poor linkage to follow-up care[9] (**Figure 2**). The need for significant equipment and human resources and for caregivers to return to the health facility with their infant(s) multiple times reduces access to EID services, especially in resource-poor, often rural settings.

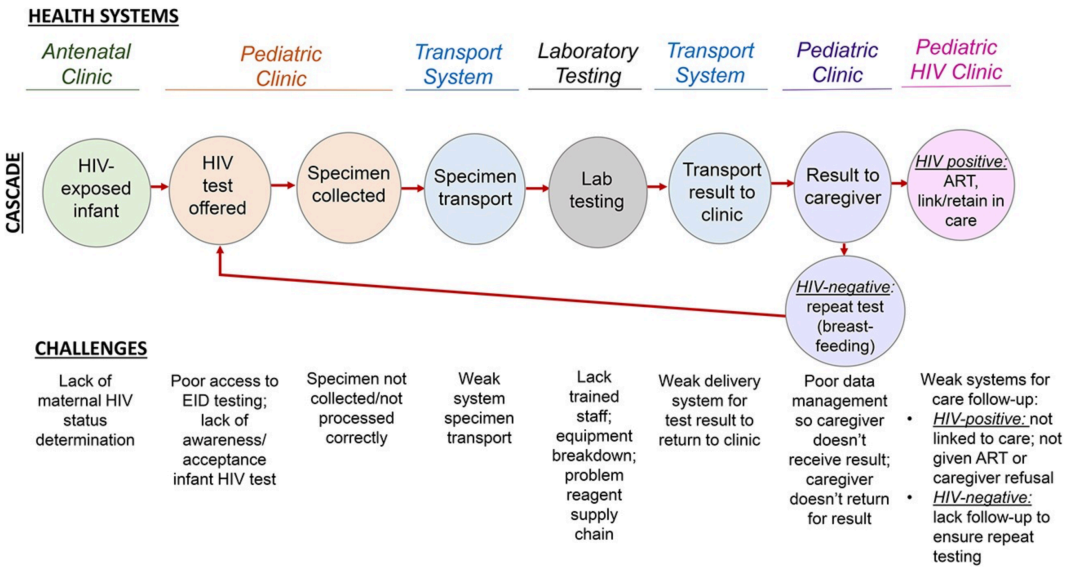

Figure 2: Early infant HIV diagnosis and treatment cascade involved health systems and challenges. Source: Challenges in the Early Infant HIV Diagnosis and Treatment Cascade. JAIDS Journal of Acquired Immune Deficiency Syndromes 84:S1-S4, July 1, 2020.

There has been substantial investment in strengthening sample transfer networks, central laboratory capacity, and communication systems. Still, the logistically complex, multi-step approach of referral laboratory-based EID can result in long turnaround times from sample collection to result dissemination and frequent loss to follow-up before completion of EID procedures and care. This leads to delays in ART initiation among HIV-positive infants, often after the peak of mortality. A systematic review of referral laboratory-based EID found that the mean turnaround time from sample collection to receipt of results by the caregiver was 45 days and mean age at treatment initiation was about seven months[10]. Across 92 studies in low- and middle-income countries, attrition from EID services (due to loss to follow-up or death) was 25% at two months of age and 39% at 18 months of age, with higher attrition observed in rural areas[11]. Among infants living with HIV, 15% died between testing and treatment initiation[10].

1.2.1 HIV testing and linkage to treatment at birth

EID services are often bundled within PMTCT programs, with access to EID limited to infants whose mothers are retained in these programs or presenting to the health system with symptoms warranting an HIV test. However, mothers who receive only some or no PMTCT interventions generally have higher HIV transmission risk compared to those fully engaged with PMTCT services[12], contributing to the gaps in EID and ART coverage among infants and children. Although the uptake of facility-based delivery varies widely by region and individual characteristics of the mother, in southern and eastern African countries, a majority of women deliver in health facility settings[13]. Testing for HIV at birth offers potential for better population coverage of EID and is the earliest possible timepoint to identify and initiate treatment in the most vulnerable HIV-exposed infants. Immediate linkage to ART in the first weeks of life has the potential to reduce early mortality and morbidity, prevent or lessen the development of long-lasting viral reservoirs, and improve virologic control[4, 14-17]. In South Africa, the introduction of routine birth testing in 2016 resulted in lower pre-treatment viral load and less loss to follow-up[18].

Only a few sub-Saharan African countries have implemented HIV testing of exposed neonates at birth into routine practice, partially due to a lack of experience but also due to uncertainty around affordability and cost-effectiveness. The WHO conditionally recommends birth testing only after optimizing 6-week EID programs[6], as vertical transmissions occurring very late in pregnancy or around delivery can only be detected several weeks later. A modelling study examining survival and life expectancy for various scenarios of test timing and frequency suggests that testing at birth and six weeks of age improves survival compared to testing only at six weeks of age and is cost-effective. Among HIV-positive infants, 1-year survival increased from 74.9% to 76.6% with an incremental cost-effectiveness ratio (ICER) of $2,900 per year of life saved, which was less than the 50% of per capita gross domestic product (GDP) used as a willingness to pay threshold[19]. In countries with high coverage of PMTCT interventions and low intrauterine transmission rates, targeted testing of infants at high risk of HIV acquisition (e.g., maternal HIV infection or ART initiation late in pregnancy or poor maternal virologic control) at birth combined with standard 6-week testing may be a better use of resources economically, but is highly dependent on prompt linkage to ART and the degree to which ART improves long-term clinical outcomes[20].

1.2.2 Point-of-care early infant HIV diagnosis

Point-of-care (PoC) testing for EID, increasingly available in sub-Saharan Africa and strongly supported by the WHO, has decreased turnaround times to communication of results and treatment initiation by streamlining EID and linkage to care processes[6, 21-24]. PoC EID testing does not require extensive infrastructure and can be accurately performed by nurses in primary healthcare settings without extensive training, improving access to EID services in high HIV-burden, remote locations[25, 26]. Across seven studies of same-day PoC EID, median turnaround time from sample collection to the communication of results to the caregiver was reduced from 35 days using laboratory-based testing to 0 days with PoC testing in the same setting. Time from sample collection to ART initiation decreased from 40 to 0 days, and the proportion of infants initiating ART within 60 days of diagnosis increased from 52% to 90%[21]. Compared to HIV-positive infants who received laboratory-based EID, no significant decrease in 12-month mortality was observed among PoC-tested HIV-positive infants in Zambia, however, only about a quarter of infants were alive and retained in care at the end of follow-up[27]. In Mozambique, HIV-positive infants who received PoC EID had a higher likelihood of being retained in care after 90 days compared with HIV-positive infants receiving referral laboratory-based EID[28].

Costs of PoC EID tests range from $21.46 to $51.80 compared to $16.21 to $42.73 for laboratory tests, with substantial variability in the services included in these cost estimates[29]. In several model-based analyses of 6-week testing, PoC EID has been demonstrated to be cost-effective compared to referral laboratory-based EID[30-33]. In Zimbabwe, 1-year survival among HIV-positive infants increased from 69.0% to 78.0% with PoC EID compared to laboratory-based testing, with the greatest gains seen in the first 12 weeks of life in one study[32] and 67% to 76% in a similar study using the same modelling approach[30]. In Zambia, ART initiation within 60 days of diagnosis increased from 28% to 81% and was cost-saving[31].

1.3 Scale-up of early infant HIV diagnosis programs and the need for empirical cost and cost-effectiveness analyses

Birth testing has the potential to identify infants with HIV in the first days of life and increase uptake of EID by offering HIV testing at a point of service where a majority of mothers may be in contact with the health system. PoC testing has potential for same-day treatment initiation and improving retention in care. Combining birth testing and PoC technology may greatly improve progress toward reducing early HIV-related mortality among children but requires adding PoC EID infrastructure at another service delivery point (i.e., maternity wards) and ensuring that age- and weight-appropriate ART formulations are available to avoid delays in treatment initiation. To sustain health benefits, scale-up of EID programs will additionally need to consider interventions to strengthen long-term retention of infants in care and improve ART adherence for better virologic control[34].

Realistic cost estimates for PoC EID are urgently needed for planning and optimizing scale-up of EID programs in high HIV burden low-and-middle income countries. There is a lack of empirical cost data, especially in resource-poor, rural primary healthcare settings where effective EID programs are most needed. In the context of implementing

interventions in routine practice under budget constraints, health economic analysis is increasingly important for health care decision-making which ultimately aims to increase access to and optimize health care. There is only one model-based cost-effectiveness analysis of birth testing to data, and the majority of cost-effectiveness evidence for PoC EID versus laboratory-based EID is based on mathematical modelling studies with inherent limitations due to limited long-term health outcome data for HIV-positive children, model structure, and necessary assumptions[33]. Together with the substantial evidence supporting accuracy, feasibility, and acceptability of birth and PoC EID, empirical cost-effectiveness data can drive program-level implementation of PoC EID to increase coverage of neonatal HIV diagnosis in high-burden settings.

1.4 Objectives

This study used implementation data collected in field conditions to estimate the costs and health benefit of public (i.e., ministry of health; MoH), primary healthcare facilities offering one of two PoC EID approaches to all infants born to mothers living with HIV: (1) PoC EID and immediate linkage to ART at birth and 4-6 weeks of age (very early infant diagnosis; VEID) and (2) PoC EID and immediate linkage to ART at 4-6 weeks of age only (standard of care; SoC). The overarching study aim was to provide health economic information to inform public health decision-making on the current feasibility and sustainability of expanding PoC EID programs. Specific aims were (1) to compare empirical costs and cost-effectiveness of the two PoC EID approaches using probability of ART initiation and age at ART initiation as indicators of clinical effectiveness in the context of the LIFE cluster-randomized trial (CRT); (2) to evaluate the effect of PoC platform utilization in rural, primary healthcare facilities on costs and cost fluctuation; (3) to simulate costs for the two PoC EID approaches based on routine demand for EID and shared PoC platform use across health programs; and (4) to simulate EID program costs only across a broad range of demand for EID for the two PoC EID approaches to improve generalizability and provide information for decision makers to optimize the utilization of PoC testing platforms. The aims were evaluated separately for each of the two countries participating in the LIFE CRT, i.e., Mozambique and Tanzania. As different PoC testing platforms were used in each of the two countries, an indirect comparison of costs and cost-effectiveness for mPIMA™ (Abbott) versus GeneXpert® (Cepheid) platforms was additionally possible.

2. Material and Methods

2.1 Study context

The LIFE CEA project was nested within the LIFE study (NCT04032522), a longitudinal CRT which enrolled and followed 6505 mothers living with HIV and their 6602 infants at 28 primary health facilities in Mozambique and Tanzania (14 health facilities per country) between 2019 and 2023. A total of 125 (1.89%) infants were diagnosed with HIV by 16 weeks of age. The primary objective of the LIFE CRT was to evaluate the 18-month clinical benefit (e.g., mortality, morbidity, retention in care) of PoC testing with immediate linkage to ART beginning at birth compared to the SoC of HIV testing and linkage to ART at 4-6 weeks of age among HIV-positive infants. Mothers were recruited at the time of delivery if they were at least 18 years of age, were documented to be living with HIV, had delivered less than 72 hours prior to study enrollment, provided written informed consent for themselves and their neonate(s) to participate in the study, and agreed to telephone and home contact tracing. Stillbirths and neonates with severe malformations or presenting with a medical emergency were excluded.

Ethical approvals for the LIFE CRT and therefore the LIFE CEA project were obtained from the ethics committee of the Ludwig Maximilians University Hospital (LMU Klinikum) in Germany and the local and national ethics committees at the study sites in Mozambique and Tanzania: Comité Institucional de Bioética para a Saúde do INS (CIBS-INS) and Comité Nacional de Bioética em Saúde (CNBS) in Mozambique and the Mbeya Medical Research and Ethics Committee (MMREC) and the Medical Research Coordinating Committee of the National Institute for Medical Research (NIMR) in Tanzania.

2.1.1 Geographic location and population characteristics of study sites

The LIFE study took place in the Sofala and Manica provinces of central Mozambique and the Mbeya and Songwe regions of southwestern Tanzania. Health facilities were selected for study participation based on annual numbers of HIV-positive deliveries, vertical HIV transmission rates, availability of infant antiretroviral drugs, availability of laboratory and other infrastructure needed for the CRT, and affiliation to a pediatric HIV care clinic. Randomization was stratified by country and the annual number of HIV-positive deliveries in the year prior to study recruitment (2018), classified as low versus high volume health facilities. The majority (79%) of health facilities in Mozambique were considered urban or semi-urban, whereas the majority (79%) of the health facilities in Tanzania were considered rural. A map of the study sites is shown in **Figure 3**.

In Mozambique, approximately 93% of pregnant women living with HIV had access to ART through PMTCT services in 2022[1]. The vertical transmission rate, including during the breastfeeding period, was estimated at 10.4%[35]. Evidence from southern Mozambique suggests that a large proportion of vertical transmissions result from acute HIV-infection in pregnancy and the post-partum period[36], diminishing the effect of high population ART coverage during pregnancy for preventing vertical transmission. Approximately 13,000 new HIV infections among children aged 0-14 were recorded in 2022[1].

In Tanzania, an estimated 92% of pregnant women living with HIV had access to ART in 2022[1]. Vertical transmission was approximately 6.9%, with the Mbeya region reporting substantially higher transmission rates in previous years[37]. Country-wide, an estimated 79% of neonates born to mothers living with HIV received EID testing and 5,200 new HIV infections were recorded among children aged 0-14 years in 2022[1].

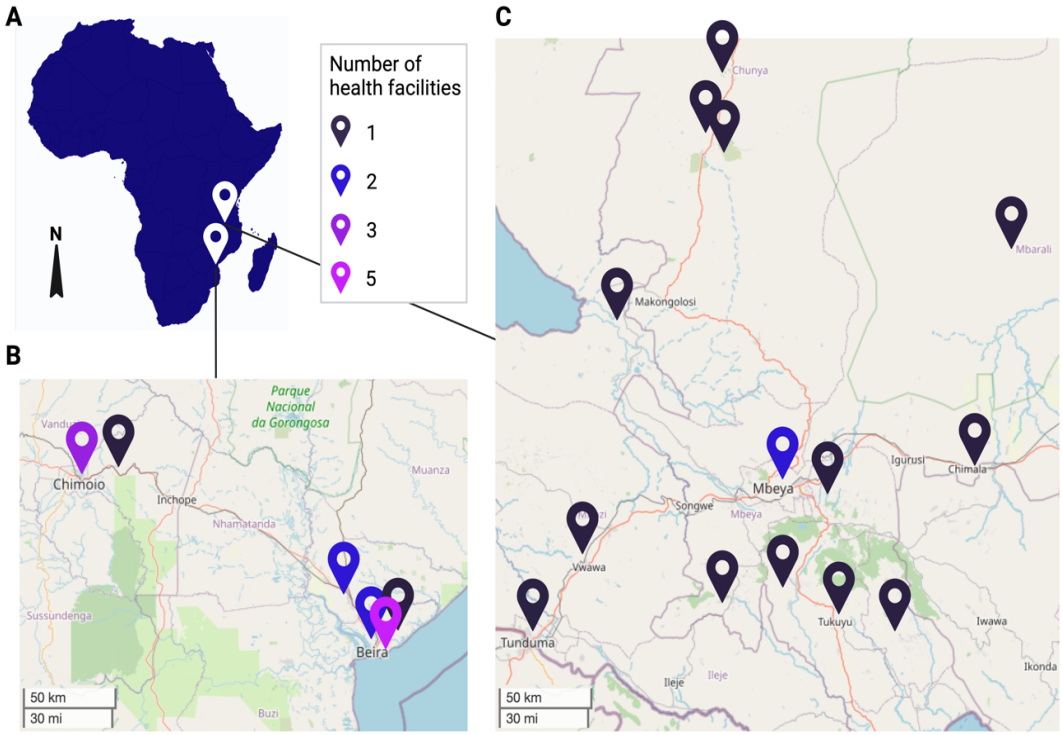

Figure 3: Map depicting locations of LIFE study sites. **(A)** Location of countries, macro view, **(B)** Mozambique, Sofala and Manica provinces. **(C)** Tanzania, Mbeya and Songwe regions. Number of participating health facilities represented per pin depicted by colors. (Created with Open Street Map and Biorender.com).

2.1.2 Study procedures

The LIFE study intervention was randomized at the health facility level with half of the sites implementing PoC EID within 72 hours of birth (VEID) and the other half performing PoC EID beginning at 4-6 weeks of age (SoC). Infants testing HIV-negative or not tested (at birth in the SoC) were given post-natal HIV prophylaxis according to local guidelines and continued to receive PoC EID testing at subsequent study follow-up visits at 4-6 and 12 weeks of age. All HIV-positive results were confirmed either by a second PoC EID test or, if a valid result could not be obtained at the health facility, NAT performed at a central laboratory from dried blood spot samples. HIV-positive infants were immediately initiated on ART, unless there were clinical reasons (e.g., not meeting the minimum weight requirement) not to do so. We additionally collected dried blood spot samples for all infants at SoC health facilities at birth for retrospective analysis at the central laboratory to resolve unknown HIV status in the case of death or loss to follow-up and to determine whether infants testing positive at follow-up visits were already positive at

birth. Enrolled infants attended study visits at birth, week 4-6, and week 12 with a 4-week window period for a total follow-up time of up to 16 weeks of age.

Following routine guidelines, infants in Mozambique were provided enhanced post-natal prophylaxis, regardless of vertical transmission risk. In Tanzania, only high-risk infants (i.e., mother newly diagnosed with HIV at delivery, not on ART or on ART less than four weeks at delivery, or with high HIV viral load at delivery or in the last four weeks if results were not available at delivery), were given enhanced post-natal prophylaxis. As AZT syrup is not reliably available in Tanzania, AZT/3TC dispersible tablets plus NVP syrup were used in most cases as enhanced post-natal prophylaxis.

2.1.3 Study equipment

PoC assays used in the LIFE study detect HIV-1 total nucleic acid qualitatively using real-time PCR. In Mozambique, the Abbott mPIMA™ HIV-1/2 Detect[38], which requires 25µL of peripheral blood and provides results in 52 minutes, was used for PoC EID testing. The mPIMA analyzer is also approved to run HIV viral load assays and can be procured with an external battery, ensuring reliability in areas with frequent power outages. In Tanzania, the Cepheid GeneXpert® HIV-1 Qual[39], which requires 100µL of peripheral blood and has a runtime of 90 minutes, was used for PoC EID testing. External backup power systems are recommended for areas with frequent power outages. The GeneXpert analyzer can run HIV viral load as well as tuberculosis diagnosis and other assays (though equipment sharing across programs is not currently common practice in the study setting) and has the capacity to run up to four tests concurrently. In Tanzania, two variations of the GeneXpert analyzer were available: the GeneXpert II has the capacity to run two and the GeneXpert IV four assays concurrently. In general, GeneXpert IV analyzers were placed at higher volume health facilities in the LIFE study.

In the Tanzanian sites, PoC analyzers were located either in the pediatric outpatient clinics or nearby in the health facility laboratory. In Mozambique, PoC analyzers were placed at the pediatric outpatient clinic where children affected by HIV received routine follow-up care and an additional analyzer was placed at or near the maternity ward in each VEID health facility. Nurses were trained in sample collection and in the use of the PoC analyzers, performed all PoC testing as well as pre- and post-test counselling and communication of results, and led ART initiation with physician support. A schematic of the LIFE study interventions is shown in **Figure 4**.

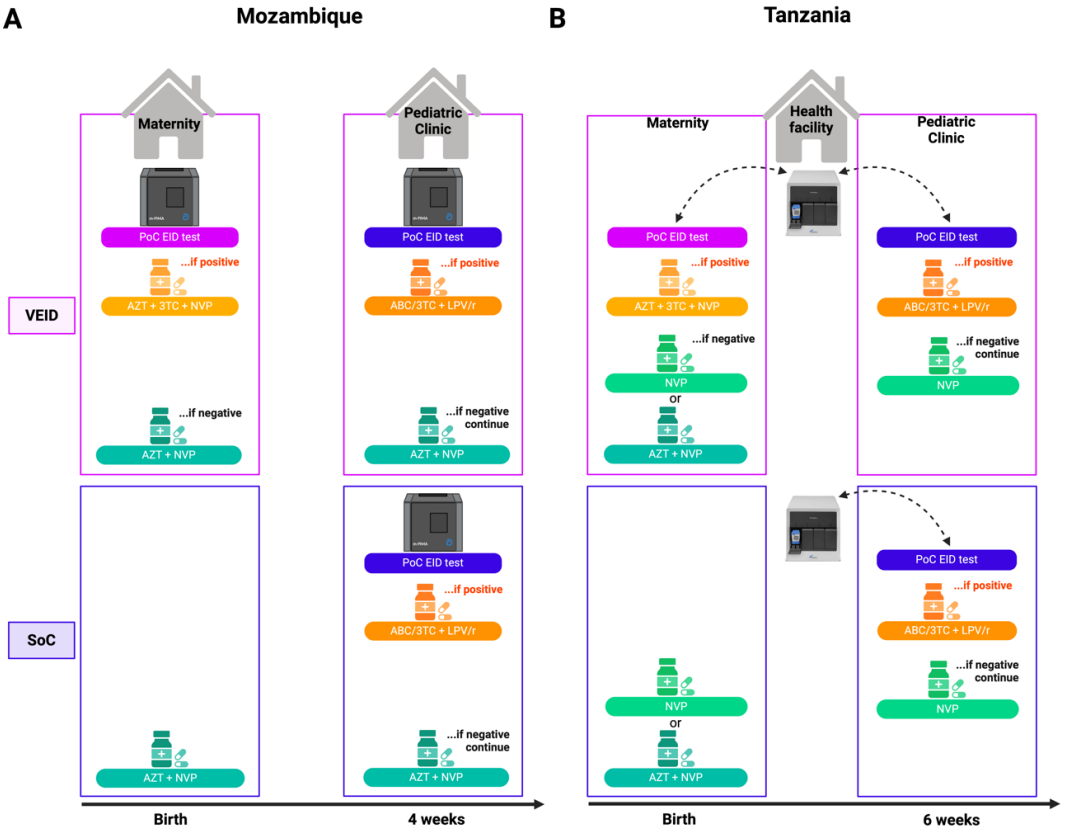

Figure 4: Testing and treatment algorithms. HIV-exposed infants receive their first test either in maternity (VEID) or the respective pediatric clinic (SoC), abbreviated CCR (Mozambique) and RCH (Tanzania), where follow-up visits are also performed in both study arms. **(A)** In Mozambique, each clinic performing PoC testing had one mPIMA analyzer. **(B)** In Tanzania, each health facility had one PoC analyzer, either GeneXpert II or GeneXpert IV. Infants with HIV-positive test results were immediately initiated on the indicated ART regimens. Infants with HIV-negative test results were initiated on post-natal prophylaxis according to country guidelines: AZT + NVP for all infants in Mozambique and high-risk infants in Tanzania and NVP only for low-risk infants in Tanzania.

Abbreviations: VEID = very early infant (HIV) diagnosis; SoC = standard of care; CCR = child at risk clinic; RCH = reproductive and child health clinic; PoC EID = point-of-care early infant diagnosis; AZT = zidovudine; 3TC = lamivudine; NVP = nevirapine; ABC = abacavir.

2.2 Costing methodology

In a micro-costing study, we compared costs of VEID with costs of SoC from a health provider perspective. We estimated costs of implementation and operations, reflecting both one-time fixed (capital) costs and recurrent variable costs incurred by the health system for both VEID and SoC approaches over the LIFE CRT recruitment period. A project proposal was created outlining key methodological decisions (see **Table 1** at the end of this section for a summary of costing methodology). Cost data was collected for 2020 and 2021, though few costs were available for both years. All costs were converted into United States dollars (US$) using the mean conversion rates for the respective year[40]. At the time of analysis these were 66.8 Mozambique Metical and 2304.4 Tanzanian Shillings per 1 US$ in 2020 and 64.4 Mozambique Metical per 1 US$ for 2021. No costs paid in Tanzanian Shillings were available for 2021.

Cost data was compiled in Microsoft Excel (Microsoft Corp.) and analysis was performed using R version 4.2.3 (R Foundation for Statistical Computing. Vienna, Austria). Reporting followed CHEERS 2022 guidelines[41], with a checklist provided in Appendix B. Figures were created with R and BioRender.com.

2.2.1 Identification, measurement, and valuation of resources needed to deliver point-of-care HIV testing interventions

Using an ingredients and activity-based costing approach, we first identified cost components and resources used for PoC EID and determined whether these costs fell under VEID, SoC, or both. LIFE study documents including the study protocol and manual of procedures, local HIV testing and care guidelines, and communication with study operations teams and implementing partners were used for this purpose. Site visits were also utilized to understand the flow of patients through testing procedures, study visits, and through the health facility.

To measure quantities of PoC EID testing resources used per test and per infant and additional weeks of ART given to HIV-positive infants, we used empirical data entered into the LIFE study database and extracted directly from the PoC analyzers. A 12-week EID test was for study purposes only and is not part of routine guidelines in Mozambique or Tanzania. However, if infants missed their 4-6-week EID test but returned to the health facility for the week 12 study visit, we included this test in analysis assuming infants missed at week 4-6 would be tested upon returning to the health facility in normal practice. Consumables (i.e., PoC EID test cartridge and neonatal sample collection kit), labor, and additional ART were collected using a bottom-up approach by measuring the quantity of resources used on an individual patient level. Time required for nurses to conduct PoC EID tests were collected as self-reported average active work time (i.e., not including the time when other activities could be performed while the test was running). After they had logged sufficient experience with PoC testing (>50 tests/individual), nurses were asked in an anonymous, cross-sectional survey to report the average time required from pre-test counselling and sample collection to the receipt of the result, average time needed to communicate an HIV-negative result to the caregiver, and average time needed to communicate an HIV-positive result to the caregiver, provide post-test counselling, and initiate ART. We also collected information on the number and types of PoC analyzers available at each site. Share of equipment cost (PoC testing platform purchase, installation, and maintenance), utilities, communication, training, and facility upgrades were allocated using a top-down approach, dividing total costs per health facility or per country by the number of tests or number of infants tested. Facility upgrades included purchase of cabinets to store reagents for PoC testing and installation of air conditioning units in some of the health facilities.

Prices for resources needed to conduct PoC EID testing were collected from health facility and MoH budgets and expenditure reports, study budgets and purchase tenders, manufacturer contracts, government salary scales, and when not available elsewhere, literature. Test cartridges for the PoC analyzers were procured at a flat rate inclusive of shipping, customs clearance, distribution, and administration costs. Costs of other consumables (e.g., neonatal sample collection kit) were gathered from study financial documents. We calculated PoC platform purchase and maintenance costs assuming a 5-year lifespan according to manufacturer specifications, extended to 10 years in a

sensitivity analysis according to WHO guidelines which estimate equipment lasts 5-9 years in low- and middle-income country settings[42] and discounted at 3% per year in the base case. Costs of training in using PoC platforms as well as facility upgrades were assumed to be capital costs with value extending beyond the evaluation period of the study and were therefore calculated assuming a 10-year lifespan and discounted at 3% per year. Overhead costs, including electricity and communications, were only available at the health facility level as an average for all facilities participating in the study. We assumed the proportion allocated to PoC EID testing to be 10% of health facility costs, as no other information was available.

2.2.2 Calculation of point-of-care analyzer capacity and empirical testing volume

Analyzer capacity was calculated assuming analyzers and nurses were available to run PoC tests 38 hours per week, run times specified by the manufacturers of 52 and 90 minutes for mPIMA and GeneXpert, respectively, and sample loading time between tests based on the above-described anonymous survey administered to the nurses near the end of the study and rounded down to the nearest whole number.

Number of PoC tests run at each site were recorded for all mother-infant pairs throughout the LIFE study, and we considered tests performed during the recruitment period between October 2019 and September 2021 in analyses. In both countries, PoC analyzers were used for maternal HIV viral load testing at birth (VEID sites only), at week 12 visits, and at the time of infant HIV diagnosis in the LIFE CRT. Assuming that maternal HIV viral load testing in the study provided a reasonable estimate of routine viral load monitoring volume in PMTCT programs, we included these tests to reflect integrated equipment use across programs. In Tanzania, GeneXpert analyzers were additionally used for other routine (i.e., non-study) testing including HIV viral load and tuberculosis (TB) diagnostic testing at some health facilities, however, data on the number of tests was only available as an average across all sites over the entire study period. This point estimate was added to inflate testing volumes in Tanzania.

For calculations of volume and costs, we excluded the first six weeks of data collected for each health facility to account for an implementation period during which health facilities were adjusting to providing PoC EID testing, which was not part of routine procedures at all sites or in all relevant departments at the start of the LIFE CRT. We also excluded weeks affected by a recruitment pause due to COVID-19 lockdowns from 13 May to 27 July 2020 in Mozambique and from 17 April to 25 May 2020 in Tanzania. While follow-up testing was still occurring during this time, health facilities were not operating at usual capacity.

Time intervals were defined as (1) weekly and (2) annual. We used the International Organization for Standardization (ISO)[43] week date system with weeks starting on Monday and week 01 defined as the first week with 4 or more of its days in January. This ensures that weekend days are distributed uniformly over each of the time intervals. We constructed the annual time interval using the averages of the number of recruited study participants and PoC tests per ISO week for weeks when data from more than one calendar year were available (at most two years). We then determined the number of EID and other PoC tests performed on the same analyzers per time interval and applied gamma smoothed curves to visualize the trend over the study period. For

the few sites that recruited participants for less than one year, we filled missing values for PoC testing volume with the mean of all other weeks available.

2.2.3 Estimation of unit costs

Costs of the equipment were distributed uniformly across the lifetime of the PoC platform (5 years in the base case) to obtain equipment cost for each health facility and added to overhead cost to make up fixed costs, then divided then by the number of tests run. Fixed costs were evaluated in weekly and annual time intervals. In empirical and scaled estimates, we included maternal HIV viral load testing volumes in the LIFE CRT and additional routine use of PoC analyzers in Tanzania, effectively reducing the share of equipment cost per test to reflect integrated fixed costs across programs. The need for confirmatory testing at the central laboratory occurred so infrequently in the LIFE CRT, with health facilities favoring same-day or next day results with (more expensive) repeated PoC testing, that these costs were excluded.

Table 1: **Methodological summary of costing and cost-effectiveness analyses.**

Purpose	Costs and cost-effectiveness analysis of neonatal PoC EID (VEID) versus SoC in Mozambique and Tanzania
Perspective	Estimation of the costs and benefits incurred by the health care provider
Type of cost	Incremental costs (comparator is SoC) Real world costs of implementation
Units of cost	Costs per point-of-care test (PoC EID) Costs per infant tested and started on ART
Time horizon	Snapshot in time, 12-week follow-up
Scope of inputs	On-site health care costs Research costs excluded
Costing methods	Micro-costing combining bottom-up and top-down approaches
Sampling strategy	LIFE CRT
Data sources for services	Quantities of services and consumables captured in LIFE CRT, self-reported health worker time required to deliver services
Timing of data collection	Birth, weeks 4–6 and week 12 after birth
Sources for price data	Local and national price data from budgets, purchase orders, and expenditure records from MoH, other government, and non-government sources
Capital costs depreciation	Annualized costs for PoC EID equipment
Discount, inflation, and currency conversion rates	3% (both costs and health benefits), −, World bank annual exchange rates
Shadow prices	Out of scope
Limitations	Clinical trial setting, short-term data collection
Differences in cost by sub-population	By country
Uncertainty	Sensitivity analysis

Abbreviations: VEID = very early infant (HIV) diagnosis; SoC = standard of care; PoC = point-of-care; ART = antiretroviral treatment; LIFE CRT = LIFE cluster randomized trial; MoH = ministry of health.

Labor costs were calculated assuming an average of 248 working days per year. Cost of labor per test was estimated by multiplying the median time required for PoC EID testing and communication of results reported by nurses by the calculated share of salary per time. Labor costs were added to consumable costs to obtain the variable cost per test.

Variable costs were then added to fixed costs to obtain total cost per test. Cost per infant was calculated by multiplying by the number of tests performed per infant and adding costs of additional weeks of ART for the share of HIV-positive infants. For simplicity, we assumed HIV-positive infants would receive an additional four and six weeks of ART in Mozambique and Tanzania, respectively, i.e., the additional time on ART according to routine visit schedules with no delays in ART initiation or late attendance of visits. While this may slightly underestimate additional treatment costs in the case ART initiation is delayed at birth (VEID) or overestimate additional treatment costs in the case of late visit attendance in the SoC, ART costs on top of existing post-natal prophylaxis regimens are minimal compared to testing costs. Unit costs were calculated within the CRT environment assuming (1) average fixed costs over the calendar year and (2) weekly fixed costs, with the second approach reflecting variability in costs resulting from fluctuating PoC testing volumes.

2.3 Analyses

2.3.1 Health outcomes

We used early ART for HIV-positive infants as a key indicator for clinical effectiveness. Following the LIFE CRT design, infants testing HIV-positive at birth would have the first opportunity to initiate ART within 72 hours of birth in VEID health facilities and at 4-6 weeks in SoC health facilities. Summary measures for age at ART initiation were reported as medians and ranges, and Wilcoxon rank sum tests were used to evaluate differences between study arms. We also calculated the proportion of HIV-positive infants started on ART in the first week of life and at all during the study period (i.e., within the first 16 weeks of life).

2.3.2 Economic outcomes

Economic outcomes were estimated from the perspective of the EID program, considering the share of costs paid by the EID program in the first 16 weeks of life for each infant participating in the LIFE CRT. Unit costs per test and per infant included the fixed, one-time cost of PoC platform purchase, installation, and maintenance and variable costs associated with running each test. Fixed costs were assumed to be shared with routine services including HIV viral load monitoring and other unspecified use of analyzers in Tanzania.

Incremental costs, incremental effectiveness, and ICERs were calculated relative to outcomes for the SoC approach. Cost-effectiveness outcomes were expressed as incremental cost per HIV-exposed infant receiving an EID test within the first eight weeks of life and each intrauterine-infected HIV-positive infant (i.e., positive PoC EID or PCR from DBS at birth) starting ART within the first one week and first 16 weeks of life. Infants testing positive at birth but delaying ART initiation due to clinical reasons (e.g.,

low weight) were not included in the denominator for one week ART outcomes. We also calculated ICERs for each additional week on (early) ART among all HIV-positive infants.

To represent statistical uncertainty including constructing uncertainty intervals for ICERs, we used bootstrap sampling, a non-parametric technique involving resampling (i.e., with replacement) from the empirical distributions of costs and health benefits described above. We drew 1000 repeated samples of cost and health benefit pairs, calculated ICERs for each pair, and present mean and BCA 95% confidence intervals (CIs) calculated from the resulting bootstrap distribution. Relationships between costs and health outcomes are visualized in cost-effectiveness planes showing additional costs versus and additional health benefit for VEID compared to the SoC. The probability of each PoC EID approach being cost-effective at plausible values of willingness to pay per unit of incremental health benefit are shown in cost-effectiveness acceptability curves. As willingness to pay thresholds, i.e., the amount society is willing to pay for VEID per unit of health benefit, may not be clearly defined and/or decision makers may not be willing to commit to a willingness to pay threshold for a particular health problem, we compare ICERs to health expenditure per capita and present ranges in cost-effectiveness acceptability curves[44-46].

2.3.3 Sensitivity analyses

Univariate sensitivity analysis for empirical cost per test estimates was performed under a deterministic framework to test the influence of key assumptions. We varied cost inputs including extending the lifespan of the analyzer to 10 years, varying the discount rate of depreciating resources (including equipment and training) to 0% and 6%, and varying the price of the test consumables by 20% in either direction. We also estimated a “best case” and “worst case” scenario assuming: 10-year equipment lifespan, discount rate of 6%, and 20% decrease in the price of consumables and 5-year equipment lifespan, no discounting, and 20% increase in the price of consumables, respectively.

In cost-effectiveness analyses, we also varied the observed vertical transmission rate and recalculated costs and cost-effectiveness in terms of additional weeks of early ART for HIV-positive infants. For additional sensitivity analyses, we refer to the following separate sections on scaling of PoC EID costs to routine demand with capital costs shared across programs (2.3.4) and EID program cost only (i.e., without shared resources across programs) across broad EID demand (2.3.5).

2.3.4 Scaling-up point-of-care early infant HIV diagnosis costs to routine demand

Because the LIFE CRT did not expect to recruit all mothers living with HIV presenting for delivery whose infants would be eligible for EID (e.g., mothers not meeting LIFE CRT eligibility criteria or declining study participation), unit costs were additionally calculated for PoC EID volume scaled to routine HIV-positive deliveries per site. To appropriately account for weeks with zero deliveries and retain whole numbers of deliveries and PoC tests, we used a nonparametric bootstrap procedure to construct 10,000 bootstrap samples for each health facility by resampling annual deliveries from the empirical distribution. This effectively allocated the higher number of deliveries from the annual routine data to calendar weeks based on weekly probabilities of deliveries in the LIFE

CRT. Deliveries were then converted to PoC tests on an individual patient level using multipliers estimated from LIFE CRT data, and we calculated median costs with bias-adjusted and accelerated (BCA) 95% uncertainty intervals to adjust for asymmetry of the bootstrap distribution. Additional tests due to multiple births (twins and triplets), repeat PoC tests due to errors or confirmatory testing, maternal PoC viral load or other routine system PoC tests, and loss to retention at follow-up testing visits were considered in the conversion of number of deliveries to number of PoC tests (for more information, see **Appendix B**).

Scaled cost estimates reflect the fixed, one-time cost of PoC platform purchase and installation and variable costs associated with running each test as in the empirical cost estimates. Fixed costs were also assumed to be shared with routine services including HIV viral load monitoring using study and routine testing volumes observed in the LIFE CRT in the absence of other information.

2.3.5 Early infant HIV diagnosis program costs across broad demand

To complement the analysis of cost estimates under empirical and scaled scenarios and offer more generalizable cost estimates, we additionally assessed the required capacity and costs attributable to the EID program over a range of EID demand. PoC platform use at the included health facilities was prioritized for the LIFE CRT and therefore, the proportion allocated to EID testing may not represent routine conditions. To address this, we simulated costs for each PoC EID approach to the EID program only, (i.e., no shared resources or cross-utilization of PoC analyzers for HIV viral load) across a broad range of annual HIV-positive deliveries. Similarly to the approach described above, we resampled across 1-1000 annual deliveries per health facility from the empirical distribution and converted these to costs under VEID and SoC scenarios, assuming that EID tests accounted for 100% use PoC analyzers. Simulated cost per test and cost per infant was expressed as a median per site and per PoC approach in each country with BCA 95% uncertainty intervals.

3. Results

3.1 Empirical costs and cost-effectiveness of very early infant HIV diagnosis

The LIFE study enrolled 6602 HIV-exposed infants between October 2019 and September 2021: 3294 in the VEID group and 3308 in the SoC group. There were 4015 (61%) infants enrolled in Mozambique and 2587 (39%) in Tanzania. Empirical costs and cost-effectiveness results presented in this section reflect health provider costs of VEID and SoC approaches and outcomes observed in the LIFE CRT, with shared fixed costs across maternal HIV viral load monitoring in the LIFE CRT in both countries and 12% additional non-study use by routine programs in Tanzania (determined from data extracted from the PoC analyzers). We primarily focus on the outcome cost per test, as the VEID and SoC approaches mainly varied due to test frequency and timing and less due other costs related to HIV care (i.e., ART). We present cost per infant, including ART costs, as an additional outcome where applicable as well as ICERs with respect to additional HIV-exposed infants receiving a PoC EID test within two months of life, HIV-positive infants started on ART within one week of life and at all, and HIV-positive infant additional weeks on early ART.

3.1.1 Point-of-care analyzer capacity and testing volume

Nurses reported that it took 10 minutes on average to collect and prepare samples for PoC testing and communicate results. Together with the run times specified in section 2.2.2, this translated to 32 tests per week for mPIMA, 44 tests per week for GeneXpert II, and 88 tests per week for GeneXpert IV. All VEID sites in Mozambique had two mPIMA analyzers, meaning capacity at these sites was 72 tests per week.

PoC testing volume generally increased over time, with many sites showing considerable variability on the weekly scale, and Mozambique had more sites with higher volume compared to Tanzania. In Mozambique on average, four health facilities (29%) ran over 15 tests per week and two (14%) ran less than five tests per week. In Tanzania on average, only one health facility (7%) ran over 15 tests per week and six (43%) ran less than five tests per week. All available data on PoC testing volume over the study period is shown in Appendix B Figure SM1.

3.1.2 Costs of very early infant diagnosis versus standard of care

Within the LIFE CRT environment, estimated median cost per test was $39.12 (95% CI: $37.69, $39.99) for the VEID approach and $40.57 ($40.57, $42.84) for the SoC approach using mPIMA in Mozambique. Using GeneXpert in Tanzania, these costs were $36.23 ($34.99, $38.40) for VEID and $43.88 ($41.12, $45.21) for SoC. Estimated median cost per HIV-exposed infant receiving PoC EID testing and if appropriate, initiating ART, were $85.44 ($84.17, $87.64) for VEID versus $37.05 ($36.47, $38.51) for SoC in Mozambique and $68.34 ($67.15, $71.99) for VEID versus $37.38 ($35.31, $38.82) for SoC in Tanzania. Cost per infant was lower than cost per test in the SoC because of loss to follow-up between birth and week 4-6 PoC EID testing. Unit cost inputs are listed in **Table 2**.

Table 2: Costs inputs. Costs (expressed in 2020 US$) are presented in major categories and shown for each country/PoC testing platform separately.

	Mozambique mPIMA	Tanzania GeneXpert	Source
Fixed and capital costs			
Equipment			
PoC platform purchase price	$15,000	GeneXpert IV $17,500 GeneXpert II $12,280	CHAI/ Cepheid
PoC platform maintenance (per year)	$2,500	GeneXpert IV $1,000 GeneXpert II $500	
Undiscounted PoC platform cost (5 years)	$25,000	GeneXpert IV $21,500 GeneXpert II $14,280	
Discounted PoC platform cost (5 years)	$22,232	GeneXpert IV $18,813 GeneXpert II $12,451	
Facility upgrades			
Cabinets for equipment and consumable storage per site	$224	$1,996[b]	CHAI
Air conditioning units average per site[a]	$265		
Other upgrades per site	$143		
Undiscounted cost per site (10 years)	$632	$1,996	
Discounted cost per site (10 years)	$470	$1485	
Training			
Undiscounted cost per site	$213	$252	CHAI
Discounted cost per site (5 years)	$183	$217	
Overhead			
Electricity share per site (1 year)	$27.95	$40.47	MoH
Communication share per site (1 year)	$394	$260	MoH
Variable costs			
Consumables			
Test cartridge[c]	$25.00	$21.87	CHAI
Neonatal sample collection	$1.20	$1.50	
Labor			
Personnel cost per test	$0.77	$1.33	Gov. salary scales
ART			
AZT + 3TC + NVP syrups (per week)	$2.10	$2.10	WHO
AZT/3TC disp. tablets + NVP syrup (per week)	$1.85	$1.85	

[a] Not all sites had air conditioning units installed

[b] Available only as an aggregate figure

[c] Inclusive of shipping, customs clearance, distribution, and administration costs

Abbreviations: PoC = point-of-care; CHAI = Clinton Health Access Initiative; MoH = Ministry of Health; Gov. = Government; ART = Antiretrovirals; AZT = Zidovudine; 3TC = Lamivudine; NVP = Nevirapine; disp. = dispersible; WHO = World Health Organization.

In most scenarios, the majority of the unit cost per test could be attributed to consumables, primarily the test cartridge (**Figure 5** and Appendix A Supplementary Figure 1). Consumables accounted for 64% of the cost per test overall in Mozambique and 59% of the cost per test overall in Tanzania. Equipment cost, by contrast, varied substantially by testing volume. We categorized health facilities into high (>12 tests per week), medium (5-12 tests per week) and low (<5 tests per week) volume for ease of comparison (see Appendix B for more details). At high volume sites, consumables made up 73% and 81% of the cost per test in Mozambique and Tanzania, respectively, with total cost per test reduced to $36.11 in Mozambique and $28.91 in Tanzania. Because of a greater number of relatively low volume sites in Tanzania, there were larger fluctuations in the ratio of consumables to equipment cost as well as total cost per test in Tanzania compared to Mozambique. Labor and overhead costs were small in comparison to consumables and equipment costs in both countries.

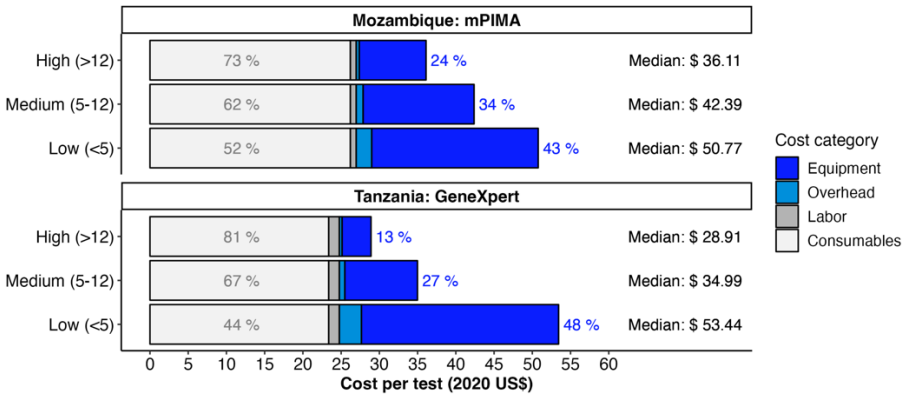

Figure 5: Point-of-care early infant diagnosis test components. Cost estimates (expressed in 2020 US$) calculated from LIFE study data. Sites are categorized as high (>12 tests per week), medium (5-12 tests per week), and low (<5 tests per week) volume. Equipment includes apportioned costs of initial purchase, installation, and yearly maintenance of PoC analyzers. Overhead includes apportioned costs of electricity and facility upgrades. Proportion of total test cost attributable to consumables is annotated in grey, equipment in blue, and median cost per test for each category in black.

3.1.3 Timing of early infant HIV diagnostic testing and treatment initiation

In all VEID health facilities, 100% of HIV-exposed infants received a PoC EID test by the recommended eight weeks of age[34] (median 1 day, IQR: 0-1 days). In SoC health facilities, 84.4% of HIV-exposed infants received a PoC EID test by eight weeks of age at median 4.7 (IQR: 4.4-6.4) weeks (**Figure 6A**). However, 96.6% of HIV-exposed infants in SoC sites received an EID test by eight weeks of age with central laboratory services utilized as a backup and performing retrospective testing in the case of loss to retention after birth. The proportion of infants receiving PoC EID testing by eight weeks in SoC sites differed substantially by country: 91% (87%, 95%) in Mozambique and 75% (69%, 81%) in Tanzania.

Among the 125 infants identified as HIV-positive by 16 weeks of age, 108 (86.4%) were from Mozambique and 17 were from Tanzania (13.6%)[34]. Vertical transmission was 1.89% (95% CI: 1.58, 2.25). Median time to diagnosis was significantly lower for infants in VEID sites at 0.29 [Range: 0, 14] weeks compared to 4.71 [4, 16] weeks in SoC sites

(Wilcoxon rank sum p<0.0001). Out of 69 infants in VEID sites, 38 (55.1%) were diagnosed at birth, 21 (30.4%) at 4-6 weeks of age, and 10 (14.5%) at 12 weeks of age. Out of 56 infants in SoC sites, 32 (57.1%) were HIV-positive at birth by retrospective PCR including six (10.7%) who subsequently died or were lost to retention after the first study visit. A total of 40 infants (72.7%) in SoC sites were diagnosed at 4-6 weeks of age and 10 (18.2%) at 12 weeks of age[34].

HIV diagnosis generally translated to immediate ART initiation. Median age at ART initiation among the 118 (94.4%) infants starting ART was 0.86 [0, 14] weeks in VEID sites and 4.71 [4, 16] weeks in SoC sites (p<0.0001) (**Figure 6B**). In VEID sites, 98.5% of HIV-positive infants started ART compared to 89.3% in the SoC sites (p=0.112)[34]. Reasons for not starting ART were death or loss to retention before EID testing could be carried out. Reasons for delayed treatment initiation at birth in VEID sites included not meeting the minimum weight requirement for starting ART (n=2) and a delay in confirmatory HIV testing (n=1). On average, infants diagnosed at birth started ART 3.7 weeks earlier in Mozambique and 5.6 weeks earlier in Tanzania than they would have if they had not been offered birth testing (based on the conservative first opportunity for starting ART according to SoC procedures; four and six weeks of age in Mozambique and Tanzania, respectively). Timing of EID testing and ART initiation are shown by health facility in Appendix A Supplementary Figure 2.

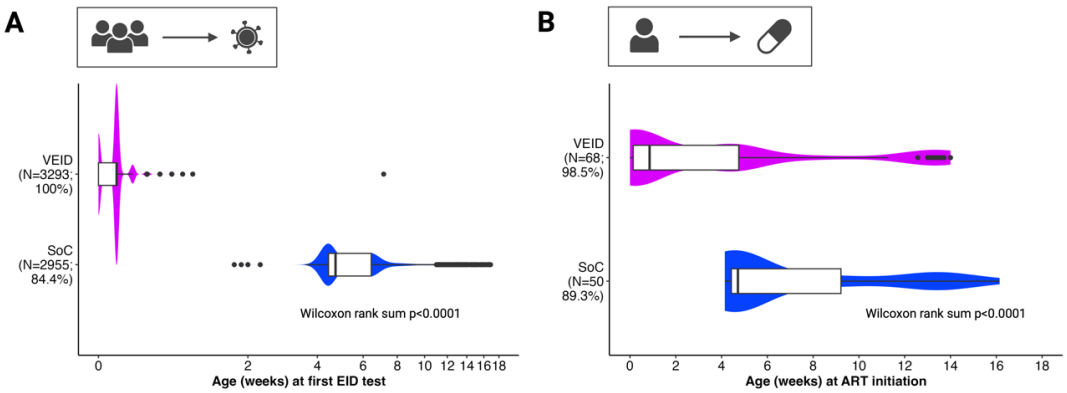

Figure 6: Time from birth to PoC HIV EID testing and treatment initiation. **(A)** First EID test among all HIV-exposed infants; proportion receiving an EID test indicated in vertical axis labels. **(B)** ART initiation among HIV-positive infants diagnosed up to 16 weeks; proportion initiating ART at all indicated in vertical axis labels.

Abbreviations: VEID = very early infant (HIV) diagnosis; SoC = standard of care; PoC EID = point-of-care early infant diagnosis; ART = antiretroviral treatment.

3.1.4 Cost-effectiveness of very early infant HIV diagnosis

Incremental costs of VEID compared to the SoC were $477.06 ($428.96, $518.54) per additional HIV-exposed infant tested by eight weeks of age and $4,138 ($3,763, $4,434) per additional eligible HIV-positive infant initiated on ART in the first week of life in Mozambique. Putting these costs into context, this represented 13.9 times and 120.7 times health expenditure per capita in Mozambique in 2020, respectively[40, 47]. The cost-effectiveness planes in **Figure 7** display the relationship between costs and health

outcomes of VEID compared to the SoC. **Figure 7A** shows added costs per population percentage point increase in HIV-exposed infants receiving a PoC EID test in the first eight weeks of life. **Figure 7E** shows added costs per population percentage point increase in HIV-positive infants initiating ART in the first week of life. Most estimates for both 8-week EID and 1-week ART outcomes are associated with higher costs and improved health benefit, with the majority of points lying in the upper right quadrant. Few estimates are associated with lower costs and improved health benefit, with points lying in the lower right quadrant. **Figures 7C and 7G** show cost-effectiveness acceptability curves for 8-week EID and 1-week ART outcomes, respectively for a range of willingness to pay values. The probability of VEID being more cost-effective than the SoC in Mozambique for both 8-week EID and 1-week ART outcomes is high at willingness to pay values above the incremental costs listed above but depends on the budget constraints and the amount decision makers are willing to invest.

In Tanzania, we calculated incremental costs of $209.23 ($148.21, $276.10) per additional HIV-exposed infant tested in the first eight weeks of life and $10,924 ($6,445, $16,452) per additional HIV-positive infant initiated on ART in the first week of life. These costs were 2.8 times and 274.2 times health expenditure per capita in Tanzania in 2020, respectively[40, 47]. **Figures 7B and 7F** show cost-effectiveness planes and **Figures 7D and 7H** show cost-effectiveness acceptability curves for 8-week EID testing and 1-week ART outcomes in Tanzania, respectively. Like in Mozambique, the majority of estimates indicate that both outcomes are associated with higher cost and improved health benefit, with few estimates associated with lower costs and improved health benefit. The probability of VEID being more cost-effective for the 8-week EID outcome compared to the SoC in Tanzania is high but for the 1-week ART outcome, reaches a maximum of 70% at a willingness to pay of $15,000 or 382 times the health expenditure per capita.

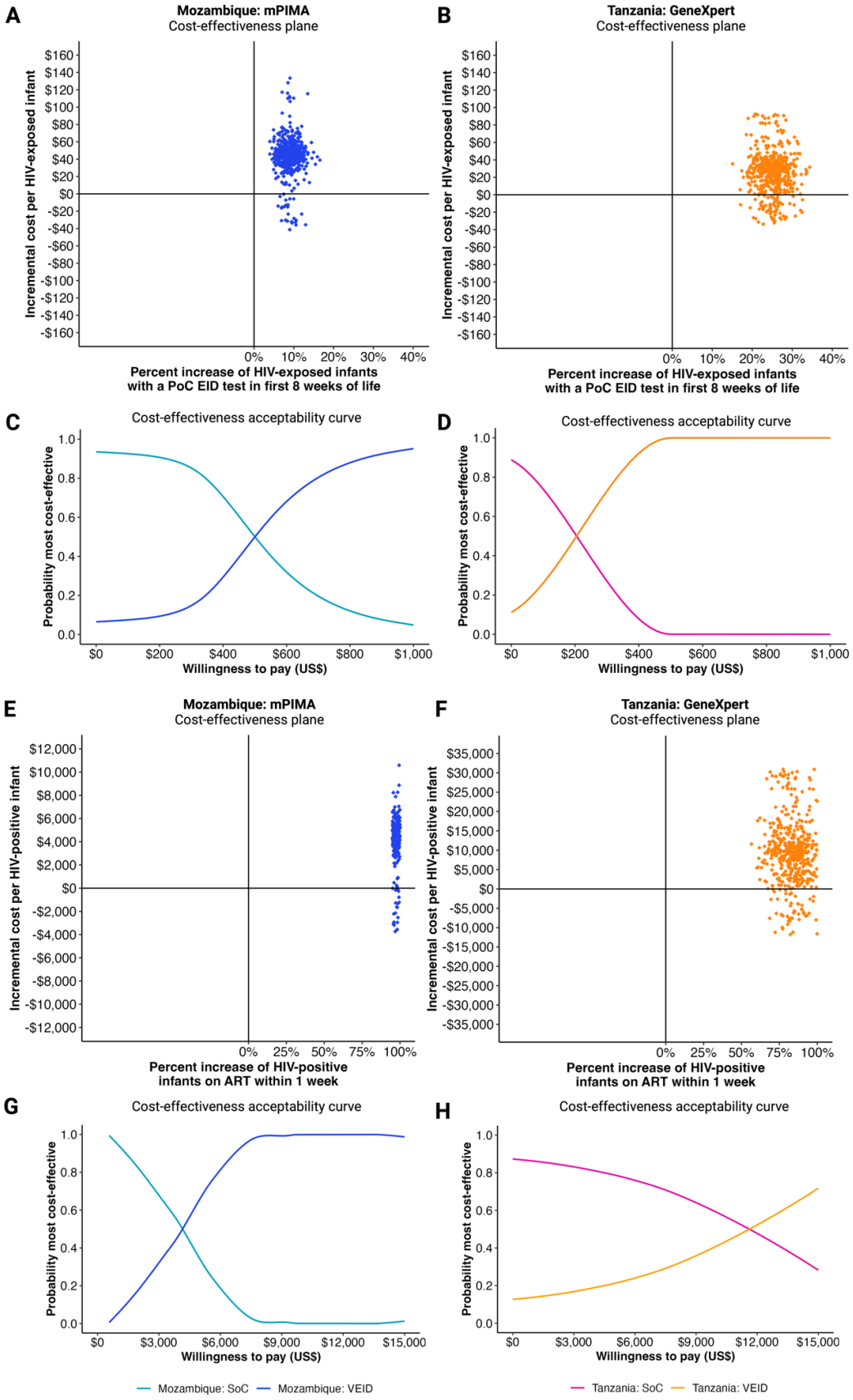

Figure 7: Cost-effectiveness of VEID with respect to PoC EID testing and early ART. Cost-effectiveness planes presenting the incremental costs and **(A-B)** 8-week EID benefit (%) for VEID or **(E-F)** early ART benefit

(% of eligible HIV-positive infants initiated on ART within 1 week of life; eligible infants include those meeting clinical criteria for treatment, e.g., weight). Points represent estimates of costs and health benefit for VEID relative to the SoC at the origin. A random sample of 500 points is plotted. **(C-D & G-H)** Cost-effectiveness acceptability curves for each of the outcomes shown in A-B and E-F, respectively, showing cumulative probabilities of each testing strategy being cost effective at a particular willingness to pay value. Costs are presented as 2020 US$.

Abbreviations: PoC EID = point-of-care early infant diagnosis; ART = antiretroviral treatment; SoC = standard of care; VEID = very early infant (HIV) diagnosis.

We additionally examined the relationship between costs and the proportions of infants initiating ART at all during the study period (i.e., within 16 weeks of life). In both countries, VEID resulted in higher proportions of HIV-positive infants started on ART: 91% (88%, 95%) in SoC sites to 100% (100%, 100%) at VEID sites in Mozambique and 80% (75%, 86%) in SoC sites to 86% (80%, 90%) in VEID sites in Tanzania. We calculated incremental costs of $47,417 ($43,422, $51,504) in Mozambique and $151,126 ($136,646, $184,325) in Tanzania per additional ART initiation within 16 weeks of life. Costs and effects for both countries are shown in **Figure 8** with ICERs interpreted as the slopes of the dashed lines. In Mozambique, incremental costs were lower and incremental health benefits were higher compared to Tanzania, resulting in a significantly lower ICER. However, in this scenario, VEID is unlikely to be considered cost-effective compared to SoC at plausible willingness to pay thresholds for Mozambique and Tanzania[46]. Cost-effectiveness planes and cost-effectiveness acceptability curves are available in Appendix A Supplementary Figure 3.

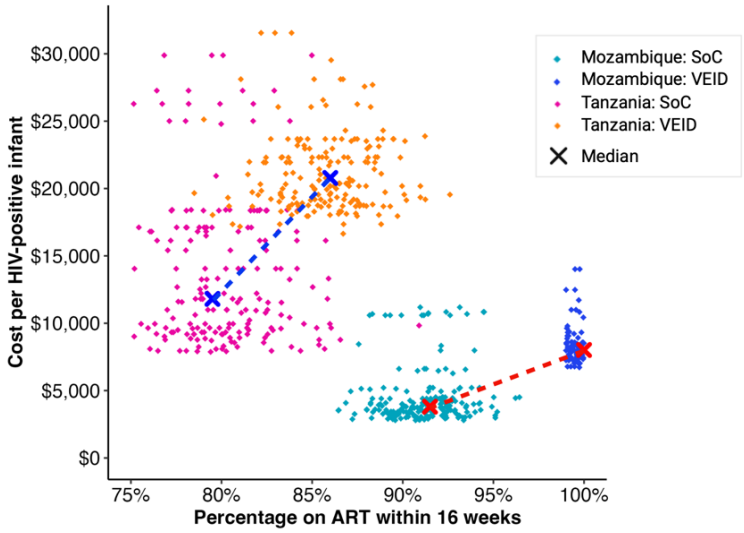

Figure 8: Total costs and proportion of HIV-positive infants initiated on ART. Simulated total costs per HIV-positive infant (2020 US$) versus proportion initiating ART within 16 weeks of age plotted as points per country and PoC testing strategy. Medians are represented by crosses. Incremental cost effectiveness ratios can be interpreted as the slopes of the dashed lines.

Abbreviations: VEID = very early infant (HIV) diagnosis; SoC = standard of care; ART = antiretroviral treatment

3.1.5 Sensitivity analysis results

Varying key cost inputs, including the PoC analyzer lifespan, discount rate, and the price of consumables, showed that cost per test was most sensitive to changes in the price of consumables and at low volume sites (i.e., GeneXpert IV in Tanzania), longer equipment lifespan. In the best-case scenario, assuming a 10-year equipment lifespan, 6% discount rate, a 20% decrease in the price of consumables, and that sites followed the VEID approach, median cost per test across all sites was reduced to $27.45 ($26.77, $27.86) in Mozambique and $25.47 ($24.97, $26.60) in Tanzania. In the worst-case scenario, with a 5-year equipment lifespan, no discounting, a 20% increase in the price of consumables, and that sites followed the SoC approach, cost per test increased to $47.39 ($47.39, 49.92) in Mozambique and $51.27 ($48.09, $52.75) in Tanzania. The full results of univariate sensitivity analysis are available in Appendix A Supplementary Table 1 and Supplementary Figure 4.

Intrauterine transmission rates observed in the LIFE CRT were 1.03% in Mozambique and 0.31% in Tanzania. This represents approximately half of the infants diagnosed in the first 16 weeks of life, for whom an additional (early) ART initiation would apply. With the VEID approach, cost per HIV-positive infant was sensitive to intrauterine transmission rate. Per additional (early) week on ART, empirical ICERs were $1,103 ($1,018, $1,201) in Mozambique and $1,916 ($1,586, $2,325) in Tanzania. Varying the intrauterine transmission rate from 0.5-5-fold the rate observed in the LIFE CRT, ICERs ranged from $2,206 ($2,031, $2,375) in Mozambique (64.4 times health expenditure per capita) and $3,856 ($3,161, $4,712) in Tanzania (98.1 times health expenditure per capita) to $220 ($201, $238) in Mozambique (6.4 times health expenditure per capita) and $385 ($314, $464) in Tanzania (9.8 times health expenditure per capita) **(Table 3)**. Cost-effectiveness planes and cost-effectiveness acceptability curves for transmission rates 0.5-, 1-, 2-, and 5-fold the observed rate in the LIFE CRT are shown in **Figure 9**.

Table 3: Effect of intrauterine transmission rate on incremental cost-effectiveness ratios.

	ICER per week of early ART[a]	
Vertical transmission	**Mozambique**	**Tanzania**
VT 0.5x	$2,206 (2,031, 2,375)	$3,856 (3,161, 4,712)
VT 1x	**$1,103 (1,018, 1,201)**	**$1,916 (1,586, 2,325)**
VT 2x	$550 (506, 594)	$955 (775, 1,170)
VT 5x	$220 (201, 238)	$385 (314, 464)

[a] ICER for VEID compared to SoC

Abbreviations: ICER = incremental cost-effectiveness ratio; ART = antiretroviral treatment; VT = vertical transmission; VEID = very early infant diagnosis; SoC = standard of care.

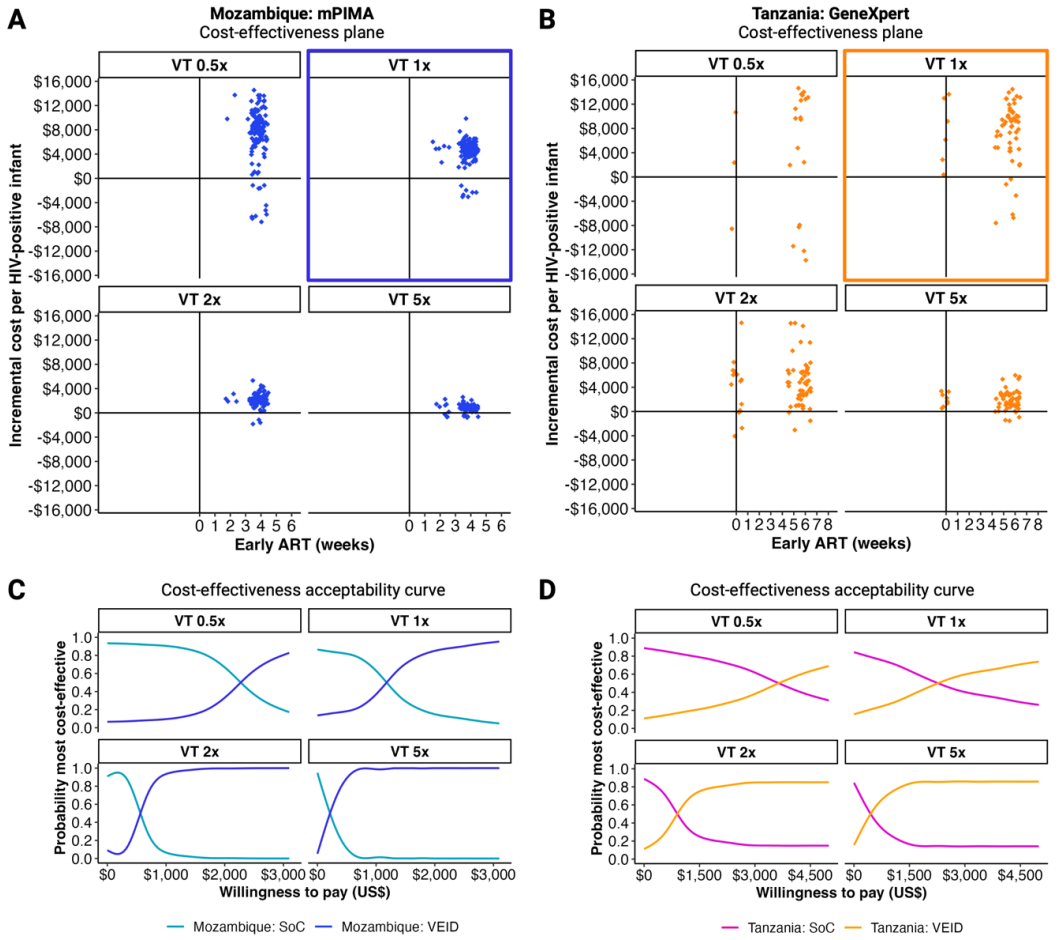

Figure 9: Cost-effectiveness of VEID with respect to additional weeks of early ART with varying vertical transmission rate. HIV vertical transmission ranging from 0.5-fold to 5-fold the observed rate in the LIFE study shown with the observed vertical transmission rate (VT 1x) highlighted by colored boxes. **(A-B)** Cost-effectiveness planes showing incremental costs and incremental early ART benefit (weeks) for VEID compared to SoC. Early ART benefit is defined as additional weeks on ART for the VEID strategy. **(C-D)** Cost-effectiveness acceptability curves depicting cumulative probabilities of each testing strategy being more cost effective compared to the other at a particular willingness to pay value.

Abbreviations: VT = vertical transmission; ART = antiretroviral treatment; SoC = standard of care; VEID = very early infant (HIV) diagnosis.

3.1.6 Budget impact

Total annual costs for VEID across all 14 health facilities participating in the LIFE CRT were $345,138 ($282,697, $514,207) in Mozambique and $180,177 ($137,383, $304,234) in Tanzania. Total annual costs of SoC were $172,783 ($116,246, $440,403) in Mozambique and $109,250 ($62,936, $210,895) in Tanzania. This translates to yearly average incremental costs of $172,355 ($-115,954, $349,045) and $70,927 ($-56,626, $221,721) or $12,311 and $5,066 per site in Mozambique and Tanzania, respectively. Total incremental costs of VEID across all 14 sites were 83% higher in Mozambique than in Tanzania. The number of HIV-exposed infants was 43% higher in Mozambique compared to Tanzania. Total annual costs per site are available in Appendix A Supplementary Table 2.

3.1.7 Utilization of point-of-care testing platforms

Empirical data from the LIFE CRT environment show substantial variability in testing costs across time and health facility (**Figure 10A** and Appendix A Supplementary Figure 5), explained by variation in testing volume. The median cost per test varied between sites by 37% and 67% in Mozambique and Tanzania, respectively. Cost per test decreased rapidly with increasing PoC platform utilization up to a certain threshold (**Figure 10B-D**). We defined a pragmatic threshold of $0.50 reduction in total cost per test per 1% increase in utilization. This was 23% utilization for mPIMA (corresponding to nine tests per week per mPIMA analyzer), 16% for GeneXpert II (eight tests per week), and 13.6% for GeneXpert IV (12 tests per week). Below this threshold, cost per test is driven by equipment cost and above the threshold, by the cost of consumables. Therefore, sites operating with testing volumes above the threshold for the majority of the calendar year have relatively stable and predictable unit costs and cost per test can be reduced to slightly more than the cost for consumables, even below 50% utilization. This explains the right tail in the distribution of cost per test observed in the study mainly in SoC health facilities which more often dipped below the utilization threshold because EID volume was roughly half compared to VEID sites.

Average utilization in the LIFE study ranged from 11 to 32% in Mozambique and 2 to28% in Tanzania, but many sites also exhibited significant spread in utilization over time (Appendix A Supplementary Figure 6). Peak utilization reached 64% in Mozambique, with health facilities operating above the utilization threshold 40% of the time. In Tanzania, peak utilization reached 73% with 23% of weeks above the utilization threshold for GeneXpert II and 28% of weeks above the utilization threshold for GeneXpert IV.

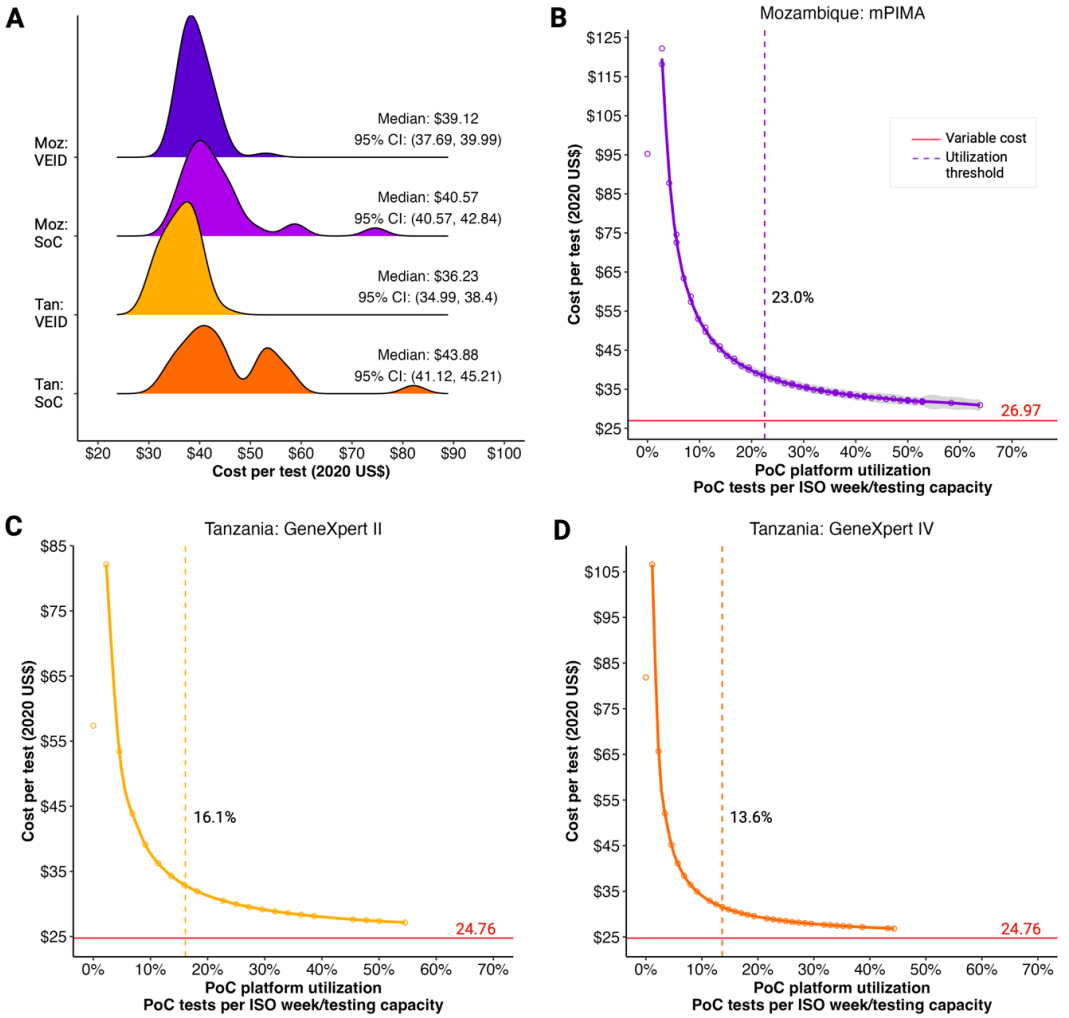

Figure 10: PoC EID test cost, variability, and relationship between utilization and cost. Costs and utilization calculated from LIFE study data. **(A)** Distribution, median, and 95% confidence interval (Hodges Lehman estimate) of cost per test across study weeks. **(B-D)** Relationship between PoC platform utilization and cost per test. Vertical dashed lines indicate the utilization percentage at which the slope of the cubic spline fit is less than 0.5, meaning each additional 1% gain in utilization results in <$0.50 savings per test to the right of this line. Variable costs (consumables, labor) are indicated by red horizontal lines and annotations.

Abbreviations: Moz = Mozambique; Tan = Tanzania; VEID = very early infant (HIV) diagnosis; SoC = standard of care; 95% CI = 95% confidence interval; PoC = point-of-care; ISO week = International Organization for Standardization week date system.

3.2 Scaling costs of point-of-care early infant HIV diagnosis to routine demand

The cost estimates from the empirical LIFE CRT data provide information on the relationship between PoC platform utilization and resulting cost fluctuations over short time intervals (weeks in this case) but underestimate the demand for PoC EID testing under routine conditions. The LIFE study recruited approximately 49% and 62% of HIV-positive mothers presenting at the sites for delivery in Mozambique and Tanzania,

respectively, based on annual HIV-positive deliveries recorded at each health facility (Appendix B Table SM1). To understand costs under a more realistic scenario of EID demand, we scaled recruitment numbers to annual HIV-positive deliveries and recalculated costs and uncertainty intervals. We used a resampling technique to avoid non-integer numbers of deliveries and PoC tests which may result from multiplicative scaling. We did this on a weekly timescale because, particularly in Mozambique, deliveries and thus PoC EID testing demand shows variability throughout the calendar year (see Appendix B for more details), and even with scaling, a significant number of sites would have weeks well below the utilization thresholds described in Section 3.1.7. While costs may even out over the year or the lifespan of the analyzer, a more accurate estimate of costs can be obtained in case analyzers are moved between facilities or leased for shorter time periods by preserving the variability in PoC testing demand over the calendar year.

Scaled costs per test in Mozambique were $33.99 ($33.68, $34.30) for the VEID approach and $38.98 ($38.46, $39.54) for the SoC approach. In Tanzania, scaled costs per test were $32.20 ($32.10, $32.94) for VEID and $44.52 ($43.02, $44.55) for SoC **(Figure 11A)**. Scaled cost estimates per infant were $76.17 ($75.72, $76.92) for VEID versus $36.33 ($36.03, $36.84) for SoC in Mozambique and $65.71 ($65.10, $67.09) for VEID versus $40.38 ($39.83, $41.38) for SoC in Tanzania **(Figure 11B)**. Scaled cost estimates per health facility as well as additional cost per HIV-exposed infant are available in Appendix A Supplementary Figure 7.

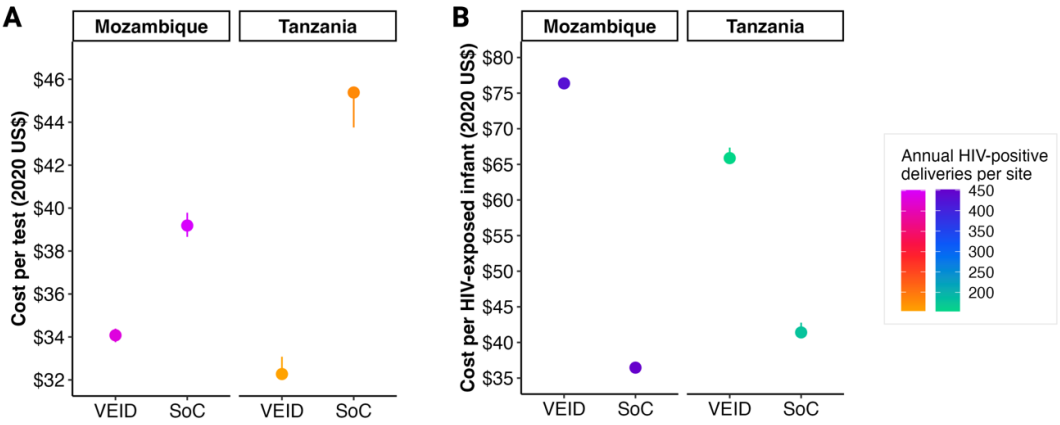

Figure 11: PoC EID costs based on EID demand. Costs (2020 US$) estimated from LIFE study data scaled to the number of annual HIV-positive deliveries per site from routine data. **(A)** Cost per test and **(B)** cost per infant tested and started on treatment. Vertical lines show bias-corrected adjusted (BCA) 95% uncertainty intervals. Color ramps indicated mean annual number of HIV-positive deliveries per site.

Abbreviations: VEID = very early infant (HIV) diagnosis; SoC = standard of care.

Estimates of costs in the study were generally higher than cost estimates for scaled data, expect for relatively high-volume sites where the two estimates were similar **(Appendix A Supplementary Figure 8)**. In several SoC sites, particularly in Tanzania, median scaled cost estimates were actually higher than median study costs because testing demand still fell below utilization thresholds, resulting in relatively high fixed

costs plus increased variable costs due to the higher testing volume. Median cost per test and per infant as well as additional cost per infant for scaled costs are shown in **Table 4.** Using scaled costs per infant, ICERs were approximately 5% lower in Mozambique, but 6-25% higher in Tanzania (Appendix B).

Table 4: Cost comparison between empirical and EID scaled to routine demand estimates.

	Mozambique: mPIMA		Tanzania: GeneXpert	
Outcome	**VEID**	**SoC**	**VEID**	**SoC**
	Median (95% CI)	**Median (95% CI)**	**Median (95% CI)**	**Median (95% CI)**
LIFE CRT				
Cost per test	$39.12 (37.69, 39.99)	$40.57 (40.57, 42.84)	$36.23 (34.99, 38.40)	$43.88 (41.12, 45.21)
Cost per infant	$85.44 (84.17, 87.64)	$37.05 (36.47, 38.51)	$68.34 (67.15, 71.99)	$37.38 (35.31, 38.82)
Additional cost of VEID per infant[a]	$48.39	-	$30.96	-
Scaled to routine demand				
Cost per test	$33.99 (33.68, 34.30)	$38.98 (38.46, 39.54)	$32.20 (32.10, 32.94)	$44.52 (43.02, 44.55)
Cost per infant	$76.17 (75.72, 76.92)	$36.33 (36.03, 36.84)	$65.71 (65.10, 67.09)	$40.38 (39.83, 41.38)
Additional cost of VEID per infant[b]	$35.79 (35.71, 35.84)	-	$33.06 (33.04, 33.45)	-

[a] Cost difference VEID versus SoC in the LIFE CRT (no confidence interval estimated).

[b] Based on simulated counterfactual estimation, i.e., costs in VEID sites if they had not offered PoC EID at birth.

3.3 Early infant HIV diagnosis program costs across broad demand

Required PoC testing capacity and costs for the EID program only further highlight the differences between countries and testing platforms. Unlike the scaled costs presented above, we included only EID testing and not HIV viral load monitoring or other routine use of the analyzers. The results, shown in **Figure 12**, show that cost per test remains consistently lower for VEID compared to the SoC in Tanzania, but costs per test are comparable in Mozambique above approximately 100 annual deliveries per health facility **(Figure 12A)**. In Mozambique, where all VEID sites had two mPIMAs and all SoC sites had one mPIMA, the cost of additional analyzers to cover increased testing capacity required for VEID means that cost per test is less expensive for SoC at lower volume sites. Cost differences between VEID and SoC in Tanzania were more sensitive to utilization, as equipment costs are lower than for mPIMA**.** SoC sites in both countries experience higher costs at very low volumes due to high frequency of weeks with low testing volumes where the increased cost of consumables in addition to the high fixed costs means cost per test is near its maximum. VEID sites do not experience this increase in per test cost at low volumes as repeat testing at week 4-6 means testing volumes are both higher and more stable across time. Simulated results per site can be found in Appendix A Supplementary Figure 8 and aggregated cost per infant in Appendix A Supplementary Figure 9.

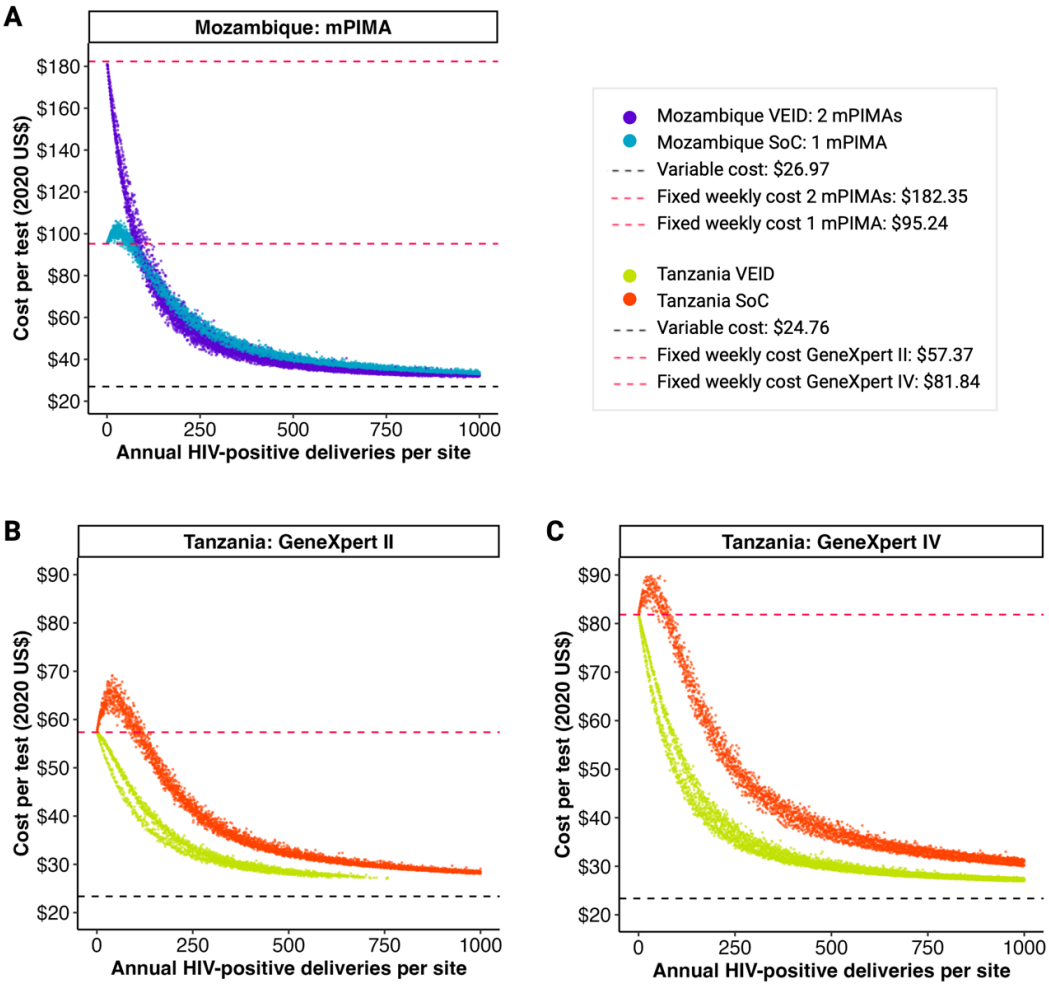

Figure 12: Simulated EID program cost per test. Costs are represented as 2020 US$. Different colors represent VEID and SoC conditions. Variable costs including consumables and labor are shown by dashed black lines, and fixed costs including equipment and overheads are shown by dashed red lines.

Abbreviations: VEID = very early infant (HIV) diagnosis; SoC = standard of care.

4. Discussion

There remains a lack of knowledge around the costs and value for money of offering EID at birth universally in low- and middle-income country settings. This information is needed to inform design decisions about EID program scale-up to reach more infants at risk of HIV acquisition. Focusing on rural, primary health care settings in two sub-Saharan African countries, this study provides a comprehensive analysis of costs incurred by health providers and the health benefits of earliest possible treatment initiation of offering PoC HIV diagnostic services at birth and 4-6 weeks of age compared to the SoC of HIV testing at 4-6 weeks of age only. By conducting both empirical and simulation-based analyses, we additionally provide information on cost fluctuations based on EID demand useful for strategically placing PoC analyzers and optimizing equipment utilization.

4.1 Costs of point-of-care very early infant HIV diagnosis are driven by reagent costs

Costs estimated in this analysis were generally consistent with other studies of PoC EID using the same or comparable testing systems[29]. Cost per test varied significantly by testing volume and was dominated by the cost of the reagents, apart from at sites with very low testing volumes. Differences between low- and high-volume sites were 34% and 58% in Mozambique and Tanzania, respectively. Thus, per test costs were most sensitive to changes in the prices of consumables, namely the test cartridge.

We included broad capital and variable costs in our calculations, explaining higher cost per test estimates compared to some studies that omitted costs of equipment procurement and initial set-up[48, 49]. Without the initial investment in equipment (i.e., in scenarios where existing PoC testing infrastructure allows for repurposing of analyzers for PoC EID or integration with other programs), which eliminates the need to consider testing volumes solely from the EID program perspective, cost per test can be reduced by up to 40-43% in Mozambique and 28-47% in Tanzania. However, as manufacturer specifications quote relatively short PoC analyzer lifespans, estimating costs with initial equipment investment remains important for comprehensive budget planning.

4.2 Point-of-care very early infant HIV diagnosis resulted in more frequent and earlier treatment initiation

VEID at birth increased not only the proportion of infants initiated on ART, but also significantly reduced the age at ART initiation. Previous studies also show PoC HIV testing in newborns in primary healthcare settings in sub-Saharan Africa results in earlier ART initiation[26, 28, 50, 51], including a multi-country observational study which reported that 92.3% of infants with HIV diagnosed at the PoC initiated ART within 60 days of sample collection[24]. In our study, all infants delivered at VEID sites received a PoC HIV test within the recommended eight weeks of age, the majority within the first 24 hours of life, and initiated ART at median 0.86 weeks of age. This is crucial in ensuring timely linkage to treatment and potentially improving the health outcomes of

vulnerable neonates diagnosed with HIV. ART initiation shortly after birth may suppress viral replication and reduce or prevent the rapid establishment of long-lasting viral reservoirs, potentially leading to slower disease progression and reduced mortality and morbidity[15, 16, 52]. Improved long-term health outcomes among children living with HIV certainly have economic implications, and thus as additional data on very early ART initiation and health outcomes of HIV-positive children becomes available, incorporation of health economic evaluations alongside clinical and implementation studies should be prioritized.

4.3 Cost-effectiveness of point-of-care very early infant HIV diagnosis

Previous studies have demonstrated that PoC compared to laboratory-based EID testing is cost-effective, increases the proportion of infants rapidly initiated on ART, and improves life expectancy across a range of programmatic and economic conditions[32, 48]. A model-based analysis of birth plus 6-week testing in South Africa improved survival and was deemed cost-effective as long as uptake was high[19]. Our study adds to the growing literature on the costs of PoC EID and costs and cost-effectiveness of HIV test timing and frequency during early infancy in two countries with different intrauterine transmission rates using different PoC testing platforms.

Cost-effectiveness of birth plus 4–6-week testing depends on intrauterine transmission rates. ICERs were $4,138 per additional ART initiation in the first week of life and $1,103 per week of additional ART in Mozambique and $10,924 per additional ART initiation in the first week of life and $1,906 per week of additional ART in Tanzania. Mozambique and Tanzania observed intrauterine transmission rates of 1% and 0.3%, respectively. A key challenge in assessing the efficiency of interventions to make decisions about resource allocation is the lack of widely accepted cost-effectiveness thresholds[53, 54]. We use epidemiologic outcomes relevant to EID programs as key indicators of health benefit, however, long-term health data on infants living with HIV is scarce. Whether very early ART initiation results in gains in life expectancy or other commonly reported measures of health benefit in decision analysis[46] is still uncertain. Settings with very low intrauterine transmission rates similar to Tanzania may alternatively consider targeted EID testing at birth based on risk factors for vertical transmission (e.g., high maternal HIV viral load)[20, 55, 56] to increase cost-effectiveness, but economic evaluation studies are needed to determine the value of this approach.

Retention in care and adherence to treatment are other important considerations when evaluating the economic value of PoC EID approaches. Very early initiation of ART can only be translated into longer-term health benefits if infants continue receiving treatment. With dolutegravir-containing ART, which is expected to address common barriers to adherence[57] due to once daily dosing and improved palatability, now available for infants, we may see further improvements in longer-term health benefits. The upcoming LIFE2Scale study, beginning recruitment in 2024, aims to evaluate 12-month mortality and morbidity outcomes among HIV-positive infants who will primarily receive dolutegravir-based ART.

4.4 Strategies for optimizing point-of-care platform utilization

We identified PoC analyzer utilization thresholds of 23.0% for mPIMA, 16.1% for GeneXpert II, and 13.6% for GeneXpert IV, below which cost per test is primarily dominated by the share of equipment cost and above, by the cost of consumables. This suggests that compared to the price of the test cartridge, equipment costs can be low, and the price of the test can be reduced to slightly more than the cost of the consumables and labor. In the study environment, many sites oscillated over this threshold from week to week and thus showed substantial fluctuation in PoC testing costs.

While the observed fluctuation in cost per test may even out over the lifetime of the PoC analyzer, evaluating utilization and costs over shorter time intervals than annually or the lifetime of the analyzer allows health systems to optimize placement of a limited number of PoC testing platforms according to demand. This may increase health benefit and provides information to support decisions about cost sharing across sites or programs. As PoC analyzers are portable devices which require minimal training, relocating them periodically is possible. In a model-based approach of SoC EID in Zimbabwe, re-allocating limited PoC analyzers would increase the proportion of infants initiated on ART within 30 days of testing by 9%[58]. Both systems evaluated here can be linked to lab information systems or other automated data capture systems and processed either fully automated or with minimal input, making monitoring of weekly PoC platform utilization feasible. This approach also can be extended to estimating value within equipment leasing arrangements, which are available for both mPIMA and GeneXpert platforms.

To increase utilization and reduce and stabilize costs of PoC platforms with excess available capacity, health facilities can consider sharing equipment and staff across programs, using PoC analyzers for example, for routine HIV treatment monitoring (e.g. viral load testing) and TB diagnostics. Multi-disease testing, especially with GeneXpert, offers the potential to reduce costs to EID programs and improve cost-effectiveness while still offering these services at the PoC, particularly in areas where demand for EID does not meet analyzer capacity. Alternatively, health systems can improve access to testing in remote areas by extending PoC testing to surrounding health facilities in a hub-and-spoke delivery model, where smaller sites without PoC infrastructure refer samples to larger nearby sites with PoC infrastructure. Hub-and-spoke systems have been successful in increasing access to HIV diagnosis and care services and TB diagnostics in some settings[59-61]. Depending on geographic and infrastructure constraints, such semi-decentralized testing can also be flexibly adapted based on testing demand supported by continuous monitoring.

4.5 Resource requirements and costs for scaling up point-of-care early infant diagnosis

Assuming the current distribution of deliveries over the calendar year, one GeneXpert II would not provide sufficient testing capacity beyond approximately 700 annual HIV-positive deliveries per site. The highest volume site in Tanzania recorded an average of

350 deliveries per year with a maximum of 36 PoC tests in one week across all simulations. This equates to a maximum utilization of 41% with GeneXpert IV. Similarly in Mozambique, VEID sites with high variability in delivery volume over the year would need a second mPIMA to meet demand for EID only beyond 600 annual deliveries. This finding highlights the importance of considering not only current testing volumes but also scalability and long-term cost implications when evaluating PoC EID testing strategies.

With analyzers operating at a realistic benchmark 70% of capacity, which accounts for periods where the analyzer is down for maintenance, power outages, stock outs of reagents, etc., cost per test could be reduced by an additional 3.1-4.2% for mPIMA, 21-27% for GeneXpert II, 18-24% for GeneXpert IV. Several health facilities included in the LIFE study in Mozambique exceed this threshold with current EID and maternal PoC HIV viral load monitoring demand. In Tanzania, there is sufficient available capacity to run additional assays, particularly in health facilities with GeneXpert IV analyzers.

This underscores the importance of considering both short-term fluctuations and long-term demand patterns when assessing costs, planning EID program expansion, and making decisions about PoC analyzer placement. By accounting for true EID demand and variability over time, policymakers and healthcare providers can make more informed decisions to ensure efficient and sustainable delivery of essential healthcare services for HIV-exposed infants. Increasing EID coverage and linkage to ART will likely require tailored approaches based on local context which may need to combine service delivery approaches semi-decentralized systems[31] and be flexible to reallocating PoC EID resources periodically.

4.6 Strengths and limitations

To our knowledge, this is the largest study providing empirical cost estimates under real-world implementation conditions but has some limitations. Due to the difficulties of obtaining prices for resources procured or paid for by the health system in this setting, we were limited in that there was a lack of available uncertainty estimates for most cost inputs. However, since the cost of the test cartridge represents such a large share of the unit cost per test, cost estimates are sufficiently stable at high utilization, and would change accordingly if the price of test cartridges were to vary. Although we assume it to be minimal, the full share of building costs was also not available, and we included only electricity and one-time investments in key upgrades, namely air conditioning and storage cabinets. Neither recruitment figures from the LIFE CRT nor health facility records of annual HIV-positive deliveries include home deliveries. Further, this analysis excludes explicit examination of cost-effectiveness in terms of value of life and economic costs, which are beyond the scope of this project. Both are important areas of investigation for future studies.

4.7 Conclusions

From a health system perspective, universally offering PoC EID at birth to HIV-exposed infants is more expensive but results in more frequent and significantly earlier ART initiation. Strategic placement and use of limited available PoC platform infrastructure

has the potential to identify and immediately treat neonates with HIV, potentially reducing unacceptably high HIV-related mortality and morbidity. In addition to clinical benefits, economic considerations are important for evaluating the feasibility and sustainability of implementing new interventions HIV testing of neonates and infants. Cost-effectiveness of early infant diagnosis at birth thus depends on the extent to which very early ART initiation reduces mortality. When considering scale-up of EID programs, alternative solutions that increase efficiency of PoC analyzers such as multiplexing for cost-sharing across programs or increasing access to PoC testing through hub-and-spoke service delivery can improve cost-effectiveness.

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Funding

This project was supported by the European and Developing Countries Clinical Trials Partnership (EDCTP), UNAIDS, and German Center for Infection Research (DZIF).

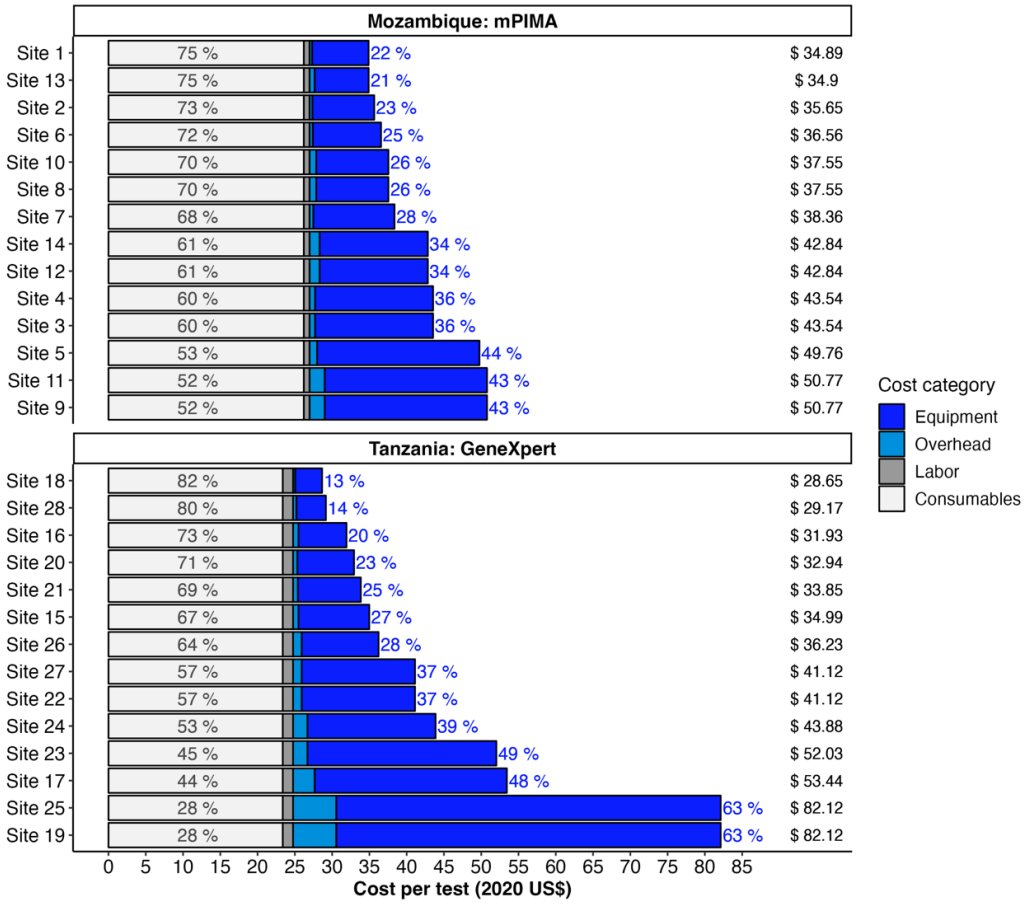
Conflicts of interest

None to declare.

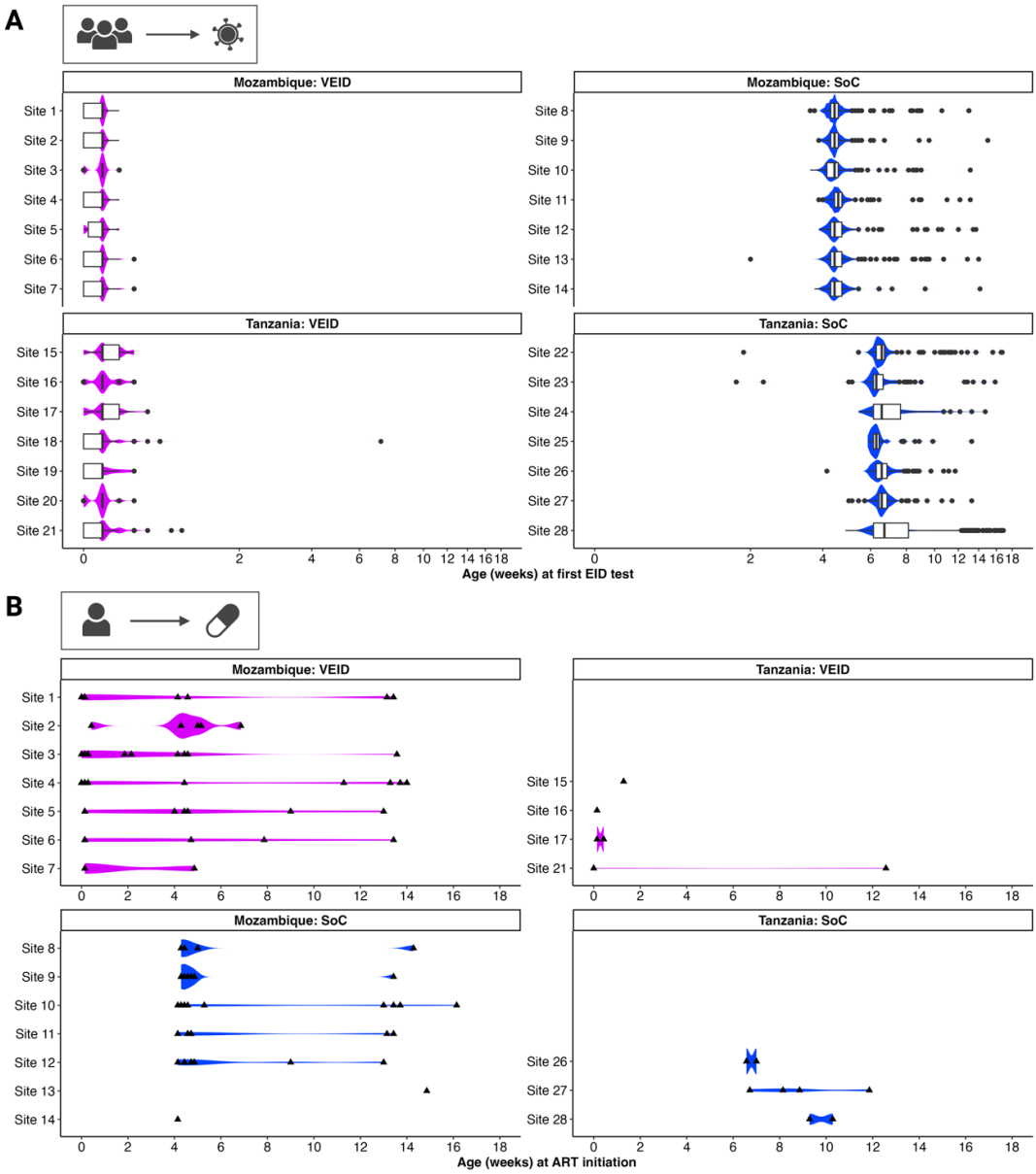
Appendix A: Supplementary figures and tables

List of supplementary figures

List of supplementary tables

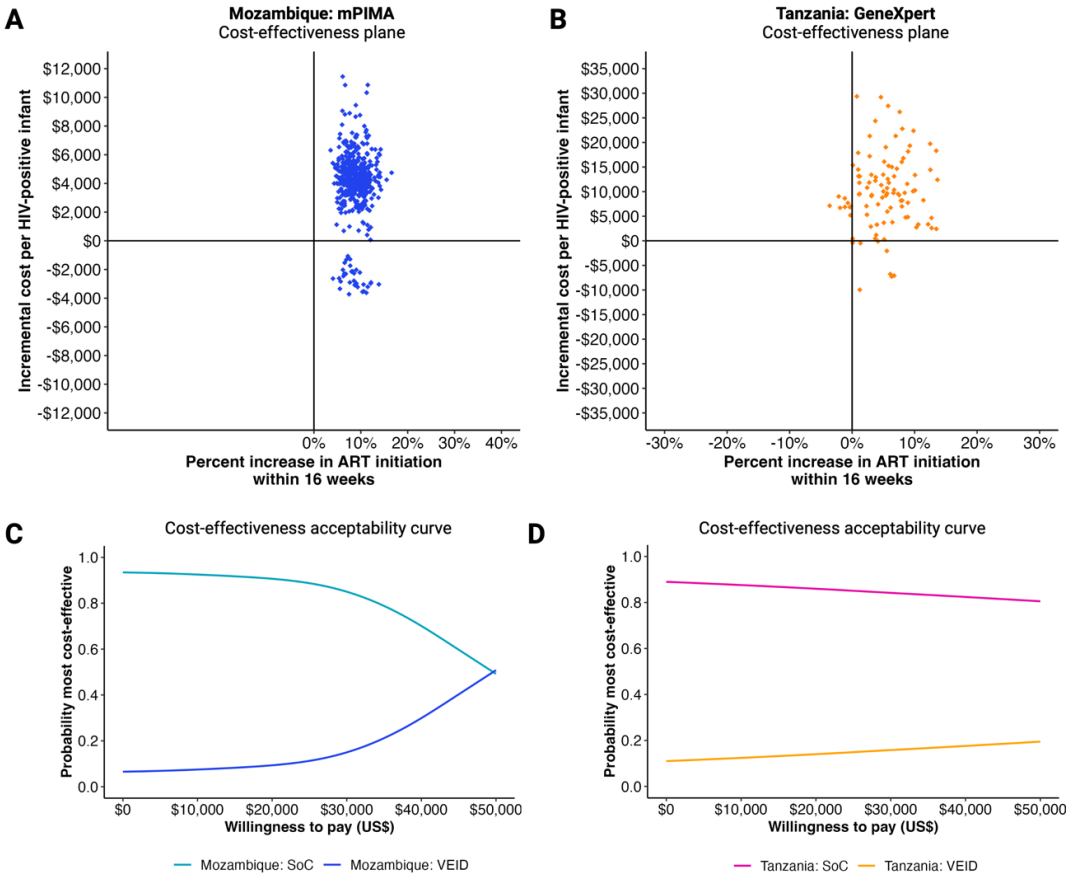


Supplementary Figure 1: Per site point-of-care early infant diagnosis test components. Cost estimates (expressed in 2020 US$) were calculated from the LIFE study data. The proportion of total test cost attributable to consumables is annotated in grey, equipment in blue, and median cost per test in black.



Supplementary Figure 2: Per site time from birth to PoC HIV EID testing and treatment initiation. (A) First EID test among all HIV-exposed infants; **(B)** ART initiation among HIV-positive infants diagnosed up to 16 weeks. VEID sites are in red and SoC sites are in blue.

Abbreviations: VEID = very early infant (HIV) diagnosis; SoC = standard of care; EID = early infant diagnosis; ART = antiretroviral treatment.

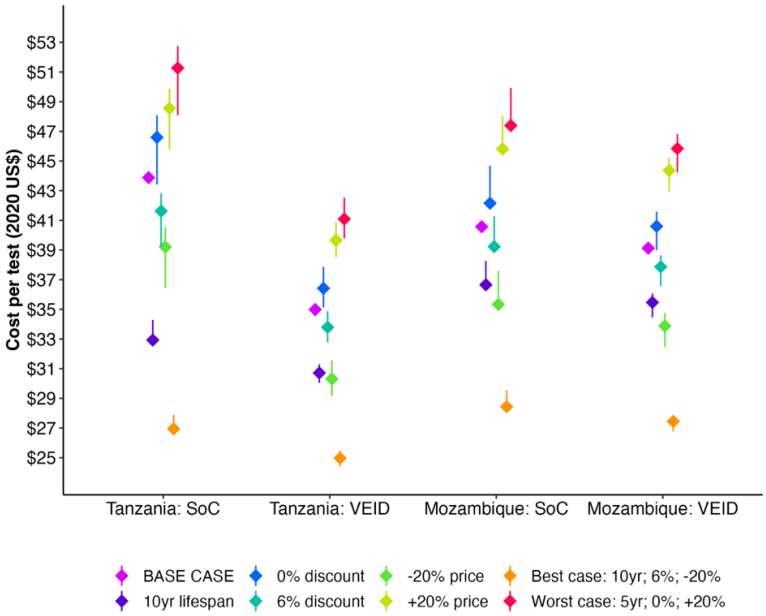


Supplementary Figure 3: Cost-effectiveness of VEID for ART initiation within 16 weeks of age. **(A-B)** Cost-effectiveness planes presenting the incremental costs (2020 US$) and proportion of HIV-positive infants initiated on ART within 16 weeks of age. **(C-D)** Cost-effectiveness acceptability curves showing cumulative probabilities of each testing strategy being cost effective at a particular willingness to pay. Costs are presented as 2020 US$.

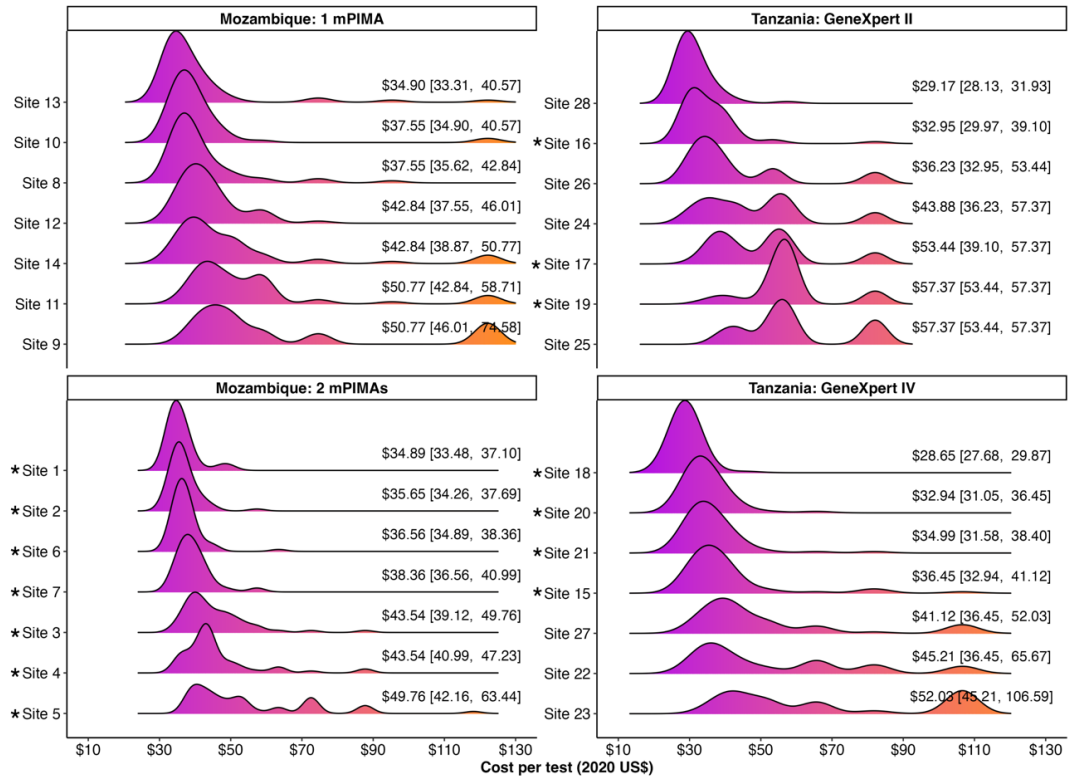
Abbreviations: PoC EID = point-of-care early infant diagnosis; ART = antiretroviral treatment; SoC = standard of care; VEID = very early (HIV) infant diagnosis.

Supplementary Table 1: Sensitivity analysis results.

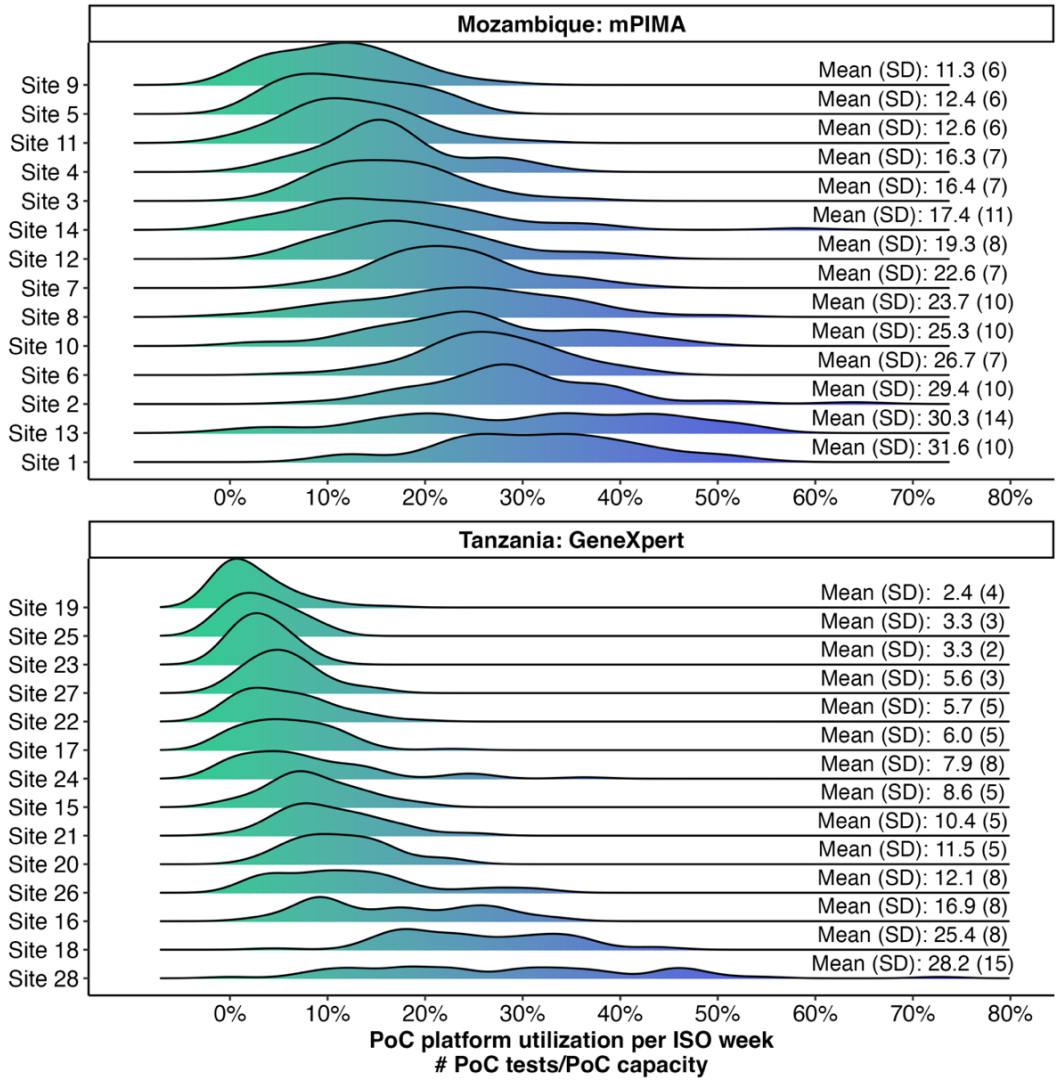
	Mozambique: mPIMA		Tanzania: GeneXpert	
Cost (2020 US$)	**VEID**	**SoC**	**VEID**	**SoC**
Base case: 5yr equipment lifespan, 3% discounting				
Cost per test	39.12 (37.69, 39.99)	40.57 (40.57, 42.84)	36.23 (34.99, 38.40)	43.88 (41.12, 45.21)
Cost per infant	85.44 (84.17, 87.64)	37.05 (36.47, 38.51)	68.34 (67.15, 71.99)	37.38 (35.31, 38.82)
Best case: 10yr equipment lifespan, 6% discount rate, -20% consumables				
Cost per test	27.45 (26.77, 27.86)	28.44 (28.44, 29.55)	24.97 (24.43, 25.47)	26.95 (26.95, 27.90)
Cost per infant	60.31 (59.17, 61.37)	29.56 (25.59, 26.77)	49.72 (48.16, 49.92)	24.80 (23.80, 26.31)
Worst case: 5yr equipment lifespan, 0% discount rate, +20% consumables				
Cost per test	45.84 (44.23, 46.81)	47.39 (47.39, 49.92)	41.09 (39.79, 42.53)	51.27 (48.09, 52.75)
Cost per infant	100.33 (98.48, 102.57)	43.16 (42.59, 44.86)	80.46 (78.82, 84.32)	43.48 (41.28, 45.29)
10yr equipment lifespan				
Cost per test	35.47 (34.47, 36.07)	36.65 (36.65, 38.27)	30.71 (30.05, 31.29)	32.93 (32.93, 34.29)
Cost per infant	77.88 (76.11, 79.76)	33.36 (32.96, 34.49)	60.95 (59.18, 61.31)	30.44 (29.20, 32.04)
0% discount rate				
Cost per test	40.60 (38.99, 41.57)	42.15 (42.15, 44.68)	36.42 (35.12, 37.86)	46.59 (43.41, 48.08)
Cost per infant	88.33 (86.79, 91.54)	38.64 (37.89, 40.16)	71.50 (70.17, 74.92)	40.12 (37.12, 41.28)
6% discount rate				
Cost per test	37.87 (36.59, 38.65)	39.23 (39.23, 41.27)	33.79 (32.79, 34.88)	41.63 (39.21, 42.83)
Cost per infant	83.04 (81.12, 84.49)	35.70 (35.27, 37.10)	66.64 (65.01, 69.00)	35.10 (33.67, 36.77)
20% lower consumable prices				
Cost per test	33.88 (32.45, 34.75)	35.33 (35.33, 37.60)	30.31 (29.18, 31.56)	39.21 (36.45, 40.54)
Cost per infant	74.05 (72.06, 76.30)	32.53 (31.77, 33.81)	59.58 (57.99, 62.14)	33.74 (30.95, 34.81)
20% higher consumable prices				
Cost per test	44.36 (42.93, 45.23)	45.81 (45.81, 48.08)	39.66 (38.52, 40.90)	48.55 (45.80, 49.89)
Cost per infant	97.50 (94.84, 98.95)	41.57 (41.17, 43.21)	78.52 (76.39, 81.04)	40.74 (39.32, 42.91)



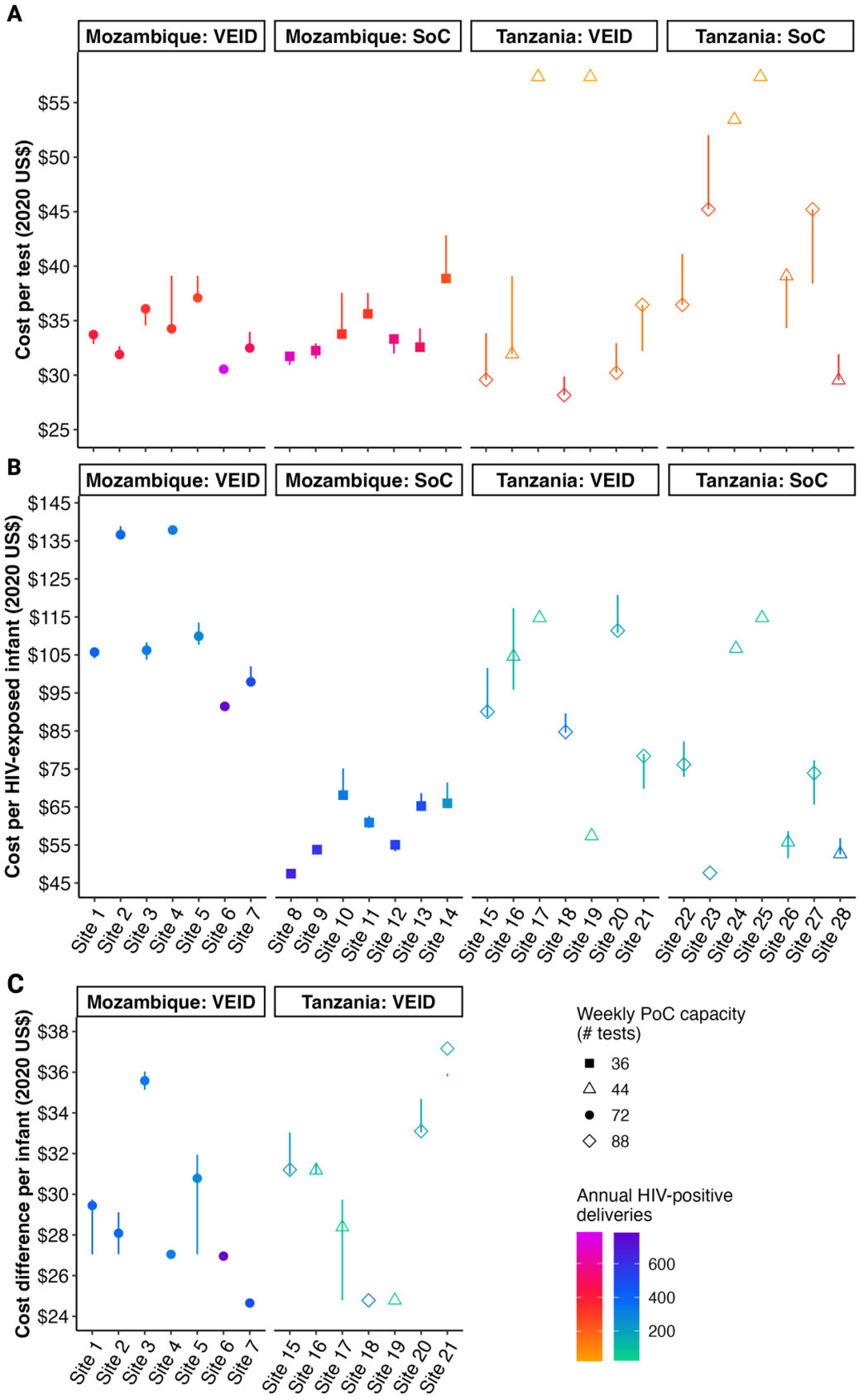
Supplementary Figure 4: Sensitivity analysis results, cost per test. For each country and PoC testing approach, median cost (2020 US$) and 95% uncertainty intervals are shown. The base case, which assumes a 5-year PoC platform lifespan and 3% discount rate is depicted in pink. Equipment lifespan extended to 10 years is shown in purple, 0% and 6% discount rates in blue, and 20% increase and decrease in the price of consumables (e.g., test cartridge) in green. A best-case scenario is shown in orange and a worst-case scenario in red.



Supplementary Figure 5: Per site PoC EID test cost and variability. VEID sites are marked with **"*"**. Distribution, median, and 95% confidence interval (Hodges Lehman estimate) of cost per test (2020 US$) across LIFE study weeks.



Supplementary Figure 6: Per site PoC platform utilization. Distribution, mean, and standard deviation (SD) of number of PoC tests run weekly divided by weekly platform capacity and expressed as a percentage. Early infant diagnosis and HIV viral load testing recorded in the LIFE study and average unspecified routine use of analyzers in Tanzania (12%) were included.



Supplementary Figure 7: Per site PoC EID costs based on EID demand. Costs (2020 US$) estimated from LIFE study data scaled to the number of annual HIV-positive deliveries per site from routine data. **(A)** Cost

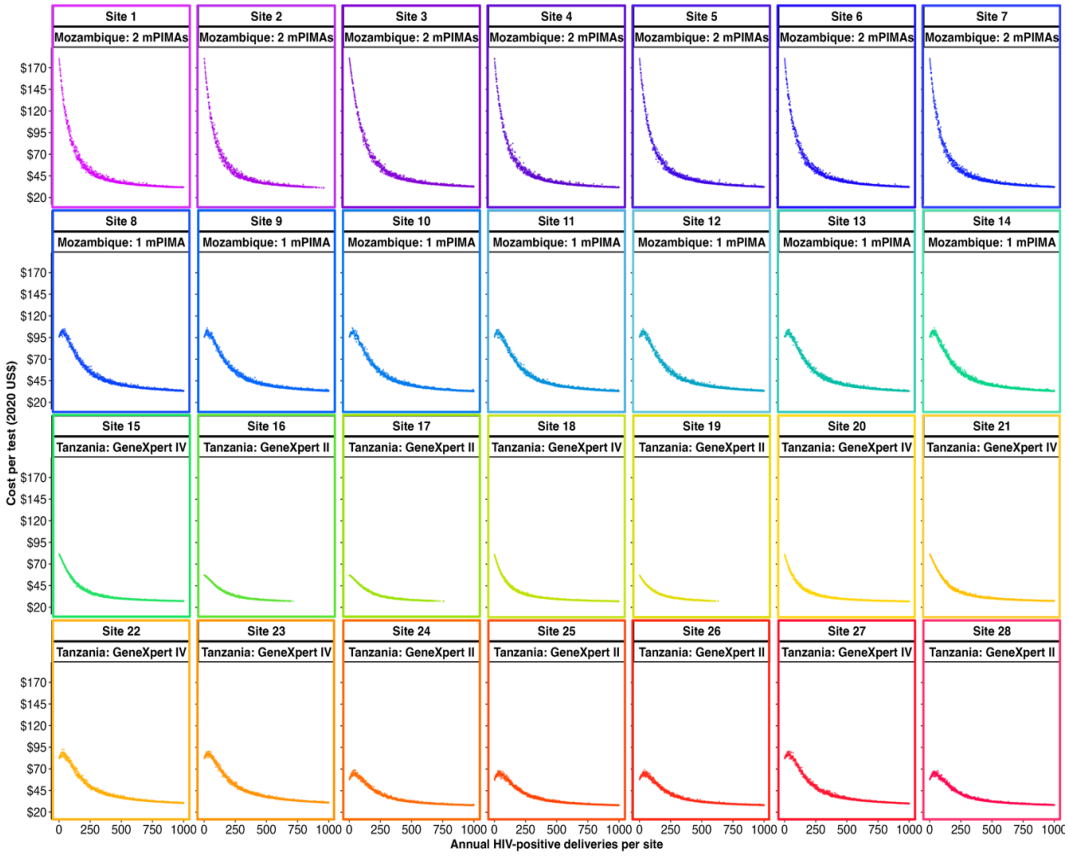
per test, **(B)** cost per infant, and **(C)** additional cost of VEID compared to SoC per infant. Vertical lines show bias-corrected adjusted (BCA) 95% uncertainty intervals. Different shapes indicate weekly capacity of PoC analyzers. Color ramps indicate mean annual number of HIV-positive deliveries per site.

Abbreviations: VEID = very early infant (HIV) diagnosis; SoC = standard of care; PoC = point-of-care.

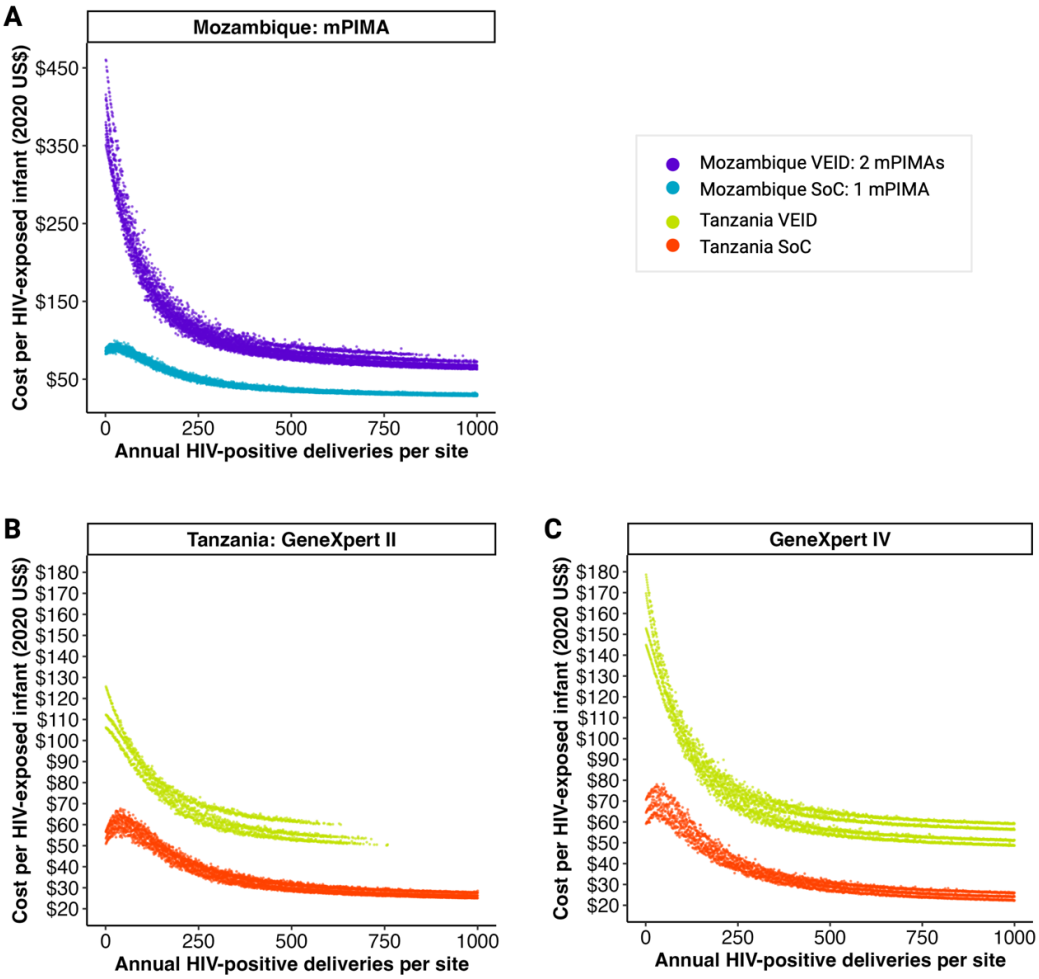
Supplementary Table 2: Yearly costs per site. Estimated costs are based on PoC EID test costs scaled to EID demand and cross-utilization of PoC platforms by routine programs.

Cluster	PoC tests per delivery[a]	Median cost (2020 US$) per HIV-exposed infant	Total cost (2020 US$) per year
Mozambique: VEID			
Site 1	3.25	$79.29 (77.67-80.38)	$33,983
Site 2	3.49	$88.17 (87.41-94.64)	$32,243
Site 6	3.04	$65.51 (64.67-66.44)	$30,207
Site 7	3.00	$70.32 (69.91-73.61)	$26,274
Site 3	2.87	$74.08 (71.94-75.87)	$20,054
Site 4	3.25	$86.02 (85.52-97.28)	$19,392
Site 5	2.99	$79.67 (77.48-82.79)	$17,311
Mozambique: SoC			
Site 13	0.91	$35.20 (35.17-38.76)	$18,190
Site 8	0.87	$30.53 (29.55-30.69)	$16,517
Site 10	0.95	$40.91 (40.30-47.75)	$16,056
Site 12	0.87	$33.18 (31.57-35.09)	$14,563
Site 14	0.91	$46.87 (45.63-65.87)	$11,864
Site 11	0.92	$40.13 (39.05-41.94)	$10,868
Site 9	0.90	$33.08 (31.75-33.46)	$10,710
Tanzania: VEID			
Site 18	3.41	$59.94 (59.83-63.55)	$24,450
Site 20	3.64	$69.91 (69.41-76.90)	$13,035
Site 21	3.09	$64.42 (58.56-64.79)	$11,375
Site 15	3.23	$58.71 (57.38-68.34)	$9,656
Site 16	3.33	$69.41 (64.56-76.60)	$8,887
Site 17	3.05	$106.3 (-)	$4,416
Site 19	3.60	$126.24 (-)	$1,722
Tanzania: SoC			
Site 28	1.01	$29.07 (29.01-31.77)	$17,946
Site 22	0.91	$44.45 (40.76-51.43)	$9,519
Site 27	0.99	$52.98 (44.67-56.37)	$9,375
Site 26	1.05	$38.67 (36.14-40.56)	$8,702
Site 23	0.84	$34.22 (32.49-37.38)	$7,602
Site 24	1.13	$52.33 (43.02-43.02)	$5,972
Site 25	1.14	$56.21 (-)	$3,591

[a] Includes multipliers for twins and triplets, repeated tests due to error or confirmatory testing, and loss to retention at follow-up testing



Supplementary Figure 8: Per site simulated EID program cost per test. Costs are represented as 2020 US$. Rows 1-2 show sites in Mozambique; rows 3-4 show sites in Tanzania; rows 1 & 3 show VEID sites; rows 2 & 4 show SoC sites. Numbers and types of PoC analyzers are indicated above each plot.



Supplementary Figure 9: Simulated EID program cost per infant. Costs are represented as 2020 US$. Different colors represent VEID and SoC conditions.

Appendix B: Supplementary methodology

Categorization of PoC testing volume

Total PoC testing volume, including EID, maternal HIV viral load, and routine unspecified use of PoC analyzers in Tanzania was calculated for the entire LIFE CRT recruitment period and is shown in **Figure SM1** by health facility.

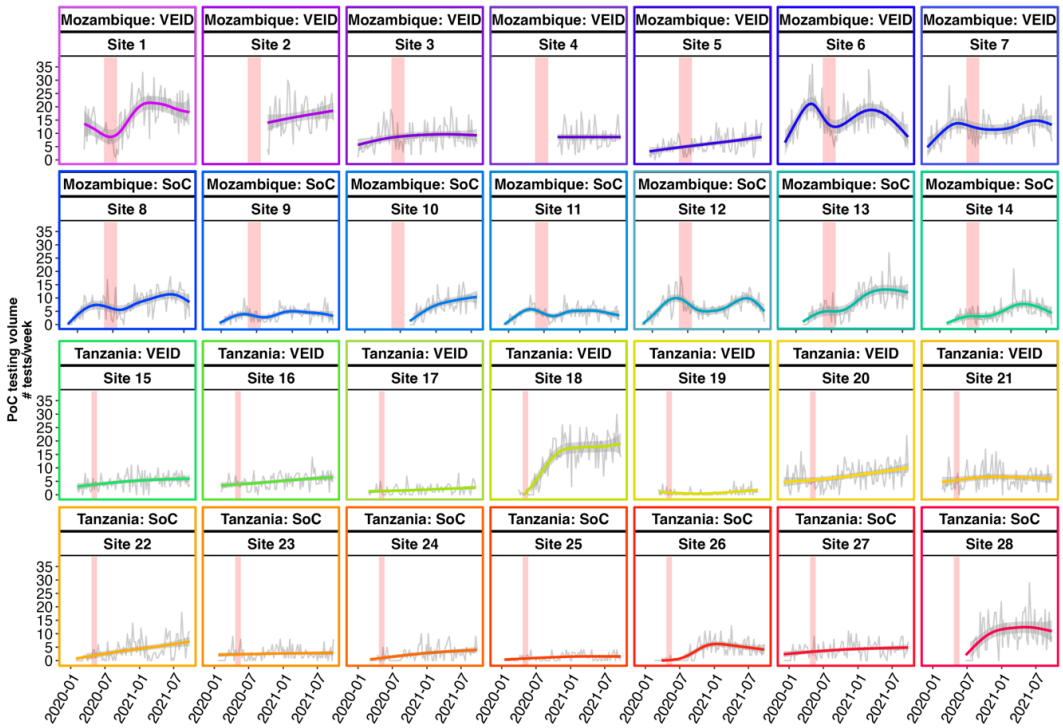


Figure SM1: Point-of-care testing volume, total number of tests per week. Data reflects testing performed over the recruitment period in the LIFE CRT, including EID, maternal HIV viral load testing, and average routine use of analyzers in Tanzania (12% of total tests). Weeks were defined using the ISO week date system to calculate testing volume, with weeks starting on Monday and week 01 defined as the first week with 4 or more of its days in January. Gamma smoothed curves with 95% uncertainty intervals are shown by colored lines and grey shading. A study recruitment pause due to the COVID-19 pandemic is indicated by pink shading; follow-up visits and testing were still occurring during this time.

Based on the distribution of PoC tests per ISO week across health facilities, excluding the first six weeks of study recruitment and recruitment pauses due to COVID-19 lock-downs from 13 May to 27 July 2020 in Mozambique and from 17 April to 25 May 2020 in Tanzania, we split sites into low (<5 tests per week), medium (5-12 tests per week), and high (>12 tests per week) volume categories for easier comparison of unit cost components shown in **Figure 5**. EID, maternal HIV viral load, and other routine use of analyzers were included in health facility PoC testing volumes. The distribution of weekly PoC testing volume and division of sites into the above categories is shown in **Figure SM2**.

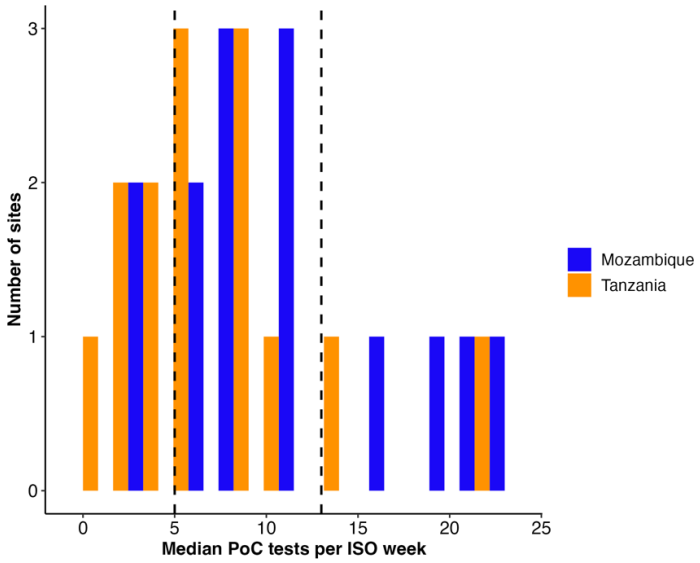


Figure SM2: Histogram of median PoC tests per ISO week with divisions for low-, medium-, and high-volume sites shown by dashed lines.

Fixed cost calculation

Five-year platform cost was calculated from CHAI estimates and purchase invoices and included initial purchase, shipping, customs clearance, installation, insurance, and yearly maintenance. Costs of PoC platforms were discounted at 3% per year in the base case. Each site in the LIFE study had one PoC platform except in Mozambique where VEID sites had two PoC platforms. Fixed costs were calculated per site by uniformly distributing equipment costs on annual and weekly time scales over the lifespan of the equipment.

$$Annual\ fixed\ cost_{test} = \frac{\left(\frac{5yr\ platform\ cost}{5yrs}\right) \times No.\ platforms + \frac{Training\ cost}{5yrs} + 1yr\ Overhead\ cost}{\lfloor No.\ PoC\ tests/yr \rfloor}$$

$$Weekly\ fixed\ cost_{test} = \frac{\frac{5yr\ platform\ cost}{5 \times 52\ wks} \times No.\ platforms + \frac{Training\ cost}{5 \times 52\ wks} + \frac{1yr\ Overhead\ cost}{52\ wks}}{\lfloor No.\ PoC\ tests/wk \rfloor}$$

where $\lfloor . \rfloor$ is the floor function.

Variable cost calculation

Prices of test consumables including the test cartridge and sample collection materials were obtained from CHAI. Salary information was obtained from MoH salary scales. We calculated the share of salary attributable to PoC EID assuming a 248-day year or 38 hours per week and multiplied this by the self-reported average estimated active work time required for pre-test counseling, sample collection, running the PoC EID test, communication of results and post-test counselling if needed.

$$Variable\ cost_{test} = \ Cost\ of\ test\ consumables + (Nurse\ salary \times Active\ work\ time)$$

Unit cost calculation

$$Cost_{test} = Fixed\ cost_{test} + Variable\ cost_{test}$$

$$Cost_{infant} = (Fixed\ cost_{test} + Variable\ cost_{test}) \times No.PoC\ test + \left(\begin{bmatrix} 1wk\ ART\ cost \times 4wks \mid Moz \\ 1wk\ ART\ cost \times 6wks \mid Tan \end{bmatrix} \middle| HIV_{pos}\right)$$

Cost estimates for referral laboratory-based testing for resolution of discrepant results or in case reagents were not available at the sites were not available and therefore were not included. However, these cases were minimal in the LIFE study.

Economic modelling approach – HIV-positive infant outcomes

An economic model was parameterized using empirical data for individual-level costs and health effects from the LIFE CRT. As HIV-positive infants represented only a small proportion of enrolled HIV-exposed infants, population point estimates and uncertainty intervals were used for proportions initiated on ART within 1-week and 16-weeks and additional weeks on early ART. To construct uncertainty intervals for ICERs, we simulated costs (**Figure SM3**) and health effects (**Figures SM4 to SM6**) for HIV-positive infant outcomes from the empirical data and calculated ICERs and 95% BCA uncertainty intervals from 1000 bootstrap samples. This ensures that uncertainty in costs and ART outcomes is propagated throughout the economic model and decision analysis.

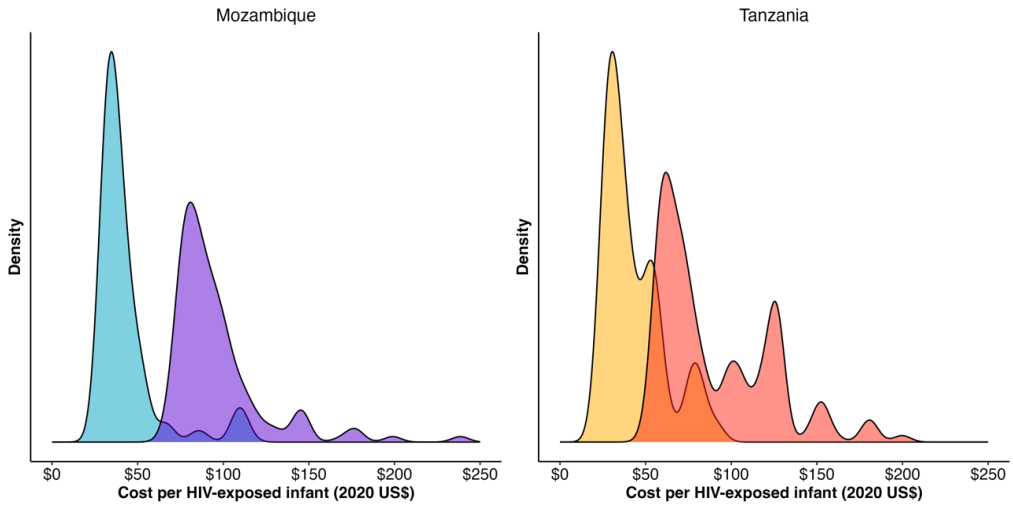


Figure SM3: Empirical cost per infant distributions used in economic model. VEID shown in purple and orange and SoC in blue and yellow.

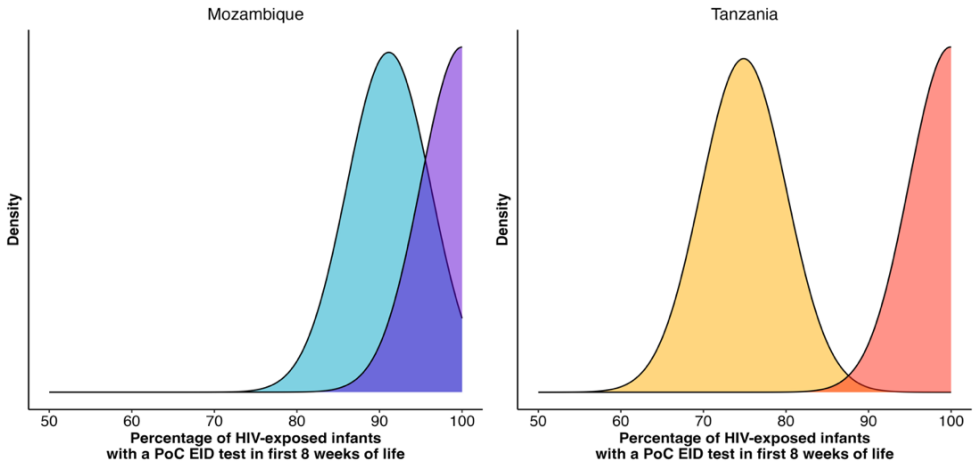


Figure SM4: Empirical health effect: percentage of HIV-exposed infants with a PoC EID test within 8 weeks of life distributions used in economic model. VEID shown in purple and orange and SoC in blue and yellow.

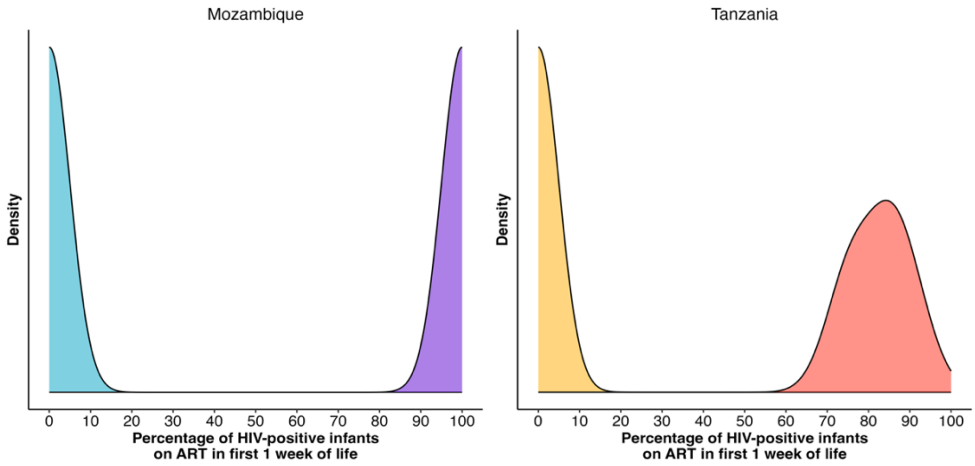


Figure SM5: Empirical health effect: percentage of HIV-positive infants on ART within 1 week of life distributions used in economic model. VEID is shown in purple and orange and SoC in blue and yellow.

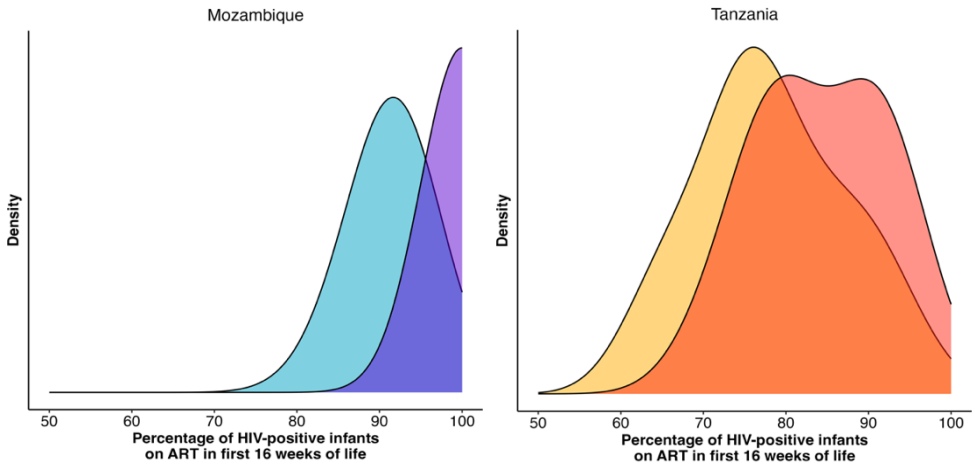


Figure SM6: Empirical health effect: percentage of HIV-positive infants on ART at all during the study (i.e., within the first 16 weeks of life) distributions used in economic model. VEID shown in purple and orange and SoC in blue and yellow.

Utilization thresholds

To determine meaningful thresholds for PoC analyzer utilization based on reduction in cost per test, we fit monotonic cubic splines to the cost per test versus utilization data for each PoC analyzer and country. The fits are shown in **Figure SM7**. Pragmatic thresholds were chosen as the first point on the fitted line where the first derivative equates to a $0.50 reduction in cost per test per 1% increase in utilization. These were 23.0% for mPIMA in Mozambique, 16.1% for GeneXpert II, and 13.6% for GeneXpert IV analyzers in Tanzania.

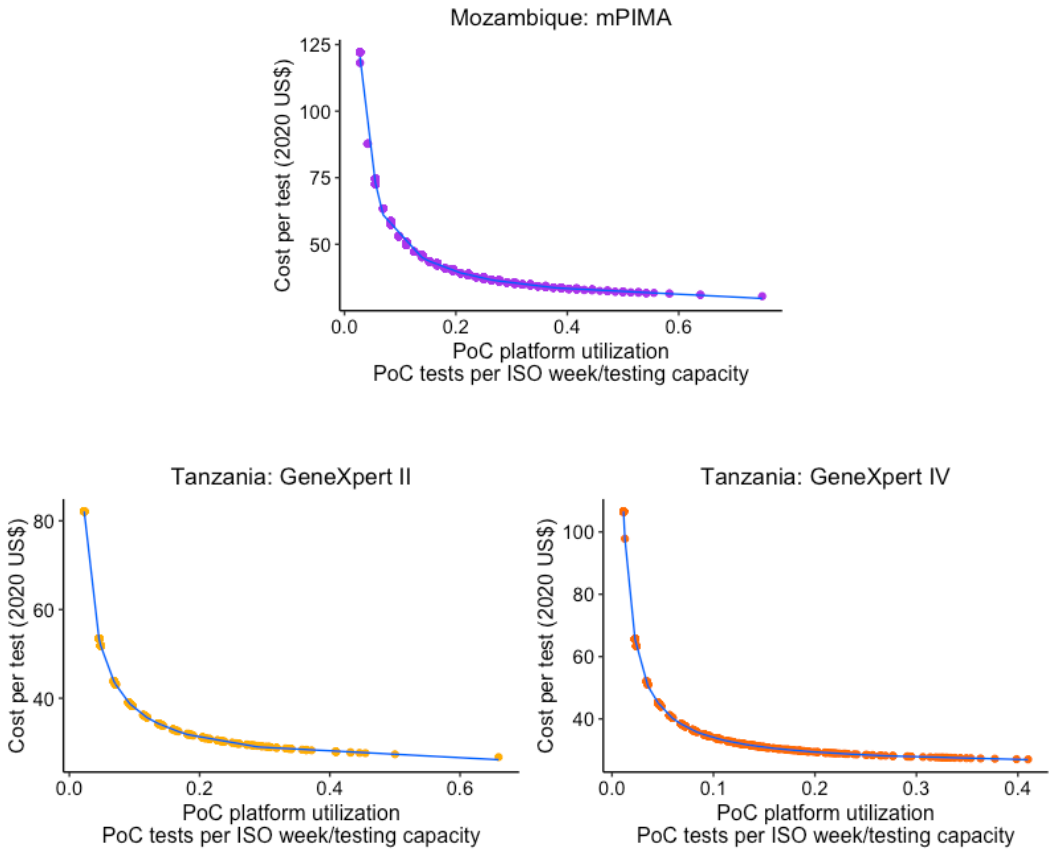


Figure SM7: Spline regression fits for cost per test versus utilization used to determine threshold values. Colored points indicate empirical values and blue lines indicate spline fits for each PoC platform.

Scaling LIFE CRT PoC testing volume to routine EID demand based on annual HIV-positive deliveries

We first examined the distribution of deliveries across ISO weeks in the LIFE CRT, and the per country results are shown in **Figure SM5**. Most individual health facilities had similar patterns of deliveries over the calendar year (results not shown), so we used the country-level distribution and resampled mean annual deliveries **(Table SM1)** from this distribution. Number of deliveries from 10,000 bootstrap samples were then converted to number of PoC tests (EID, maternal HIV viral load, and routine analyzer use in Tanzania) using LIFE CRT multipliers (Supplementary Table 2) and costs and uncertainty intervals estimated.

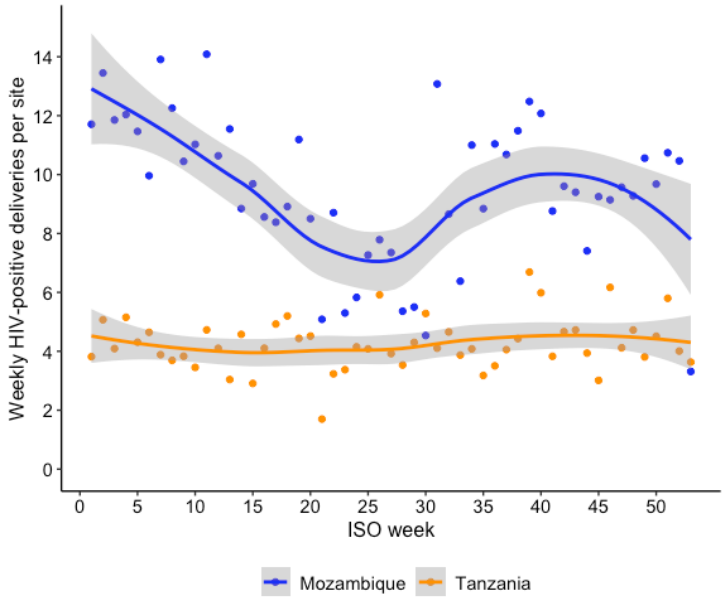


Figure SM8: Distribution of HIV-positive deliveries over the calendar year. Weeks were defined using the ISO week date system to calculate testing volume, with weeks starting on Monday and week 01 defined as the first week with 4 or more of its days in January. Monotonic cubic spline fits shown by colored lines and 95% uncertainty intervals in grey are plotted to improve visualization of trends.

Table SM1: Health facility information including annual number of HIV-positive deliveries.

Health facility	Label	Province	District	Annual HIV+ deliveries[a]
Mozambique				
1 de Maio Health Center	Site 1	Manica	Chimoio	409
7 de Abril Health Center	Site 2	Manica	Chimoio	391
Macurrungo Health Center	Site 3	Sofala	Beira	325
Mafambisse Health Center	Site 4	Sofala	Dondo	320
Mascarenhas Health Center	Site 5	Sofala	Beira	281
Munhava Health Center	Site 6	Sofala	Beira	785
Ponta Gea Health Center	Site 7	Sofala	Beira	494
Chingusurra Health Center	Site 8	Sofala	Beira	659
Dondo Health Center	Site 9	Sofala	Dondo	583
Gondola District Hospital	Site 10	Manica	Gondola	327
Manga Loforte Health Center	Site 11	Sofala	Beira	322
Nhaconjo Health Center	Site 12	Sofala	Beira	538
Nhamaonha Health Center	Site 13	Manica	Chimoio	491
Vila Nova Health Center	Site 14	Manica	Chimoio	243
Tanzania				
Chimala Hospital	Site 15	Mbeya	Mbarali	240
Igogwe Hospital	Site 16	Mbeya	Rungwe	108
Kiwanjampaka Health Center	Site 17	Mbeya	Mbeya	52
Mbarali Hospital	Site 18	Mbeya	Mbarali	337
Mtanila Health Center	Site 19	Mbeya	Chunya	24
Ruanda Health Center	Site 20	Mbeya	Mbeya	180
Songwe Regional Referral Hospital	Site 21	Songwe	Mbozi	135
Chunya Hospital	Site 22	Mbeya	Chunya	171
Igawilo Health Center	Site 23	Mbeya	Mbeya	252
Ilembo Hospital	Site 24	Mbeya	Mbeya	85
Itete Hospital	Site 25	Mbeya	Busokelo	63
Mwambani Hospital	Site 26	Songwe	Songwe	162
Tukuyu Hospital	Site 27	Mbeya	Rungwe	166
Tunduma Health Center	Site 28	Songwe	Tunduma	350

[a] Mean number of annual HIV-positive deliveries for available data from years 2018, 2021, and 2022 recorded in health facility records.

A non-parametric bootstrap procedure was employed to scale study recruitment data to routine HIV-positive deliveries per site, resampling from the empirical distribution to allocate annual HIV-positive deliveries over ISO weeks in whole number increments. We then converted deliveries to numbers of PoC tests, accounting for multiple births, confirmatory testing, errors, retention to follow-up testing, and additional use of the analyzers for maternal HIV viral load and other routine testing. Multipliers were estimated from LIFE CRT data, and we conservatively rounded down to the nearest whole number of PoC tests. Repeated testing due to errors and retention at follow-up testing varied widely between sites. An increased frequency of errors was observed for birth testing compared to testing at later timepoints (data not shown). As we had a sufficiently large number of tests and repeat tests, these differences were considered at the site level between birth and follow-up visits. The proportion of multiple births were considered at the country level.

Costs were then recalculated for each health facility based on scaled figures and median cost per test and cost per infant is reported in the main text. We estimated medians and BCA 95% uncertainty intervals from 10,000 bootstrap samples. A comparison of study (with yearly and weekly distribution of equipment costs) and scaled cost estimates is provided in **Figure SM6**.

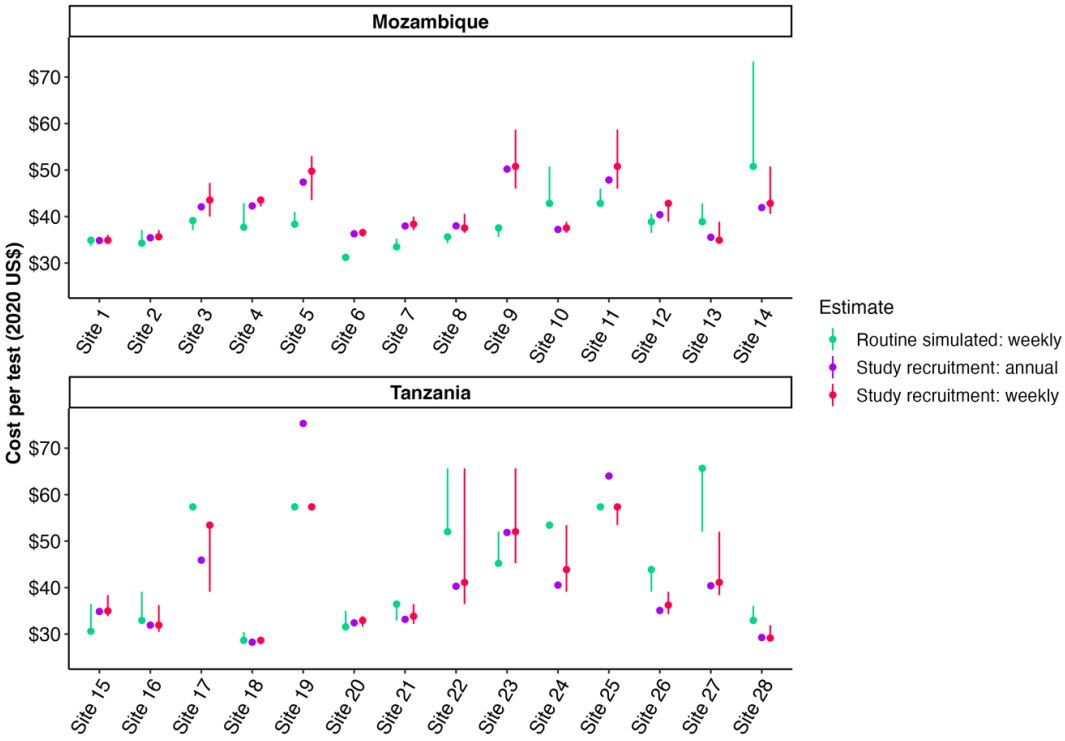


Figure SM9: Cost per test estimated from the LIFE CRT and scaled data. Routine simulated scales study recruitment data to routine annual deliveries per site while preserving variability in PoC testing demand over time using resampling to allocate whole number deliveries across ISO weeks and multipliers estimated from LIFE CRT data to convert number of deliveries to number of PoC tests. Study recruitment annual and weekly use empirical costs calculated from the LIFE CRT with equipment costs distributed uniformly over one year and one week, respectively.

Using scaled cost estimates, ICERs were approximately 5% higher in Mozambique at $455.45 ($436.02, $475.81) for HIV-exposed infant 8-week PoC EID testing and $3,945 ($3,805, $4,057) for HIV-positive infant 1-week ART initiation. In Tanzania however, ICERs across all sites were 25% higher at $140.84 ($128.27, $157.13) and $13,480 ($12,430, $15,285) with respect to the above outcomes. ICERs per additional ART initiation at all were $45,272 ($43,309, $47,462) in Mozambique and $201,953 ($174,840, $234,689) in Tanzania. However, as average HIV-positive annual deliveries from routine data were actually lower than annual adjusted study recruitment numbers in several sites in Tanzania, we did not include these results in the main text.

Appendix C: CHEERS checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	title page
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	pg. 3
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	pg. 9-13
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	pg. 19
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	pg. 15-16
Setting and location	6	Provide relevant contextual information that may influence findings.	pg. 15-16
Comparators	7	Describe the interventions or strategies being compared and why chosen.	pg. 16-18
Perspective	8	State the perspective(s) adopted by the study and why chosen.	pg. 19
Time horizon	9	State the time horizon for the study and why appropriate.	pg. 16-17, 19
Discount rate	10	Report the discount rate(s) and reason chosen.	pg. 20
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	pg. 22-23
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	pg. 19, 22
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	pg. 22-23
Measurement and valuation of resources and costs	14	Describe how costs were valued.	pg. 19-22

Topic	No.	Item	Location where item is reported
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	pg. 19
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	na
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	pg. 23-25
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	na
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	na
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	pg. 23-24
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	na
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	pg. 25-26
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	pg. 25-31
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	pg. 32-38
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	na
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	pg. 39-42

Topic	No.	Item	Location where item is reported
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	pg. 48
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	pg. 48

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008.

Appendix D: Additional contributions

A) Funding acquisition
B) Publications in preparation

Funding acquisition

To expand the scope of economic evaluation work originally planned as part of the LIFE CRT into the work presented here, supplementary funding was needed. In collaboration with the Heidelberg Institute of Global Health (HIGH) at Heidelberg University, I acquired a three-year German Center for Infection Research (DZIF) flex fund totaling 100,000 Euros. This funding was used to partially compensate this PhD position, to support a senior researcher at HIGH who provided methodological guidance throughout the project, to support the African partners sites who collected the cost data, for international travel to the African partner sites, and for publication fees. Administration of the grant was the responsibility of HIGH; however, reporting was carried out primarily by the PhD candidate.

Publications in preparation

The results presented in this dissertation have been prepared for publication in two manuscripts: one detailing the costs and cost-effectiveness evidence with respect to early ART initiation in the LIFE CRT and one containing the results of the impact of PoC platform utilization on costs, scaling costs to routine demand, and strategies to improve utilization of PoC testing devices. Both manuscripts are ready for submission. Due to result dissemination agreements within the LIFE study research consortium however, these manuscripts can only be submitted once the main results of the LIFE study are accepted for review and are therefore on hold until that time. The planned publications are currently titled:

1. Costs and cost-effectiveness of point-of-care HIV test-and-treat at birth
    a. *Target journal: Lancet HIV*
2. Scaling-up point-of-care early infant HIV diagnosis at birth in Mozambique and Tanzania: costs and cost-effectiveness
    a. *Target journal: Bulletin of the World Health Organization*

Acknowledgements

I'd like to express my gratitude to my supervisors, especially my working group leader, Dr med. Arne Kroidl, for his support and patience, for exposing me to many exciting opportunities, and for allowing me to work on multiple other projects throughout this process. Thank you to Prof. Dr med. Michael Hölscher and Prof. Dr. Dr. Till Bärnighausen for your encouragement and insightful feedback that have kept me on track and to Dr med. Stefan Kohler for your methodological guidance and thorough review of my rambling thoughts and doodles that I continue to try to pull together into a polished piece of scientific contribution.

A special thank you to the LIFE study teams in Mozambique and Tanzania for your willingness to engage in countless discussions about study procedures and resource use and for tracking down the elusive price data essential to this project. Thank you for welcoming me into your countries and cultures, experiences that I will always remember and carry with me.

Thank you to the research nurses in the field, study participants, and funders including EDCTP, UNAIDS, and DZIF, without whom this project would not have been possible. Thank you to the EPH PhD program coordinators for patiently walking me through the somewhat tedious administrative requirements and reminding me to actually submit before the deadline.

And to my family and friends, I will eventually find a way to make up the many hours you were forced to spend pretending to listen to me talk about the work that I am deeply passionate about, willingly or not. I am immensely grateful for your support, encouragement, and persistent check-ins after the occasional long periods of non-response.

The work continues, but I will acknowledge that this is a major milestone.

Curriculum vitae

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Experience

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Sep. 2012-Dec. 2016	BSc with Distinction in Microbiology and Immunology University of British Columbia, Vancouver, BC, Canada • Faculty of Science International Student Scholarship, 2015 • Outstanding International Student Award, 2012
Sep. 2013-Apr. 2015	Diploma with Honours in Biotechnology British Columbia Institute of Technology, Burnaby, BC, Canada

List of publications

1. Gudina EK, **Elsbernd K**, Yilma D, Kisch R, Wallrafen-Sam K, Abebe G, Mekonnen Z, Berhane M, Gerbaba M, Suleman S, Mamo Y, Rubio-Acero R, Ali S, Zeynudin A, Merkt S, Hasenauer J, Chala TK, Wieser A, Kroidl A. Tailoring COVID-19 Vaccination Strategies in High-Seroprevalence Settings: Insights from Ethiopia. Vaccines (Basel). 2024 Jul 5;12(7):745. doi: 10.3390/vaccines12070745.
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3. **Elsbernd K**, Emmert-Fees KMF, Erbe A, Ottobrino V, Kroidl A, Bärnighausen T, Geisler BP, Kohler S. Costs and cost-effectiveness of HIV early infant diagnosis in low- and middle-income countries: a scoping review. *Infect Dis Poverty.* 2022 Jul 15;11(1):82. doi: 10.1186/s40249-022-01006-7.
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7. Moore SL, Portz JD, Santodomingo M, **Elsbernd K**, McHale M, Massone J. Using Telehealth for Hospice Reauthorization Visits: Results of a Quality Improvement Analysis. *J Pain Symptom Manage.* 2020 Sep;60(3):e22-e27. doi: 10.1016/j.jpainsymman.2020.06.002. Epub 2020 Jun 7.
8. Portz JD, **Elsbernd K**, Plys E, Ford KL, Zhang X, Gore MO, Moore SL, Zhou S, Bull S. Elements of Social Convoy Theory in Mobile Health for Palliative Care: Scoping Review. *JMIR Mhealth Uhealth.* 2020 Jan 6;8(1):e16060. doi: 10.2196/16060.
9. Dickman Portz J, Ford K, Bekelman DB, Boxer RS, Kutner JS, Czaja S, **Elsbernd K**, Bull S. "We're Taking Something So Human and Trying to Digitize": Provider Recommendations for mHealth in Palliative Care. *J Palliat Med.* 2020 Feb;23(2):240-247. doi: 10.1089/jpm.2019.0216. Epub 2019 Sep 17.

List of international conference abstracts

1. **Elsbernd K,** Sabi I, Jani I, Mudenyanga C, Boniface S, Lequechane J, Chale F, Meggi B, Lwilla AF, Buck WC, Hoelscher M, Baernighausen T, Ntinginya NE, Kroidl A, Kohler S. Cost and cost-effectiveness of scaling-up point-of-care very early infant diagnosis in Mozambique and Tanzania. *IAS AIDS 2024,* Munich, Germany.
2. Mahumane A, Lwilla AF, **Elsbernd K**, Rauscher M, Meggi B, Pereira K, Lequechane J, Chale F, Boniface S, Edom R, Mudenyanga C, Mueller M, Buck WC, Taveira N, Hoelscher M, Jani I, Ntinginya NE, Kroidl A, Sabi I. Differences in risk factors between high and low vertical HIV transmission settings: Implications for elimination of pediatric HIV. *IAS AIDS 2024,* Munich.
3. Kisch R, Adissu W, Girma E, **Elsbernd K**, Ali S, Wieser A, Geldmacher C, Kroidl A, Gudina EK. Longitudinal SARS-CoV-2 antibody and cellular immune responses during the endemic phase in people living with and without HIV in Ethiopia. *IAS AIDS 2024,* Munich, Germany.
4. Sabi I, **Elsbernd K**, Meggi B, Lwilla AF, Ntinginya NE, Pereira K, Mahumane A, Boniface S, Edom R, Lequechane J, Chale F, Mudenyanga C, Mutsaka D, Mueller M, Buck WC, Hoelscher M, Jani I, Kroidl A. PA-276 Differences in risk factors between a high and low vertical HIV transmission setting: implications for elimination of new paediatric HIV infections. *BMJ Global Health.* Dec 2023, 8 (Suppl 10) A56-57; DOI 10.1136/bmjgh-2023-EDC.138
5. Pereira K, Mahumane A, Buck WC, Mueller M, Patrácio A, Bocharnikov S, Lequechane J, Maviga M, Ndarissone J, Chale F, **Elsbernd K**, Meggi B, Kroidl A, Jani I. Barriers to ART adherence in neonates and infants from the LIFE study in Mozambique. *IAS AIDS 2023,* Brisbane, Australia.
6. Kroidl A, **Elsbernd K**, Meggi B, Mahumane A, Lwilla AF, Pereira K, Boniface S, Edom R, Lequechane J, Chale F, Mudenyanga C, Mueller M, Buck WC, Sabi S, Jani I. Birth point-of-care test & treat reduces early mortality among HIV-infected infants. *Topics in Antiviral Medicine*, 2023; 31:2.
7. Lwilla AF, **Elsbernd K**, Mahumane A, Meggi B, Buck WC, Boniface S, Edom R, Lequechane J, Mudenyanga C, Mueller M, Kroidl A, Jani I, Sabi I. Maternal point-of-care viral load at delivery impacts infant ARV prophylaxis regimen. *Topics in Antiviral Medicine*, 2023; 31:2.
8. **Elsbernd K**, Sabi I, Lequechane J, Boniface S, Mudenyanga C, Buck WC, Mahumane A, Meggi B, Pereira K, Mueller M, Baernighausen T, Hoelscher M, Kroidl A, Jani I, Kohler S. Cost of an HIV test-and-treat strategy at birth and its effect on ART initiation. *Topics in Antiviral Medicine,* 2022; 30:1.

Affidavit

Elsbernd, Kira

Surname, first name

Address

I hereby declare, that the submitted thesis entitled

Costs and cost-effectiveness of neonatal HIV early infant diagnosis (EID) versus standard of care EID in Mozambique and Tanzania

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

Munich, 12 December 2024
Place, Date

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Signature doctoral candidate

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Dean's Office Medical Faculty
Doctoral Office

Confirmation of congruency between printed and electronic version of the doctoral thesis

Doctoral candidate: Kira Elsbernd

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I hereby declare that the electronic version of the submitted thesis, entitled

Costs and cost-effectiveness of neonatal HIV early infant diagnosis (EID) versus standard of care EID in Mozambique and Tanzania

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