Does Provision of Point-of-Care CD4 Technology and Early Knowledge of CD4 Levels Affect Early Initiation and Retention on Antiretroviral Treatment in HIV-Positive Pregnant Women in the Context of Option B+ for PMTCT?

Alexio-Zambezi Mangwiro, BSc,* Kudzai Makomva, BA,* Antoinette Bhattacharya, MPH,* Gaurav Bhattacharya, MD, MPH,* Tendai Gotora, MPhil,* Mila Owen, BSc,* Angela Mushavi, MBChB, MMed,† Douglas Mangwanya, BSc, Sekesai Zinyowera, PhD,† Simbarashe Rusakaniko, PhD,† Owen Mugurungi, MD,† Simukai Zizhou, MBChB, MPH,† William Busumani, MBChB, MPH,† and Nyasha Masuka, MBChB, MPH†

Abstract: Evidence for Elimination (E4E) is a collaborative project established in 2012 as part of the INSPIRE (INtegrating and Scaling up PMTCT through Implementation REsearch) initiative. E4E is a cluster-randomized trial with 2 arms; Standard of care and “POC Plus” [in which point-of-care (POC) CD4 devices and related counseling support are provided]; aimed at improving retention-in-care of HIV-infected pregnant women and mothers. In November 2013, Zimbabwe adopted Option B+ for HIV-positive pregnant women under which antiretroviral treatment eligibility is no longer based on CD4 count. However, Ministry of Health and Child Care guidelines still require baseline and 6-monthly CD4 testing for treatment monitoring, until viral load testing becomes widely available. Considering the current limited capacity for viral-load testing, the significant investments in CD4 testing already made and the historical reliance on CD4 by health care workers for determining eligibility for antiretroviral treatment, E4E seeks to compare the impact of the provision of POC CD4 technology and early knowledge of CD4 levels on retention-in-care at 12 months, with the current standard of routine, laboratory-based CD4 testing. The study also compares rates of initiation and time-to-initiation between the 2 arms and according to level of maternal CD4 count, the cost of retaining HIV-positive pregnant women in care and the acceptability and feasibility of POC CD4 in the context of Option B+. Outcome measures are derived from routine health systems data. E4E will provide data on POC CD4 testing and retention-in-care associated with Option B+ and serve as an early learning platform to inform implementation of Option B+ in Zimbabwe.

Key Words: PMTCT, POC CD4, retention, Option B+, Zimbabwe, time-to-initiation

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BACKGROUND

In Zimbabwe, geographical coverage and uptake of services to prevent mother-to-child transmission of HIV (PMTCT) is high. As of 2011, 95% of public health facilities offered PMTCT services, 98% of pregnant women presented for their first antenatal clinic (ANC) booking, 86% of pregnant women needing PMTCT services received antiretroviral drug (ARV) prophylaxis, and early infant diagnosis services were available in 92% of PMTCT facilities. Although mother-to-child transmission (MTCT) rates in Zimbabwe have declined from an estimated 30% in 1999 to 14% in 2010, barriers remain to achieving the global goal of less than 5% MTCT by 2015.

The Zimbabwe Ministry of Health and Child Care (MOHCC) adopted and launched Option B+ in November 2013 and began a staggered rollout in 2014. Before the introduction of Option B+, PMTCT interventions were based on the World Health Organization 2010 “Option A” and coverage of lifelong antiretroviral treatment (ART) for HIV-positive pregnant women who needed ARVs for their own health was relatively low at 27%.[1] This was mainly attributed to poor access to CD4 testing for eligibility assessment. More than 60% of PMTCT sites sent CD4 samples for testing to central laboratories, but results were often delayed or never received because of insufficient samples or transportation systems. To overcome the barriers to CD4 testing, the MOHCC introduced a rapidly scaled-up point-of-care (POC) CD4
testing, and more than 350 devices were deployed in PMTCT settings countrywide.

With the introduction of the Option B+ policy, which provides lifelong ART for all HIV-positive pregnant and breastfeeding women, eligibility assessment for ART based on CD4 count is no longer required. However, MOHCC guidelines still require baseline and 6-monthly CD4 testing for ART monitoring, until viral load testing becomes widely available. Considering the current limited capacity for viral load testing, critical resource constraints, the recent heavy investments in CD4 testing capacity (both POCD4 and conventional), and the historical reliance on CD4 by health care workers (HCWs) for determining eligibility for ART, important implementation questions emerged regarding the continued role of CD4 testing. In particular, the MOHCC sought to understand the impact of both patient and HCW knowledge of CD4 count and counseling on patient behavior under Option B+—specifically behaviors influencing initiation and adherence to ART. It was considered that providing women with their CD4 count at the time of initiating ART might change the attitudes of women toward lifelong care and result in different levels of retention-in-care.

Evidence for Elimination (E4E), Zimbabwe, is a collaborative project involving the Clinton Health Access Initiative, MOHCC, University of Zimbabwe, and the World Health Organization, with financial support from the Department for Foreign Affairs, Trade and Development, Canada. The project was established in 2012 to examine key implementation questions regarding PMTCT in Zimbabwe. E4E sites have also served as pilot sites for the rollout of Option B+ in Zimbabwe and provided early lessons to inform Option B+ policy. This manuscript describes the methods and design of the ongoing cluster randomized trial implemented in 3 provinces of Zimbabwe to examine the potential benefits of POCD4 testing, knowledge of CD4 counts, and enhanced counseling on rates of retention-in-care of HIV-positive pregnant women.

**RESEARCH QUESTION**

“In the context of Option B+ for PMTCT, does the provision of POCD4 technology at primary health centers and early knowledge of CD4 levels among HCWs and patients affect mean time-to-initiation of ART, and the proportion of HIV-positive pregnant women retained-in-care?”

The primary objective of the study is to compare rates of retention of HIV-positive pregnant women at 12 months post-initiation in settings implementing Option B+, with or without POCD4 testing capability and related counseling support.

The secondary objectives of the study will compare:

1. Rates of ART initiation and time-to-initiation of HIV-positive pregnant women
2. Retention in care of HIV-positive pregnant women at 6 months post-initiation
3. Rates of ART initiation and retention at 6 and 12 months post-initiation according to maternal CD4 count

The study will also assess:

1. Cost of POCD4 testing and related counseling support as an adjunct intervention for retaining HIV-positive pregnant women in care
2. Acceptability and feasibility of POCD4 as an adjunct intervention to improve the clinical care of HIV-positive pregnant women.

**Protocol Development, Randomization, and Site Readiness**

The original protocol, which was developed before the MOHCC decided to revise the national PMTCT protocol from Option A to Option B+, proposed to investigate whether use of POCD4, to establish ART eligibility, would significantly increase the proportion of HIV-positive pregnant women who initiated ART. Following the decision by Zimbabwe to adopt Option B+, the protocol was revised in July 2013 to examine related important questions regarding the role of CD4 within the new Option B+ policy context.

E4E worked closely with MOHCC and partners to update PMTCT training manuals and monitoring and evaluation (M&E) tools for accelerated introduction and training on Option B+. Sites were provided with updated M&E and patient management tools. Support was given to subnational authorities and sites to build capacity and to accredit all sites to offer ART services. After pre-testing in E4E sites, study-specific data collection tools (Case Report Forms, Combined Competency Checklists) and guidance on POCD4 device use were updated to further support E4E sites.

Based on 2011 MOHCC ART coverage data, the PMTCT provinces with the lowest coverage of PMTCT ARV interventions were identified. Of these 4 provinces, 1 was excluded because of other implementing partners providing significant support to facilities and it was considered that this would likely influence study outcomes. The 388 remaining PMTCT sites in the 3 other provinces were considered eligible for inclusion in the study. Based on the 2012 MOHCC ART data, sites were excluded if:

- No women had been initiated on ART in 2012 (6 sites),
- ART initiation rates were ≥80% (51 sites),
- Fewer than 24 women tested HIV positive in ANC in 2012 (222 sites) (this would require long enrolment periods to achieve sample size),
- Previous or existing POCD4 capacity (28 sites),
- Routine data were internally inconsistent (10 sites) (poor quality routine data may have jeopardized the measurement of study outcomes).

Of the remaining 71 sites, 12 were excluded because of challenging geographical access, leaving 59 facilities available for randomization into the 2 study arms.

Sensitization meetings to introduce the study to national, provincial, district, and site-level stakeholders were conducted. Before Option B+ implementation, all facilities received a comprehensive site preparation support visit. A minimum of 6 weeks elapsed between these visits...
and the start of study enrolment, during which time they received support to establish routine practices and gained experience on implementing Option B+; this allowed facilities to achieve a stable implementation state before commencement of enrolment of women to the study.

METHODS

Design, Study Population, and Summary of Interventions

The study is a 2-arm, cluster-randomized trial with 16 sites in each arm—Standard of care (SOC) and “POC Plus.” Pregnant women testing HIV positive in ANC or with previously verified positive status and presenting up to 38-week gestation and more than 48 hours before delivery were eligible for enrolment. Women already on ART or testing HIV positive in labor, delivery, or during breastfeeding were excluded from the study but still received ART as part of the Option B+ program.

Control and “POC Plus” Intervention Arms

The MOHCC recommends a baseline CD4 for treatment monitoring purposes and same-day initiation of ART. Sites in both arms received training in Option B+, supply chain management, data management and data quality.

Patients at SOC sites received the MOHCC-recommended package and quality of care for Option B+. Patients at these sites received CD4 testing at referral laboratories and with variable delays before return of test results, according to routine procedures. At these control sites, E4E staff provided limited ongoing supervision and retraining with respect to technical aspects of Option B+.

POC Plus sites were provided with POC CD4 devices and training on their use. HCWs were also trained in counseling skills and provision of CD4-specific messaging using a pre-defined counseling script and received mentoring to reinforce the recommended baseline and 6-monthly CD4 testing. E4E personnel provided supervision and mentoring that focused on consistent testing and quality control of the POC CD4 devices. In the POC Plus arm, E4E tracked counselor performance over time using a competency checklist that was based on the same counseling script and standardized messages regarding initiation of ART and how patients can be helped to understand their CD4 results, including both high and low CD4 levels and rising and falling CD4 levels over time.

Data Sources and Data Management

Outcome measures were derived from routine health systems data. Data quality is being evaluated at baseline, midpoint, and end of study, using an EXCEL-based Data Quality Assessment tool adapted from the MEASURE RDQA toolkit; feedback on findings are given to HCWs and district supervisors to inform improvements.

At baseline and end of study, E4E is administering a Site Inventory tool at all sites to collect data on key site characteristics that might have influenced study outcomes. These data are used to assess effectiveness of site randomization and to track changes in key characteristics. Patient and visit data from registers—including but not limited to age, gestational age at booking, HIV test date, CD4 count, ART initiation date, ANC, and postnatal visits information—are captured using paper-based Case Report Forms.

Working in pairs, research assistants abstract data onto Case Report Forms every 8 weeks and rotate between sites for quality assurance. At each visit, previously abstracted data are checked for accuracy, eligible women are identified, and sociodemographic and subsequent ART and ANC visit data are also collected. Standard operating procedures for each data management function were developed and tested to safeguard the quality and security of data.

Key Definitions

Retention in care is defined as:

1. Attendance at postnatal clinic at 12 months post-ART initiation, with an allowance of 2 weeks either side of the 12-month marker, as well as
2. Attendance at 75% (or more) of scheduled visits through the first 12 months on ART, as per MOHCC recommended schedule.

Loss to follow-up is defined as:

1. Failure to attend at 12 months post-initiation (with an allowance of 2 weeks either side of the 12-month marker), as well as
2. Attendance of less than 75% of scheduled visits.

Deaths are considered as loss to follow-up but are noted separately. Transfers out, even if informed to project team, are also considered loss to follow-up because the study has no mechanism for verifying this indicator.

SAMPLE SIZE ESTIMATION

National data on PMTCT retention-in-care and comparable regional data in the context of Option B+ were not available. E4E assumed the 12-month retention rate under SOC to be 69.7%. This was estimated by averaging the following:

1. Rate of retention-in-care of adults on ART in sub-Saharan Africa—median of 52.1%;
2. Rate of retention-in-care for HIV-positive adults in Zimbabwe between 2007 and 2010—average 78.1%;
3. Rate of retention-in-care at 12 months for Option B+ in Malawi—estimated at 79.0%.

In these estimates, retention-in-care was inconsistently defined but generally meant attendance at a specified time point without reference to attendance at prior visits.

We calculated the sample size required to detect a 15% absolute difference in 12-month retention rate between SOC
and POC Plus arms, that is, 69.7% and 85%, respectively. The number of clusters required was derived using the formula from Hayes and Moulton\(^5\) (Table 1). The average number of HIV-positive pregnant women enrolling in care per site per year was 45 (2012, MOHCC), and half of them were women already on ART and therefore ineligible for inclusion in this study. We therefore assumed that up to 22 HIV-positive pregnant women would be eligible to enroll per facility per year (Table 2).

Assuming that there are 16 clusters per arm, retention outcomes at 12 months post-ART initiation are required on a minimum of 22 HIV-positive pregnant women per site. To account for missing data, the sample size was increased by 15% such that 26 participants are enrolled per site, giving a total of 832 women across 32 sites over a 12- to 18-month enrolment period.

### ANALYSIS PLAN

The study’s primary outcome measure is the proportion of HIV-positive pregnant women retained on ART 12 months post-ART initiation, with or without POC CD4 and counseling support.

Secondary outcome measures are as follows:

1. Proportion of HIV-positive pregnant women retained on ART 6 months after initiation, with or without POC CD4 and related counseling support,
2. Proportion of HIV-positive pregnant women initiated and retained on ART at 6 and 12 months post-ART initiation, categorized by levels of CD4 count,
3. Proportion of HIV-positive pregnant women initiating ART within 1 month of a positive HIV diagnosis,
4. Median time-to-initiation between positive HIV diagnosis and enrolment on ART (Option B+), and
5. Cost-effectiveness of POC CD4 and counseling support over the SOC per woman retained on ART at 6 and 12 months post-ART initiation.

The study randomizes the intervention at the facility level and the analysis will control for facility-level covariates in the regression framework. The following analyses will be conducted:

- **Baseline comparisons and randomization checks** to examine differences in baseline and at end of study characteristics of health facilities that have been randomized to the study arms. The analysis will also provide point estimates and standard errors for covariates to be used in adjusting any imbalances during the multivariate analyses.
- **Univariate analyses of key outcomes** unadjusted for possible confounders to provide point estimates of key study outcomes. Estimates of the means and standard deviations of key outcomes will be compared across arms using unpaired \(t\) test at the 5% level of significance, with corresponding output (\(P\)-values and \(t\) statistics) for the difference in means across arms.
- **Multivariate analyses** including **probit** and linear probability models will be used to assess the impact of the intervention on primary and secondary outcomes.
- **Subgroup analyses** will be run for retention outcomes at 6 and 12 months post-ART initiation, to examine differential impact by patient CD4 count. Additional subgroup analyses also include cross-sectional models estimating the impact of the intervention on: time-to-initiation, turnaround time between diagnosis and provision of CD4 result, and the proportion of pregnant women initiating within 1 month of testing positive for HIV.
- **Costing analyses** to assess the relative cost-effectiveness of POC CD4 and related counseling support over the SOC will be analyzed by summarizing all start-up and recurrent costs (both financial and economic) associated with delivering Option B+ treatment across study arms.

### ETHICAL CONSIDERATIONS

The E4E study is not seeking individual informed consent because CD4 testing (laboratory-based or POC) of

### TABLE 1. Formula for Estimating Cluster Size

\[
c = 1 + \left( z_b + z_p \right)^2 \times \left( \frac{\pi_0(1-\pi_0) + \pi_1(1-\pi_1) \times [1 + (m-1)\rho]}{m(\pi_0 - \pi_1)^2} \right)
\]

- \( c \) = number of clusters per study arm
- \( z_b^2 = 1.96 \) assuming a 2-sided significance level = 0.05
- \( \beta = 0.84 \) assuming 80% power
- \( z\beta = 1.96 \) assuming a 2-sided significance level = 0.05
- \( \pi_0 = \) proportion with outcome in study arm \( x \)
- \( \pi_1 = \) proportion with outcome in study arm \( y \)
- \( m = \) number of individuals in each cluster (assumed to be 22)
- \( \rho = \) intracluster correlation coefficient (0.13)

### TABLE 2. Assumption for Estimation of Cluster Size for E4E Study

<table>
<thead>
<tr>
<th>Pairwise Comparisons for Primary Outcome</th>
<th>Intracluster Correlation Coefficient</th>
<th>No. Pregnant Women ART-Eligible per Facility</th>
<th>( \pi_0 ): Proportion With Outcome in Study Arm ( x )</th>
<th>( \pi_1 ): Proportion With Outcome in Study Arm ( x )</th>
<th>No. Clusters Needed Per Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC vs. POC Plus</td>
<td>0.095</td>
<td>22</td>
<td>0.697</td>
<td>0.85</td>
<td>16</td>
</tr>
</tbody>
</table>
HIV-positive pregnant women is part of SOC in Zimbabwe and only routine health system data are being collected for the analyses. Facility-level consent was granted by the national and provincial MOHCC authorities, and the protocol was approved by the Medical Research Council of Zimbabwe. Male partners, children, and ineligible HIV-positive pregnant women accessing care at study intervention sites will have access to all available services including POC CD4 testing, although they are not part of the study population.

**Timelines and Status**

Enrolment began in January 2014. By the end of May 2014, 2 rounds of data abstraction and mentoring/supportive supervision visits were complete (Fig. 1). Of all eligible participants (293), 96% (282) were initiated on ART in ANC. Target enrolment is expected to be completed by January 2015. Consequently, the 12-month follow-up of participants to ascertain the primary outcome is expected to end around January 2016 and data analysis and reporting of results to be completed in April 2016.

**Challenges and Limitations**

The study relies on routine health systems data, which have the advantages of ready availability, low cost to abstract, and provides an opportunity for the study procedures to strengthen the quality of future data. However, there are also inherent disadvantages—particularly the risk of poor quality data. Outcomes such as deaths and transfers of study participants may not always be available from routine data and this can potentially bias analyses on retention-in-care. The study will also not be able to disaggregate the effects of the individual components of the intervention, namely, the provision of the POC CD4 device and counseling support focused on...
early knowledge of CD4 count. Furthermore, the study does not actively measure community factors that may influence retention-in-care. Finally, by applying inclusion and exclusion criteria to the facilities that would be involved in the study, there may be some selection bias that may limit the generalizability of results.

RELEVANCE TO THE NATIONAL PROGRAM

The E4E study will provide detailed quantitative information on the feasibility and acceptability of starting ART on the same day as HIV testing, which is the current desired SOC, and assess the impact of enhanced counseling on same day as ART initiation. The study will also provide detailed information on rates of retention according to the time to ART initiation (that is; early, rapid initiation associated with better or worse retention outcomes), and the relationship of the mother’s known CD4 level to retention-in-care. The study will also provide insight into the utility and feasibility of POC CD4 in the context of Option B+ and the influence of mentoring and counseling support on retention rates. These will be important inputs for informing future investment and refinement of what should be SOC. Cost and cost-effectiveness data will be available to guide program planning, budgeting, and resource mobilization. The study also has relevance beyond Zimbabwe, especially in settings where CD4, in combination with a mentoring package, may be used as an alternative to viral load testing until viral load becomes more affordable and accessible.

As an early learning platform for the implementation of Option B+, E4E provides regular updates and feedback to MOHCC through quarterly investigator bulletins and the quarterly MOHCC PMTCT Partnership Forum. In this way, E4E is contributing to learning at national level and has informed Option B+ rollout and implementation (Fig. 2).

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