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Improving PMTCT Uptake and Retention Services Through Novel Approaches in Peer-Based Family-Supported Care in the Clinic and Community: A 3-Arm Cluster Randomized Trial (PURE Malawi)

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Abstract: In July 2011, Malawi introduced an ambitious public health program known as "Option B+," which provides all HIV-infected pregnant and breastfeeding women with lifelong combination antiretroviral therapy, regardless of clinical stage or CD4 count. Option B+ is expected to have benefits for HIV-infected women, their HIV-exposed infants, and their HIV-uninfected male sex partners. However, these benefits hinge on early uptake of prevention of mother-to-child transmission, good adherence, and long-term retention in care. The Prevention of mother-to-child transmission Uptake and REtention (PURE) study is a 3-arm cluster randomized controlled trial to evaluate whether clinic- or community-based peer support will improve care-seeking and retention in care by HIV-infected pregnant and breastfeeding women, their HIV-exposed infants, and their male sex partners, and ultimately improve health outcomes in all 3 populations. We describe the PURE Malawi Consortium, the initial work conducted to inform the trial and interventions, the trial design, and the analysis plan. We then discuss concerns and expected contributions to Malawi and the region.

Key Words: HIV, PMTCT, peer, retention, uptake, antiretroviral therapy, Option B+, Malawi

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BACKGROUND

In July 2011, Malawi introduced an ambitious public health program known as "Option B+," which provides all HIV-infected pregnant and breastfeeding women with immediate, lifelong combination antiretroviral therapy (ART), regardless of clinical stage or CD4 count.[1] By eliminating complex prevention of mother-to-child transmission (PMTCT) algorithms, delays from CD4 testing, and ART reinitiations with each pregnancy, Option B+ has simplified the PMTCT process, with expected important benefits for HIV-infected women, their HIV-exposed infants, and their HIV-uninfected sex partners.[2–4] Although early results indicate dramatic increases in ART initiation for the target population, important concerns have surfaced about suboptimal uptake and retention.[5,6]

Peer-based strategies have been effective for improving maternal and infant uptake and retention in comparable settings.[6–12] However, most assessments were not delivered in an Option B+ setting, and it is not known how best to operationalize these interventions in Option B+. Furthermore, most published assessments were not randomized and did not

have consistent outcome measures, making it difficult to determine whether, and to what degree, apparent benefits were simply because of selection of higher functioning sites and participants with better care-seeking behaviors. It is not known whether peer-based strategies will be as effective when studied using a more rigorous randomized design. Nor is it known whether a clinic-based model or a community-based model is more effective in retaining patients on treatment, or encouraging them to return to care if they drop out.

The PMTCT Uptake and REtention (PURE) study is a 3-arm cluster randomized controlled trial to evaluate whether clinic- and community-based peer support by women living with HIV who have been involved in PMTCT interventions themselves will improve uptake and retention of mothers and infants under Malawi's Option B+ program. The overarching hypothesis is that clinic-based peer support and community-based peer support will improve maternal uptake and 2-year retention, as well as other maternal, infant, and male partner outcomes. We describe the trial management structure, interventions, design, and analysis plan, as well as challenges and expected contributions that this study can make.

THE PURE MALAWI CONSORTIUM

The PURE trial is managed by the PURE Malawi Consortium, comprised of governmental, nongovernmental, and academic partners. Consortium members were selected based on experience with Malawi-based PMTCT programming with a goal of national representation. The Consortium is led by Lighthouse Trust, an organization dedicated to integrated HIV/AIDS prevention, clinical care, and capacity building in Malawi. Dignitas International, the University of Malawi College of Medicine Malaria Alert Centre, and University of North Carolina Project are each responsible for trial implementation in 1 Malawian zone—the South East, South West, and Central West, respectively. Mothers2Mothers, Dignitas International, and Lighthouse led intervention development as these organizations were already working with peer-based programs and back-to-care interventions.[13–15] Technical assistance is provided by Management Sciences for Health. Support for health economics research is provided by the University of Malawi Chancellor College. The Malawi Ministry of Health is an integral partner providing strategic leadership and guidance, and is directly involved at national and district levels. The Consortium oversees the PURE Malawi trial, initial site assessments, the formative research that informed intervention development, a qualitative and economic substudy, and ancillary analyses.

SITE ASSESSMENTS, SELECTION, AND RANDOMIZATION

The trial is being conducted in the South East, South West, and Central West health zones of Malawi. In these zones, a situational analysis was conducted in 35 sites from 8 districts to identify potential trial sites. During situational analysis site visits, partners gathered information on the type of facility, nature of HIV-related services, staffing, and presence of community, clinic and research activities already in place for women enrolled in Option B+. In addition, information on rates of ART initiation and retention were obtained from national Ministry of Health monitoring data from Quarter 3 of 2012.

Sites were eligible if they provided Option B+ services, did not have other PMTCT interventions or research activities beyond the Malawi national standard of care, and were expected to have at least 20 women eligible for Option B+ in a 6-month period. The expected number of eligible women was estimated by doubling the number of quarterly pregnant and breastfeeding women initiating Option B+.

Across the 3 zones, 29 of 35 sites met these eligibility criteria. Based on power and budget considerations, 21 of these 29 eligible sites were included in the trial (7 per zone). In the Central West and South West the 7 sites were selected at random. In the South East, the 3 largest sites were all selected to ensure a mixture of large and small facilities, and the remaining 4 were selected at random (Fig. 1).

The 21 sites were stratified into 7 groups of 3, with each group having sites of comparable size and expected retention. The facilities in each group of 3 were then randomly allocated into 1 of the 3 study arms: standard of care, clinic-based peer support, or community-based peer support. The randomized controlled study is being complemented by a longitudinal mixed methods qualitative and economic substudy at 6 of these sites.

FORMATIVE RESEARCH

Formative research was used to establish a baseline for the qualitative and economic substudies and to refine and finalize the 2 intervention arms. Economic and qualitative research was conducted in the first quarter of 2013. Six trial sites were purposively selected—2 from each region with an attempt to include a mixture of patient volumes, levels of care, ownership, location, and PMTCT experience.

In the economic component, a survey was implemented to learn about health service delivery, including the types of services offered, equipment available, staffing levels, and caregiver involvement. Through this survey, we learned that defaulter tracing was rarely, if ever, occurring in any of the facilities. Additionally, most facilities had few or no health surveillance assistants (HSAs), lay health providers, who were trained in PMTCT. There was reported to be substantial support given to patients by caregivers in the homes, but little spouse accompaniment to facilities.

In the qualitative component, barriers and facilitators of Option B+ uptake and retention were explored through focus group discussions with 48 health providers and in-depth semistructured interviews with 24 patients. This work identified a need for patient education and psychosocial support.[16,17] Support was especially needed with respect to the immediacy of ART initiation on the day of HIV diagnosis and disclosure to husbands/male sex partners. Participants were generally welcoming of peer support but concerned about confidentiality and stigma. Together, these results affirmed the model of using lay health workers capable of providing Option B+ education and support, as long as confidentiality could be protected.

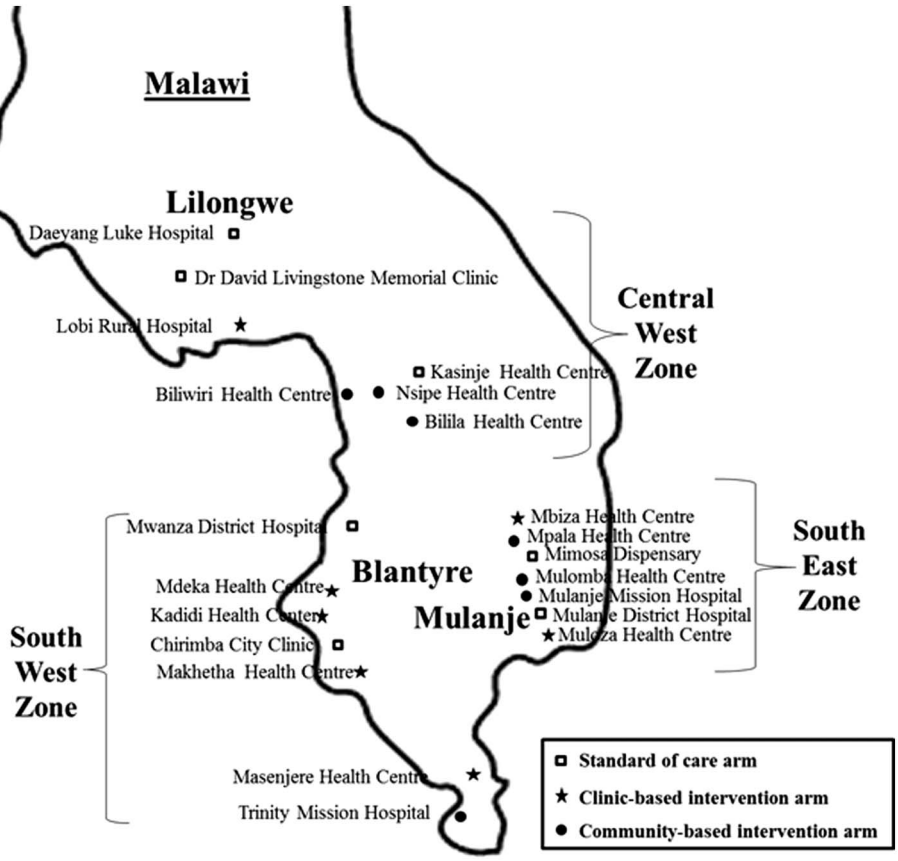

FIGURE 1. Geographic distribution of the 21 PURE sites in the South East, South West, and Central West zones of the country.

METHODS

Study Design

PURE Malawi is a 3-arm cluster randomized controlled trial comparing clinic-based and community-based models of peer support to Option B+ standard of care. The 3 arms differ with respect to the presence and location of one-on-one patient education and support, support groups, visit reminders, and missed visit follow-up (Table 1).

Arm 1: Standard of Care (HIV Care Clinic)

These clinics provide the routine standard of care according to Malawi Ministry of Health guidelines. Women are expected to receive education about ART and routine adherence counseling, although the quality often varies. Women who default are expected to be contacted or traced after 2 weeks by an HSA.[18] However, this rarely occurs, especially in the suggested time frame, because of transport, staffing, or resource challenges.

Arm 2: Clinic-Based Peer Support

In addition to routine procedures described in arm 1, facility-based "mentor mothers," or women living with HIV who recently underwent PMTCT themselves, are trained to provide PMTCT education and psychosocial support. Mentor mothers are available for one-on-one support at clinic visits, lead weekly clinic-based support groups, and contact women within 1 week of a missed appointment. Contact is based on a patient-selected method—phone call, text message, or home visit. This model is adapted from the Mothers2Mothers model of clinical service delivery.[11,19]

Arm 3: Community-Based Peer Support

In addition to routine procedures described as part of standard of care, community-based "expert mothers," or women living with HIV who recently underwent PMTCT themselves, are trained to provide education and psychosocial support to women eligible for Option B+. Expert mothers provide routine community-based educational reminder visits in the home, lead monthly community-based support groups, and contact women in the community within 1 week of a missed clinic visit.

Women were eligible to become clinic-based mentor mothers or community-based expert mothers if they were HIV positive, had disclosed their HIV status to at least one other person, were willing to disclose their HIV status to clients, had been involved in the PMTCT program within the past 2 years, had completed primary school, and could read and write. Expert mothers also had to be able to ride a bicycle. The primary difference between the 2 groups is that mentor mothers are clinic based and expert mothers are community based. Mentor and expert mothers received a 2-week training about patient education and psychosocial topics, including counseling principles, HIV natural history and prevention, PMTCT, ART adherence, HIV status disclosure, and care-seeking schedules for HIV-infected mothers and HIV-exposed infants. They also received intensive training about

TABLE 1. Comparison of the 3 Trial Arms

	Standard of Care	Clinic-Based Support Mentor Mothers	Community-Based Support Expert Mothers
Personnel	All ART care is provided by health providers, including group HIV pretest counseling, individual posttest counseling, ART adherence counseling, and PMTCT education	Most care is provided by health providers. In addition, "mentor mothers" are available in the clinic to provide education and psychosocial support to all women and male partners	Most care is provided by health providers. In addition, "expert mothers" are available in the community to provide education and psychosocial support to women and male partners
Mother:patient ratios	Not Applicable	One mentor mother per 20–40 PURE clients	One expert mother per 10–20 PURE clients
Appointment reminders	None	None	Before each scheduled clinic visit, the expert mother visits the patient and reminds her about her appointment
One-on-one education and psychosocial support	Health providers are expected to routinely assess ART adherence as part of their routine work	Mentor mothers are available at each visit for one-on-one education or psychosocial support on topics such as ART adherence, disclosure, breastfeeding, and PMTCT	Expert mothers are available at each reminder visit for one-on-one education or psychosocial support on topics such as ART adherence, disclosure, breastfeeding, and PMTCT
Support groups	None	Mentor mothers organize clinic-based weekly support groups	Expert mothers organize community-based monthly support groups
Missed visits	Clinic-based staff are expected to contact a patient who has missed a visit more than 2 weeks ago and encourage them to come back to care. This often does not occur because of staffing, transport, or tracking challenges	Mentor mothers are expected to contact a patient who has missed a visit within the week and encourage them to come back to care. This is done by cell phone call, text message, or home visit, depending on the patient's preference	Expert mothers are expected to contact a patient who has missed a visit within the week and encourage them to come back to care. This is done by home visit
Male involvement	If a male partner presents, clinic can implement couple HIV testing and counseling or individual male HIV testing and counseling	Mentor mothers can provide support on disclosure or provide education to couples. They encourage partner testing	Expert mothers can provide support on disclosure or provide education to couples. They encourage partner testing

This describes the differences between the 3 arms. All services provided by the clinic health care workers available in the standard of care arm are available in the clinic-based and community-based support arms, as well. Each expert mother supports fewer clients than each mentor mother due to the added time it takes to visit clients in the community.

confidentiality. Both mentor and expert mothers receive twice-yearly refresher trainings and monthly supervision of service delivery and data quality, as well as discussions of challenges faced. Refresher trainings and supervision are provided by the PURE Consortium implementing partners. Mentor and expert mothers receive stipends consistent with HSA salaries (approximately US$65/month).

Study Population

Depending on the size of the facility, each site is expected to reach a minimum enrollment target of 20, 50, 75, or 125 pregnant or breastfeeding women eligible for the Option B+ program. Enrollment initiation was staggered at trial sites from November 2013 through January 2014, with completion of cohort enrollment expected by late 2014. The enrolled participants will be followed for at least 2 years, along with their HIV-exposed infants, and their enrolled male sex partners. Follow-up completion is expected by July 2016.

HIV-Infected Mothers (Index Participants)

All pregnant and breastfeeding women with a new confirmed HIV-positive diagnosis (ie, eligible to initiate Option B+) are eligible to provide informed consent for participation in the trial. Each woman will be followed until the end of the study period, transfer out, default, or death.

HIV-Exposed Infants

All infants born to or breastfeeding from an index mother are eligible. For women enrolled during breastfeeding, the infant will be enrolled on the day the mother is enrolled. For women enrolled during pregnancy, the infant will be enrolled at the time of live birth. Infants will be under observation until the end of the study period, transfer out, default, or death.

Male Sex Partners

Up to 3 male sex partners, including a husband, can be enrolled for each index mother.

Data Collection and Management

PURE relies on routine adult and infant patient care cards and clinic registers as the primary data sources. These have been well developed as part of the Malawi national health system and are part of the basis for the quarterly supervisory review visits.[18] In all arms, data are collected by clinical staff during routine visits. Additionally, mentor and expert mothers document the timing and nature of each encounter. Clinic and intervention staff at all sites received training and certification

on good clinical practice to ensure ethical data handling. They also received training on record completion to ensure accuracy and consistency. At monthly site visits, data records are photographed or scanned by trained study staff and then double entered into a secure database. Queries are generated within 1 month and addressed at monthly supervision visits.

Study Outcomes and Analytic Methods

The primary analytic approach is intention to treat with women in the 2 intervention arms considered exposed to the intervention regardless of whether or not they receive specific intervention services. Participants in clinic-based and community-based support arms will be compared with standard-of-care participants.

The primary trial outcome is the proportion of women retained at 2 years after initiating Option B+. The denominator includes women who are eligible for Option B+ and enrolled in the trial. The numerator consists of all enrollees who are alive and retained in Option B+ at 2 years without any default (ie, a ≥60-day period without ART). Women who officially transfer out of the facility will be excluded from analysis and analyzed separately. Uptake is defined as accepting ART at the first visit and not defaulting at the first 1-month visit. Generalized estimating equations with a log link and binomial distribution will be used to compare both uptake and retention between arms. Exchangeable correlation matrices and robust variance estimators will be used to account for correlation between observations at each site. To explore timing of default, Kaplan–Meier curves and log-rank tests will be fit to these data. The proportion of visits attended, the proportion attended punctually, and the proportion returning after default will also be calculated. Secondary outcomes are viral suppression and drug resistance. Other outcomes collected include ART adherence, side effects, tuberculosis status, use of Cotrimoxozole Preventive Therapy, administration of the contraceptive injectable Depo Provera, and condom use.

Infant and male partner outcomes will be compared as secondary endpoints. Three infant outcomes include the proportion tested, the proportion HIV infected, and the proportion with HIV resistance. For all infant analyses, only those experiencing milestones after maternal enrollment will be included, a consideration for women enrolled during breastfeeding. Male outcomes include the proportion presenting to the clinic and the proportion HIV positive.

Sample Size and Power

Sample size was estimated using power calculations for cluster randomized controlled trials.[20] These calculations account for the number of clusters per arm, mean number of participants per cluster, variation in cluster size, and correlation within each cluster. At an alpha level of 0.05, with 7 clusters per arm, a mean cluster size of 50, a variance in cluster size of 37, and an intraclass correlation coefficient of 0.04, there is 80% power to detect a difference of 65% female retention (standard-of-care arm) and 82.5% retention (clinic- or community-based arm). Because the 2 intervention arms are expected to have comparable retention, there is unlikely to be sufficient statistical power to detect a difference between these 2 arms. Each arm is expected to enroll a minimum of 360 women with a total minimum sample size of 1080 participants. Standard-of-care retention was estimated based on Malawi-specific and regional data.[5,6,21–23]

Ethical Considerations

The protocol was approved by Malawi's National Health Sciences Research Commission, the University of North Carolina Institutional Review Board, the University of Toronto, and the Ethics Review Committee of the World Health Organization. All female participants provide informed consent for themselves and their infants. Male partner participants consent separately.

DISCUSSION

PURE Malawi is expected to provide evidence that peer-based education and psychosocial support can enhance uptake and retention, as well as multiple other maternal, infant, and male partner outcomes in an Option B+ setting. Additionally, the trial will provide information on the costs, outcomes, and clinic-based impacts of clinic- and community-based models of support.

The PURE Malawi trial design has several notable strengths. Intention-to-treat analysis enables assessment of intervention assignment, rather than intervention self-selection. Similar studies have evaluated peer-based programs in a non-randomized fashion, but suffer from self-selected intervention participants, many of whom are already good care seekers. Randomizing clusters, rather than participants, is an additional strength. Cluster randomization helps prevent contamination of interventions, a phenomenon commonly observed when multiple interventions are coimplemented at the same sites, and allows for full implementation of the intervention at the site.

Trial implementation in a range of Malawian settings and populations is an additional strength. PURE is being implemented in different types of clinics with both pregnant and breastfeeding women. Inclusiveness at the clinic and patient level allows for broad generalizability to the larger Option B+ program. The 2-year follow-up period will provide lessons about durability. The formative and ongoing qualitative and economic work will offer an in-depth understanding of reasons underlying trial impact at both the clinical and patient levels. However, real-world settings also pose a challenge for obtaining high-quality data.

Obtaining information to inform enrollment targets and expected retention was a challenge. Historic data were used to inform targets, but may have been underestimates as the reporting period included periods of HIV test kit stock-outs. Similarly, retention estimates may not have reflected true retention if data were not collected consistently. Finally, other time-related changes in staffing, service delivery, or clinic volume can affect the trial. The Malawi national program continues to implement a unique approach of site visit quality monitoring to improve general performance indicators over time.[18] Through these efforts, the standard of care, including retention, is likely to be improving, but the randomized design should account for this.

The existence and introduction of add-on services poses another challenge. One standard-of-care site was found to have a community-based program that was missed during the situational analysis. Another site is planning new

interventions, despite requests to delay until study completion. During the follow-up period, additional sites may make similar decisions, potentially leading to bias.

Despite these challenges, the PURE trial is expected to have broad relevance for Malawi, and possibly even for the sub-Saharan African region. Option B+ is being considered or already being implemented in many nearby countries, despite its controversial attributes.[2,24–28] Malawi, as the first country to adopt the lifelong Option B+ approach, has the potential to be a leader in developing and documenting highly effective models of service delivery to provide needed support to HIV-infected pregnant and breastfeeding women and to enhance ART retention. PURE is expected to play a critical role in this process.

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