Mother–Infant Pair Clinic and SMS Messaging as Innovative Strategies for Improving Access to and Retention in eMTCT Care and Option B+ in Malawi: A Cluster Randomized Control Trial (The PRIME Study)

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Abstract: UNAIDS has set a goal of achieving the elimination of mother-to-child transmission (eMTCT) of HIV by 2015 and keeping HIV-positive (HIV+) mothers alive. In pursuit of this goal, in 2011, the Malawi Ministry of Health (MoH) adopted the Option B+ strategy, which entails lifelong antiretroviral treatment for all HIV+ mothers, irrespective of severity of HIV infection. Poor mother–child pair retention is one of the major challenges against achieving this goal. To improve retention of mother–infant pairs in the eMTCT continuum of care, the Promoting Retention among Infants and Mothers Effectively (PRIME) study is evaluating the effectiveness of 3 models of health care delivery namely, mother–infant pair clinics, which deliver integrated HIV and non-HIV services, mother–infant pair clinics plus electronic text message (SMS) reminders for mother–infant pairs who miss scheduled eMTCT follow-up clinics, and current standard of care. The primary outcome is “the proportion of HIV+ mothers and/or HIV-exposed infants (HEIs) retained in eMTCT care at 12 months postpartum and received recommended HIV and non-HIV services during preceding scheduled visits.” This 3-arm cluster randomized intervention study is being implemented in 30 primary health facilities (10 facilities per arm) in Mangochi and Salima districts, Malawi. At each clinic, a total of 41 HIV+ mothers attending maternal and child health services are being recruited and followed up for 18 months postpartum. This article describes the study methodology and interventions, successes and challenges experienced during the first 12 months of study implementation and relevance of study results to Malawi and other countries adopting the Option B+ strategy.

Key Words: HIV, eMTCT, retention, SMS, mother–infant pair clinics, ART, Option B+, Malawi

*J Acquir Immune Defic Syndr* 2014;67:S120–S124

INTRODUCTION

In July 2011, Malawi became the first country to develop and implement the Option B+ strategy for elimination of mother-to-child transmission (eMTCT) of HIV, which entails lifelong combination antiretroviral therapy (cART) for all HIV-positive (HIV+) mothers, irrespective of their immune status. Until that time, Malawi had been implementing the World Health Organization (WHO) Option A strategy, which required assessment of maternal immune status. Thus, until that time, Malawi had been using the World Health Organization (WHO) Option A strategy, which required assessment of maternal immune status using the WHO HIV clinical staging or CD4 cell count to determine HIV+ mothers’ eligibility for cART.1 Because most health facilities in Malawi did not have the capacity to perform these assessments, the proportion of eligible HIV+ pregnant women receiving cART initiation was as low as 25% in 2010.2 Following the adoption and scale-up of Option B+, this proportion increased to 75% by the end of 2013.3

Despite increases in cART coverage, retention of HIV+ mothers and HIV-exposed infants (HEIs) in a continuum of eMTCT care remains a challenge. In the first quarter of 2013, the Ministry of Health (MoH) reported that the proportion of postpartum HIV+ mothers and HEI retained in eMTCT care declined markedly from 87% at 2 months to 64% at 12 months and then to 28% at 24 months.4 This significant loss means that many HIV+ mothers and HEI do not receive necessary HIV and non-HIV interventions. Thus, Malawi needs to develop strong retention strategies for mother–infant pairs (MIPs) to assure the benefits of Option B+.

In view of the limited evidence on how retention of HIV+ mothers and HEIs can be optimized, a pilot project by Clinton Health Access Initiative (CHAI) in Machinga district (Malawi) assessed the effectiveness of integrated clinics for HIV+ mothers and HEIs (called MIP clinics) and an...
electronic text message (SMS)-based tracing system for defaulting mothers. The MIP clinics provided non-HIV and HIV services to HIV+ mothers and HEIs in a seamless manner in a single clinic visit. The clinics aimed at reducing and simplifying clinic visits by HIV+ mothers and HEIs. The SMS-based tracing system sought to improve the efficiency of tracing HIV+ mothers and HEIs who failed to attend scheduled clinics. A qualitative evaluation of these interventions found improved retention of MIPs and preference of these services by women attending these facilities. However, the effectiveness of this intervention could not be formally assessed because this was not a controlled trial.

RESEARCH QUESTION AND OBJECTIVES

The Promoting Retention among Infants and Mothers Effectively (PRIME) study is evaluating the effectiveness of novel strategies for improving retention of MIPs in the eMTCT continuum of care. The primary objective of the study was to compare the proportion of HIV+ mothers and HEI retained in HIV care at 12 months postpartum in health facilities implementing 3 types of services, namely, MIP clinics plus SMS-based tracing, MIP clinics alone, and the standard of care. In this study, retention of HIV+ mothers is defined as “attendance of the scheduled 12-month follow-up visit plus receipt of all ARV drug refills during all preceding scheduled clinics.” Retention of HEIs is defined as “infant attendance of the scheduled 12-month scheduled visit plus at least five of the six preceding scheduled visits, including a visit at 6–8 weeks when HIV DNA PCR is first performed for early infant diagnosis.”

Secondary objectives include comparing the following outcomes across health facilities in the 3 arms:

1. Proportion of HEIs who received HIV DNA PCR tests by 2 months of age and received results;
2. Proportion of HEIs receiving all cotrimoxazole prophylaxis refills from 6 weeks to 6 months of age;
3. Mean number of scheduled visits made by the mother and infant from the first antenatal care visit to 12 months postpartum;
4. Proportion of HEIs retained in care and on treatment at 18 months postpartum;
5. Proportion of women alive and on the Option B+ regimen at 18 months postpartum;
6. Cost per MIP retained at 12 months of age;
7. Cost per infant HIV DNA PCR result received and per infant initiated on ART.

STUDY SETTING

The study sites are in Salima and Mangochi districts located in the central and southern regions of Malawi, respectively. Although both are lakeshore districts, Mangochi is dominated by the Yao tribe, a large proportion of whom are Muslim, whereas Salima is dominated by the predominantly Christian Chewa tribe. In 2006, under-5 mortality rates in both districts were slightly higher than the national average (144–150 versus 140 per 1000 live births). In 2010, HIV prevalence was 16.2% among the Yao and 9.0% among the Chewa versus a national HIV prevalence of 10.8%.

SELECTION OF STUDY SITES

Before implementing the study, a baseline survey was undertaken to document the status of infrastructure and availability of health workers at the prospective study facilities to permit comparison of study site characteristics. There were 37 health facilities available for sampling and randomization. These sampling units were stratified into 16 rural and 21 semi-urban facilities. Thirty sites were randomly selected based on the stratification: 13 from rural sites and 17 from semi-urban sites. Thereafter, randomization was performed in blocks of 6 within each stratum, using STATA software version 11.

The cost-effectiveness component of the study will be conducted in 6 health facilities. Two health centers will be chosen per study arm, one from the semi-urban stratum and another from the rural stratum.

STUDY POPULATION AND STUDY SAMPLE

HIV+ pregnant women initiated on the Option B+ regimen. We excluded women meeting any of the following criteria:

1. Not permanent residents of villages surrounding the health facilities and planning to move out of the villages in the following 6–9 months.
2. Unable to give informed consent because of immediate life-threatening illness or mental disorders.
3. Participating in other studies.
4. Refused to consent.

SAMPLE SIZE

Sample size was calculated based on the primary outcome of “the proportion of women attending the 12 month follow-up visit who have received all preceding ART refills.” A point estimate of 60% was used in the MIP plus SMS arm, 40% in the MIP only arm, and 25% in the standard of care arm. An equation, which corrects for stratification, was used to determine the number of clusters needed for each treatment arm for pairwise comparisons among the 3 study arms. We used a 2-sided significance level of α = 0.05, a study power of 80%, and a coefficient of variation (k) of 0.20. Considering the pairwise comparisons, we estimated that 10 clusters per study arm were required, with a minimum of 35 HIV+ mothers and HEI per cluster. To allow for 15% of unavailable data, we planned to enroll a consecutive sample of 41 MIPs, resulting in a combined sample size of 1230 MIPs across the 3 study arms.

METHODS

Design

The PRIME study is a 3-arm stratified cluster randomized design, with a cluster defined as a health facility. Health facilities were stratified based on semi-urban or rural location. Facilities were classified as “semi-urban” when located in areas near trading centers or major road networks, and “rural,” when located far from major road networks.

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Description of Study Arms

Standard of Care Arm

The 2011 Malawi HIV treatment guidelines require the integration of clinical monitoring, preventive and treatment services for family members affected by HIV, especially HIV+ mothers and HEIs, through the establishment of the HIV Care Clinic. However, in most health facilities, HIV and non-HIV-related services (such as pre-ART clinical monitoring services, ART refills, family planning services, immunizations, and nutrition assessment) are provided in separate clinics at different times. Thus, HIV+ mothers and HEIs make several health facility visits to access services from different service points. As a result, a significant number of MIPs may miss scheduled visits. To trace mothers who have missed scheduled visits, health care workers (HCWs) complete tracing forms and pass them to government employed health surveillance assistants who, in turn, travel to the villages to locate defaulting mothers, in collaboration with community-based volunteers (CBVs). In this study, facilities providing services in this manner were classified as being in the “Standard of Care” arm.

MIP Arm

For this study, MIP clinics modeled on an enhanced HIV Care Clinic concept were designed to provide a range of HIV and non-HIV services in a single clinic at the same time or in a seamless, integrated manner. Table 1 shows the range of services provided in the MIP clinics.

In this study, a health facility is considered as an operating MIP clinic if it meets all the following criteria:

1. HIV and routine maternal and child health (MCH) services are offered at the same time and same day, every week, in the same location;  
2. At least 1 clinician or nurse is available in the MIP clinic to provide services;  
3. Essential maternal and pediatric drugs and commodities are readily available in the consultation room, and dispensed accordingly with minimal waiting.

In practice, there are variations in the implementation of MIP clinic services due to differences in numbers of HIV+ women and challenges in human resources, infrastructure, and supply of pharmaceutical and medical supplies. For example, the frequency of MIP clinics varies across facilities from once per week to once per month. Also, while some facilities provide all the services under one physical space, others provide the services in separate rooms because of space limitations.

MIP Plus SMS Arm

The MIP plus SMS arm uses SMS technology to facilitate the tracing of defaulting MIPs. In this study arm, HCWs list all MIPs who miss their scheduled visits and send SMS messages to CBVs residing in or near the defaulting mothers’ villages who, in turn, trace the mothers and/or infants and remind them to return to the clinic. Success in tracing by SMS is evidenced by the mother reattending the clinic within 2 weeks of missing the scheduled visit. This streamlined SMS-based system replaces the paper-based tracing mechanism in the “Standard of Care” and MIP arms. A health facility is considered to be implementing the SMS-reminder system site if SMSs are used consistently to register enrolled study participants and trace defaulting MIPs.

Preparation for Study Implementation

HCWs in all randomized sites received training in Good Clinical Practice (GCP) and research ethics. In addition, HCWs in the MIP and MIP + SMS study arms received training on how to organize the MIP clinics. CBVs and MOH Health Management Information Systems staff in the MIP + SMS study arms received an additional training on how to operate the SMS-based tracing system. District health authorities were also briefed about the aims and structure of the study. Furthermore, community members in the catchment areas of study facilities were sensitized on study background and rationale and basic research ethics. Before starting enrollment, each study site received a final preparatory mentorship visit to ensure that study processes and interventions were in place and operational. Twenty-nine sites were approved to begin enrollment from May to July 2013, whereas the final site was approved in November 2013.

Data Collection

GCP-trained HCWs seek written informed consent from eligible HIV+ mothers accessing health services in the randomized health facilities. Thereafter, study-specific Case Report Forms (CRFs) are used to collect basic sociodemographic information from enrolled women. At subsequent prenatal and postnatal visits, HCWs record services received by the women and their infants in health facility registers and patient cards. Every 4–6 weeks, PRIME project research assistants visit the health facilities to extract study-related data from the health registers, assess the quality of data management, and document any challenges experienced by the sites. In addition, a project mentor conducts technical support visits to the health facilities every 3 months, with more frequent visits if needed.
Supervision of Study Sites

The PRIME Study field team collaborates with the district health management team to ensure professional working relationships with HCWs responsible for screening and enrolling study subjects and recording data in registers. The PI and co-PI conduct 6 weekly supportive field visits. They also monitor the successes and challenges in implementing study activities through routine monthly reports submitted electronically by the field team. Technical advisors from the MOH and the WHO conduct external supportive visits to the study sites every 3–6 months.

Data Management

PRIME project research assistants transfer completed CRFs from study facilities to the PRIME central office where data cleaning and electronic double data entry are performed. In cases of incomplete or questionable data, research assistants verify the data with the source documents on the next visit to the health facility. The PRIME database manager performs data quality audits every 3–4 months by comparing data from a randomly selected sample of CRFs with source documents in the health facilities. Similarly, an independent data quality expert performs data audits twice yearly.

STATISTICAL ANALYSES

After randomization, a baseline analysis was performed to compare the distribution of variables for each pairwise combination across the 3 study arms. As shown in Table 2, there were no significant differences in baseline characteristics among study arms, suggesting a successful randomization process.

After completion of data collection, statistical analyses of the outcomes of interest will begin with basic cluster-level summaries. A point estimate of each outcome variable will be calculated for each health facility. A simple unweighted average of these cluster-level point estimates will then be calculated for each study arm. The outcomes will be compared across arms using independent t tests. Further regression analyses will be conducted for individual-level data using random effects models to account for clustering, and for variability both between and within arms. Logistic regression for proportions of individual-level dichotomous outcomes and random effects linear regression for means of individual-level continuous outcomes will be conducted.

ETHICAL CONSIDERATIONS

The College of Medicine Research and Ethics Committee and the WHO Ethics Review Committee approved the study. Informed consent was sought from each potential study participant before enrolment.

Attendance at MIP clinics or the tracing of an MIP mother can be argued to put mothers at an increased risk of inadvertent disclosure of their HIV status. However, this risk is probably very low. First, HIV+ mothers in the study sites have the option of attending MIP clinics or general MCH clinics, if they feel that the risk of inadvertent disclosure of HIV status is unjustifiably high. Second, tracing of mothers by health surveillance assistants is already a standard community practice for other non-HIV MCH services. Thus, tracing by CBVs does not automatically indicate that the woman being traced is HIV+.

The Standard of Care arm could be considered by some as being unjustified, given the assumption of its inferiority in service delivery and retention in those services. However, it is appropriate to use this arm as comparison because this is current care in most facilities in Malawi, and the possible benefits of improved service delivery, retention, and cost-effectiveness in the intervention arms have never been scientifically tested against the Standard of Care arm in this setting.

<table>
<thead>
<tr>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task: Calculate the distribution of baseline variables for all 10 facilities of each intervention arm.</td>
</tr>
</tbody>
</table>

**TABLE 2. Distribution of Baseline Variables for All 10 Facilities of Each Intervention Arm**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MIP</th>
<th>MIP + SMS</th>
<th>Control</th>
<th>MIP Versus MIP+ SMS</th>
<th>MIP Versus Control</th>
<th>MIP + SMS Versus Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of HCWs (MA, CO, MO, nurse, EHOs)</td>
<td>10.0 ± 8.7</td>
<td>10.0 ± 4.7</td>
<td>10.0 ± 4.8</td>
<td>0.291</td>
<td>0.340</td>
<td>0.963</td>
</tr>
<tr>
<td>Number of HSAs</td>
<td>13.0 ± 2.2</td>
<td>11.8 ± 2.2</td>
<td>12.9 ± 1.7</td>
<td>0.702</td>
<td>0.971</td>
<td>0.692</td>
</tr>
<tr>
<td>Number of CBVs</td>
<td>32.4 ± 21.6</td>
<td>56.1 ± 25.8</td>
<td>125.7 ± 53.2</td>
<td>0.505</td>
<td>0.142</td>
<td>0.241</td>
</tr>
<tr>
<td>Number and % of facilities using SMS printer for EID (n)*</td>
<td>2.0 ± 20%</td>
<td>1.0 ± 10%</td>
<td>1.0 ± 10%</td>
<td>1.000*</td>
<td>1.000*</td>
<td>1.000*</td>
</tr>
<tr>
<td>Number and % using sample transport (n)*</td>
<td>3.0 ± 30%</td>
<td>3.0 ± 30%</td>
<td>2.0 ± 20%</td>
<td>1.000*</td>
<td>1.000*</td>
<td>1.000*</td>
</tr>
<tr>
<td>Turn around time from DBS collection to results received (d)</td>
<td>52.3 ± 7.8</td>
<td>45.6 ± 8.3</td>
<td>38.2 ± 6.2</td>
<td>0.567</td>
<td>0.205</td>
<td>0.531</td>
</tr>
<tr>
<td>HIV+, delivered in last 2 mo</td>
<td>6.1 ± 1.9</td>
<td>10.0 ± 4.2</td>
<td>13.6 ± 5.7</td>
<td>0.414</td>
<td>0.231</td>
<td>0.622</td>
</tr>
<tr>
<td>Of HIV+ who delivered, number who had registered for ANC at that clinic</td>
<td>4.9 ± 1.2</td>
<td>9.8 ± 4.2</td>
<td>11.6 ± 5.0</td>
<td>0.284</td>
<td>0.212</td>
<td>0.789</td>
</tr>
</tbody>
</table>

*Fisher exact test; otherwise all others are 2-group mean comparison t tests.

ANC, antenatal care; CO, clinical officer; DBS, dry blood spots; EID, early infant diagnosis; EHOs, Environmental Health Officers; MA, medical assistant; MO, medical officer; HSA, health surveillance assistant; SD, standard deviation.
**CHALLENGES AND LIMITATIONS**

The study team experienced some resistance from HCWs in implementing the MIP clinics. Some perceived the workload of implementing the study or operating MIP clinics to be very high, whereas others had a negative attitude toward using SMS-based tracing system. These challenges slowed down enrolment during the first 12 months of the study. However, the study team provided regular mentorship to the HCWs, highlighting ways in which MIP clinics are intended to reduce workload and overcome the fragmentation of clinical services. To increase motivation of HCWs to implement study interventions, the study introduced a facility-level performance-based incentive scheme. Study sites are systematically assessed every 4–6 weeks and those that demonstrate good adherence to GCP standards receive group rewards meant to improve the working conditions at the facility. The group reward is any commodity or service chosen by the health facility staff that could be used collectively to improve the working environment of the facility (e.g., maintenance, furniture, filing cabinet, bicycle, lantern, kitchenware). The commodity/service is worth US$37.50 every 2 months for a site with a “satisfactory” score and US$75.00 for a site with an “excellent” score. The Ethics Committee formally approved this incentive scheme before implementation. After implementation of the scheme, enrolment rates across the study sites improved.

Because of the perceived benefits of integrated MIP clinics, the study team experienced pressure from some nongovernmental organizations and other stakeholders to roll out MIP clinics to the “Standard of Care” sites or implement different versions of integrated health services at the facilities. However, this problem was resolved through stakeholder meetings convened by the district health management teams and through continued support of the study by the National eMTCT Coordinator. Nongovernmental organizations planning to implement similar interventions were diverted to non-study facilities to not interfere with the trial.

In December 2013, the Malawi MOH reported improved retention rates of ~73% at 12 months postpartum among HIV+ mothers on Option B+ regimen. However, the reported high retention rates have been questioned due to exclusion of mothers who fail to return for the first follow-up visit after ART initiation. The secular trends in improved retention rates generally, as the B+ program matures, could possibly affect the point estimates used for sample size calculation in this study and hence reduce the power of the study. However, the study team contends that retention rates remain low, based on the strict definition of “retention” adopted by the study. This means the study remains powered to address the study objectives.

**RELEVANCE FOR THE NATIONAL eMTCT PROGRAM**

With our randomized controlled design of 3 service delivery approaches, the PRIME Study will generate the necessary evidence base to assist the MOH in adopting the best, cost-effective health delivery model for HIV+ mothers and HEIs in Malawi. Furthermore, by following a cohort of MIPs and carefully documenting health services provided to them and their health outcomes, this study will also interrogate the robustness of routine data collected by the national HIV program and also assess and better understand retention of mothers and infants in the innovative B+ program.

**ACKNOWLEDGMENTS**

The authors extend their sincere gratitude to the PRIME study implementation team (Nurse Nyambi, Timothy Tchereni, Vandross Chowe, Alfred Kasito, Phillip Chiume, Jeany Mamba and Maclound Mhango); District Health Management Teams in Mangochi and Salima districts; the WHO Coordinator for the INSPIRE project in Malawi, Mrs Ellen Thom; administrative and financial staff at the College of Medicine and Clinton Health Access Initiative in Malawi; all health care workers, community-based volunteers, members of village health committees and community leaders assisting the implementation of the study and all the women and infants participating in the study.

**REFERENCES**